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Phyto-oestrogens

Alison M. Duncan* PhD, RD

Assistant Professor

Department of Human Biology and Nutritional Sciences, University of Guelph, Guelph, Ont., Canada N1G 2W1

William R. Phipps MD

Assistant Professor

Department of Obstetrics and Gynecology, University of Rochester, Rochester, NY, USA

Mindy S. Kurzer PhD

Professor

Department of Food Science and Nutrition, University of Minnesota, St Paul, MN, USA

Phyto-oestrogens are oestrogenic compounds found in plants and consist of isoflavones, lignans and coumestans. Epidemiological studies provide evidence for a protective role of isoflavones, and to a lesser extent lignans, against the development of numerous chronic diseases, including several cancers, cardiovascular disease and osteoporosis. The structural similarity of phyto-oestrogens to endogenous oestrogens has prompted the hypothesis that phyto-oestrogens exert hormonal or anti-hormonal effects relevant to the risk of hormone-dependent disease and/or their suitability as a dietary alternative to hormone replacement therapy. The many human studies that have evaluated the effects of isoflavones and lignans on various endpoints relating to risk of various diseases have greatly increased knowledge of how these compounds behave. At the same time, additional questions have been generated. For example, the increasing interest in extracting isoflavones from the soybean for incorporation into dietary supplements has raised important concerns regarding safety and efficacy. Overall, it is clear that phyto-oestrogens are an area of active and advancing research with great potential to continue to affect human health.

Key words: phyto-oestrogen; isoflavone; lignan; review; health effects; cancer; cardiovascular disease; osteoporosis; menopausal symptoms; safety.

Phyto-oestrogens are naturally occurring compounds found in plants to varying degrees. The classic definition of a phyto-oestrogen is a non-steroidal plant compound that is able to exert oestrogenic effects.[1] Phyto-oestrogens consist of numerous classes, including isoflavones, lignans and coumestans.[1] A fourth class of compounds referred to as resorcylic acid lactones might better be classified as myco- or fungal-oestrogens due to their production by moulds found on cereal crops.[1] This chapter focuses on the isoflavones and lignans, which have received the most attention regarding their classification, food sources, absorption, metabolism and human health effects.

* Corresponding author. Tel.: +1-519-824-4120x5416; Fax: +1-519-763-5902.
E-mail address: amduncan@uoguelph.ca (A. M. Duncan).

CLASSIFICATION AND FOOD SOURCES

Although isoflavones and lignans are non-steroidal compounds, they are structurally similar to naturally occurring oestrogens, synthetic oestrogens and anti-oestrogens (Figure 1). Isoflavones are found in highest amounts in soybeans and soy foods, although they are also present in other beans and legumes.[2] Soy foods generally contain 1.2–3.3 mg isoflavones/g dry weight, with the precise amount depending on numerous factors, including the type of soy food[3] as well as soybean variety, harvest year and geographical location.[4] Studies have estimated typical isoflavone intakes to be 25–40 mg/day for Asians[5,6] and less than 1 mg/day for post-menopausal women living in the USA.[7] The major isoflavones present in soy foods include genistein and daidzein and, to a lesser extent, glycitein.[2] They occur in soy conjugated to sugar moieties as glycosides, termed genistin, daidzin and glycitin.[3,4] Clover is another dietary source of isoflavones as it contains high concentrations of formononetin, which is a precursor of daidzein, and biochanin A, which is a precursor of genistein.[2]

Lignans are more widely distributed in plants, being found in oilseeds, seaweed, legumes, seeds, fruits, vegetables and whole grains, and are particularly concentrated in flaxseed.[8] Flaxseed generally contains 0.96–3.15 μmol lignans/g, with the precise amount depending on factors such as variety, growing location and harvest year.[9] The median daily intake of lignans has been estimated at 578 μg in American postmenopausal women.[7]

Lignans present in flaxseed and other plant foods are termed plant lignans, and include secoisolariciresinol-diglucoside (SECO-DG) and matairesinol (MAT).[9] These compounds serve as precursors to the mammalian lignans, enterodiol and enterolactone.[9]

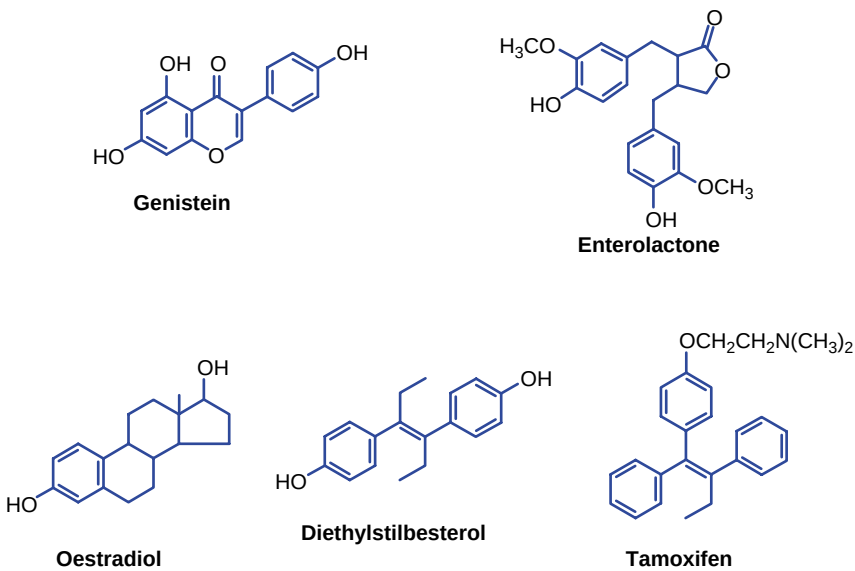

Figure 1. Structures of phyto-oestrogens, including an isoflavone (genistein) and a mammalian lignan (enterolactone), relative to structures of an endogenous oestrogen (oestradiol), a synthetic oestrogen (diethylstilbesterol) and a synthetic anti-oestrogen (tamoxifen).

Practice points

- soybeans are the richest food source of isoflavones
- isoflavones are present in foods bound to glycosidic linkages
- lignans are more widespread in the plant kingdom, with particularly high concentrations in flaxseed
- lignans are present in food as plant lignans, which are precursors of mammalian lignans

ABSORPTION AND METABOLISM

Intestinal bacteria are central to the absorption and metabolism of both isoflavones and lignans.[10–12] Steps involved in the absorption and metabolism of isoflavones are illustrated in Figure 2. Following oral ingestion, glucosidases, which are produced by intestinal bacteria, metabolize the glycosidic isoflavones to their corresponding aglycones, which are termed genistein, daidzein and glycitein.[10,11] Before absorption occurs, however, intestinal bacteria may further metabolize the isoflavone aglycones to isoflavone metabolites, specifically genistein to *p*-ethyl phenol, and daidzein to equol and/or *O*-desmethylangolensin (*O*-DMA), all of which may also be absorbed.[10,11] Following absorption, isoflavones undergo hepatic conjugation to glucuronic acid or sulphate[10,11] to produce forms that are measured in biological fluids.[13,14] Similar to endogenous steroids, they undergo enterohepatic circulation whereby they are deconjugated in the intestine and re-absorbed or excreted in the faeces.[10,11] Studies in humans demonstrate that serum and urinary concentrations of isoflavones increase in accordance with the amount consumed, indicating that absorption occurs in a dose-dependent manner.[15]

The absorption and metabolism of lignans are similar to that of isoflavones, as illustrated in Figure 3. Following oral consumption, the plant lignans, SECO-DG and MAT, are metabolized by intestinal bacteria at various steps.[12] SECO-DG is first metabolized to SECO through hydrolysis of the sugar moieties by intestinal bacteria[12], followed by dehydroxylation and demethylation to enterodiol, reactions which are also catalysed by bacterial enzymes.[12] Enterodiol may then be absorbed or further oxidized irreversibly to enterolactone, which is then absorbed.[12] Intestinal bacterial enzymes also catalyse dehydroxylation and demethylation reactions to convert MAT

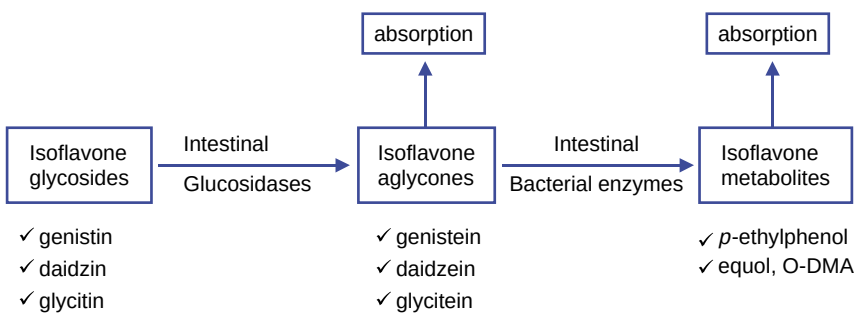

Figure 2. Summary of the absorption and metabolism of isoflavones. *O*-DMA = *O*-desmethylangolensin.

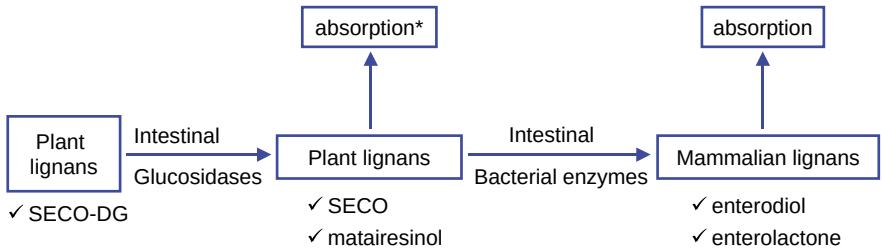

Figure 3. Summary of the absorption and metabolism of lignans. SECO-DG = secoisolariciresinol-diglucoside, SECO = secoisolariciresinol. *SECO and matairesinol have been detected in the urine, suggesting direct absorption.[12]

to enterolactone, which can then be absorbed.[12] The conversion of plant lignans to mammalian lignans is thought to be efficient; however, the detection of SECO and MAT in the urine[12] suggests that it is not a necessary process. It is also possible that there may be other unidentified plant precursors of enterodiol and enterolactone.[12]

Once the mammalian lignans are absorbed, they are conjugated to glucuronic acid or sulphate, enter the circulation and may then be excreted in the urine[14] or undergo enterohepatic circulation.[12] Urinary and plasma concentrations of the mammalian lignans have been shown to increase significantly in a dose-dependent manner following consumption of lignan-rich flaxseed.[16,17] Dietary studies focusing on the effect of specific foods on lignan metabolism have shown significant increases in serum and urinary concentrations of enterolactone following consumption of numerous grains and fruits including whole grains[18] and strawberries[19] in healthy adults. Most recently, a cross-sectional study reported that plasma enterolactone was positively associated with vegetable and fibre intake as expected; however, there were also positive associations observed with alcohol and caffeine intake, raising concern regarding the specificity of plasma enterolactone as a biomarker for exposure to lignan-containing foods.[20]

Practice points

- isoflavones and lignans are metabolized by enzymes produced by intestinal bacteria
- isoflavones and lignans are well absorbed, as indicated by amounts in the blood and urine reflecting dietary intakes

EFFECTS ON HUMAN HEALTH

There has been considerable scientific interest in the role of phyto-oestrogens in numerous aspects of human health. Of particular focus have been the prevalent Western diseases and/or conditions—including breast cancer, prostate cancer, other types of cancer, cardiovascular disease and osteoporosis, as well as alleviation of menopausal symptoms. Research linking phyto-oestrogens to these conditions is continually growing with common goals of determining the efficacy, safety and mechanisms involved.

BREAST CANCER

The epidemiological observation that Asian women have a significantly lower risk of breast cancer (BC) compared with Western women[21] has prompted the theory that high intake of isoflavone-rich soy by Asian women could contribute to this risk difference. Focused observational studies assessing cancer risk and diet have provided support for this theory through findings of significant inverse associations between BC risk and soy isoflavones, both in relation to their consumption[22–25] and their urinary excretion.[26–28] Providing further support is the observation that Asian women who emigrate to the USA and adopt a Western diet lose their lower risk of BC.[29]

Lignans have also received attention for their contribution towards reducing BC risk through results of observational studies. Vegetarians, who have a low risk of breast cancer relative to that of omnivores, also have a significantly higher dietary intake and urinary excretion of lignans.[30] Furthermore, urinary enterodiol[31] and enterolactone[31,32] are significantly lower in post-menopausal BC patients relative to controls. In addition, significant inverse correlations have been reported between BC risk and dietary lignans[33], serum enterolactone[34,35], as well as urinary concentrations of enterolactone, enterodiol and total lignans.[28] Consistent with these data are studies showing that consumption of flax or purified lignans reduces the risk of mammary cancer in rodents.[36]

Despite these supportive studies, the epidemiological studies relating BC risk to intake and/or urinary excretion of phyto-oestrogens have not been consistent. There was no observed relationship between consumption of soy foods and BC risk in a diet and cancer case–control study in Chinese women[37] or in a more recent prospective study of Japanese women.[38] Similarly, BC risk was not affected by either isoflavone or lignan intake in a case–control study involving multiethnic American women.[39] Finally, there were no significant associations observed between urinary genistein or enterolactone and BC risk in a prospective study of post-menopausal Dutch women.[40]

Substantial effort has been put towards uncovering potential mechanisms by which phyto-oestrogens may contribute toward a reduction in BC risk. The relation of BC to reproductive hormones[41], the structural similarity of phyto-oestrogens to endogenous oestrogens (see Figure 1), and the ability of phyto-oestrogens to bind to the oestrogen receptor[42], have provided a rationale for evaluating the hormonal and anti-hormonal effects of phyto-oestrogens as one of these possibilities. Although results of human intervention studies evaluating effects of soy consumption on circulating reproductive hormone concentrations have been inconsistent[43,44], effects on urinary hormones have revealed significant changes in oestrogen metabolites related to decreased BC risk, including increases in the ratio of 2-hydroxyestrone to 16α-hydroxyestrone following soy[45,46] and flax[47,48] consumption. Other potential mechanisms by which phyto-oestrogens may protect against BC risk are independent of the oestrogen receptor. In vitro studies have revealed that both isoflavones and lignans are able to inhibit enzymes involved in the synthesis of steroid hormones, including aromatase and 17β-hydroxysteroid dehydrogenase.[49,50] In addition, there is evidence that genistein is able to inhibit protein tyrosine kinases, DNA topoisomerases and angiogenesis, and exert antioxidant effects.[1]

Determining the mechanisms involved in the relation of phyto-oestrogens to BC risk is complicated by numerous factors, one of which is age of exposure. Animal studies by Lamartiniere et al[51] have demonstrated that the maximum protection against chemically induced BC in adult rats is obtained from exposure to genistein pre-pubertally and again in adulthood. These results are consistent with two recent

case–control studies reporting that exposure to isoflavone-rich soy foods in adolescence is associated with reduced BC risk as an adult.[52,53]

Practice points

- despite inconsistent data, many observational studies have shown an association between isoflavone-rich soy consumption and reduced BC risk
- early exposure to phyto-oestrogens may be necessary for BC prevention

Research agenda

- the impact of age of phyto-oestrogen exposure on the magnitude of potential BC protection requires further exploration

PROSTATE CANCER

Phyto-oestrogens have also been suggested to play a role in protection against prostate cancer (PC), with most data focusing on soy isoflavones. Population studies report a worldwide discrepancy in clinical PC incidence, with rates lower in Asian men relative to Western men.[54] The high intake of phyto-oestrogens, particularly isoflavones, by Asian men is hypothesized to contribute towards their lower incidence of clinical PC.[55] A high intake of isoflavones by Asian men is evident by elevated concentrations of soy isoflavones detected in their blood[56], urine[57] and prostatic fluid[57], compared with their European and Western counterparts. Also providing evidence are results from an immigration study reporting an increased risk of developing PC when Asians are exposed to a Western diet.[58]

Epidemiological studies relating intake of isoflavone-rich soy and PC risk have been supportive, although not consistently. Two large prospective studies, one of Japanese–Hawaiian men[59] and one of California Seventh Day Adventist men[60], reported that consumption of tofu[59] or soymilk[60] were associated with reductions in PC risk of 65 and 70%, respectively, although the tofu relationship did not reach statistical significance ($P = 0.054$).[59] Also supportive are two US case–control studies, one of which found a significant inverse relationship between consumption of soy foods and PC risk[61], and another which observed a trend towards an inverse association between daidzein intake and PC risk ($P = 0.07$).[62] Finally, Hebert et al[63] reported a significant protective effect of soy consumption, four times as large as that of any other dietary factor, in a large ecological mortality study. In contrast, two case–control[64,65] and one prospective study[66], all conducted in Asian countries, were unable to detect significant associations between soy consumption and PC risk. There have been very few studies examining the association between lignans and PC, although a very recent large longitudinal case–control study reported no significant association between serum enterolactone and PC risk in Nordic men.[67]

There have been only a few studies that have evaluated the effect of phyto-oestrogens in men at higher risk or who have PC. An individual case study report suggested that phyto-oestrogens may cause PC tumour regression by documenting that 1 week of consumption of extracted phyto-oestrogens

(160 mg/day), prior to prostatectomy, resulted in cancer cell death with no adverse side-effects.[68] A recent cross-over study in older men with elevated serum prostate specific antigen (PSA) reported no significant effects of soy protein with isoflavones (69 mg/day), relative to soy protein with minimal isoflavones (3.4 mg/day), on serum concentrations of PC-related biomarkers, including PSA and p105erB-2.[69] Finally, another intervention study focused on lignan-rich flaxseed and assessed its effect on blood hormones, PSA and histopathic features before and after an average 34-day intervention in men who had been diagnosed with PC and were awaiting surgery.[70] When compared with historic controls, flaxseed consumption significantly reduced total testosterone and the free androgen index, significantly increased apoptotic cell death and tended to decrease tumour proliferation index ($P = 0.05$); however, there was no significant change in PSA. It should be noted that the intervention also included a low-fat diet, which cannot be separated from the effect of the flaxseed.[70]

Given that reproductive hormones are thought to play a role in PC[71] and that dietary genistein was recently shown to down-regulate androgen and oestrogen receptors in the rat prostate[72], a potential mechanism by which soy isoflavones may reduce PC is through effects on blood reproductive hormones. Although epidemiological data indicate inverse associations between soy consumption and serum reproductive hormones in healthy men[73], the few intervention studies completed have largely shown insignificant effects on serum hormones.[44] Evidence pertaining to other potential mechanisms for a role of soy isoflavones in PC protection include inhibition of 5α-reductase, the enzyme that converts testosterone to the more potent dihydrotestosterone[74], inhibition of other enzymes involved in steroid hormone synthesis, including aromatase and 17β-hydroxysteroid dehydrogenase[49,50], and induction of apoptosis in PC cells.[75]

Practice points

- populations that consume large amounts of isoflavone-rich soy have low rates of clinical PC

Research agenda

- there is a need for human intervention studies designed to evaluate the potential beneficial effects of isoflavone and lignan consumption on PC risk

OTHER TYPES OF CANCER

There has also been research investigating the role of phyto-oestrogens in other cancers such as gastric, colon, endometrial and others.[1] It is prudent to keep in mind that the majority of epidemiological studies relating phyto-oestrogens to these cancers were conducted prior to the hypothesis that phyto-oestrogens could protect against cancer.[76] As such, quantifying phyto-oestrogen intake was often not the focus, raising concern regarding the accuracy of the data.[76]

The relationship between consumption of soy foods and gastric cancer risk appears to depend on whether or not the soy food is fermented. A recent meta-analysis by Wu

et al[77] reported that soy consumption was significantly protective against stomach cancer, provided the analysis did not include studies with fermented soy foods, which actually resulted in a significantly increased risk of stomach cancer. The discrepant results could be due to the high salt content, *N*-nitroso compounds or other unidentified components of fermented foods[77]; however, the authors noted that the studies were not focused on the investigation of soy foods in particular and pointed out the existence of numerous other confounders, particularly intake of fruits and vegetables.[77]

Studies that have assessed the relationship between soy intake and risk of colon and rectal cancers have generally not been supportive of a protective effect.[76] For example, a large cross-cultural study involving 38 countries found no significant association between soy intake and colon cancer risk[78], and another Japanese case–control study reported that miso significantly increased the risk of rectal cancer.[79] Studies that have reported a protective effect have often related the effect to low quantities of soy foods, thereby questioning the true effect.[76] Despite the unconvincing epidemiological data, this area warrants more investigation to provide clarity on the conflicting results regarding the relationship between soy foods and colorectal cancer.

Regarding other types of cancer, consumption of soy products and other legumes has been significantly associated with a decreased risk of endometrial cancer within Asians and non-Asians in a case–control study performed in Hawaii.[80] In addition, a recent case–control study relating phyto-oestrogens to hepatocellular carcinoma found that cases had significantly lower intakes of genistein but not daidzein, SECO or MAT.[81]

Practice points

- consumption of soy isoflavones has the potential to decrease risk of several types of cancer; however, the limited studies preclude consistent conclusions
- the role of isoflavones in gastric cancer appears to depend on whether the isoflavones are fermented in the soy food, although the high salt and other compounds of such foods may confound the relationship

CARDIOVASCULAR DISEASE (CVD)

There have been several epidemiological observations supporting a protective role for phyto-oestrogens in modulating numerous markers of CVD risk. Consumption of soy products has been inversely associated with serum total cholesterol[82], and consumption of both isoflavones and lignans has been significantly inversely associated with plasma triglycerides (TG) and CVD risk metabolic score.[83] Other studies have observed significant inverse associations between dietary isoflavones and aortic stiffness[84], dietary lignans and aortic pulse-wave velocity[84], as well as serum enterolactone and risk of acute coronary events.[85]

Intervention studies evaluating the effect of phyto-oestrogens on CVD risk have focused largely on blood lipid concentrations. A meta-analysis assessing the effects of isoflavone-rich soy protein on blood lipids reported overall reductions in total cholesterol by 9.3%, low-density lipoprotein (LDL) cholesterol by 12.9% and TG by 10.5%, following an average soy protein intake of 47 g/day.[86] This evidence contributed toward the approval of a health claim by the US Food and Drug Administration, allowing the food industry to promote soy protein for heart health on their products.

Although the health claim approval is for soy protein and not the isoflavones specifically, the hypothesis that isoflavones are the responsible component has been advanced[86] and supported by results from clinical interventions designed to assess whether isoflavones as part of the soy protein matrix are able to effectively decrease serum lipids.[87–90] Interestingly, clinical studies assessing effects of isoflavone extracted from the soybean matrix have found no significant effects on serum lipids[91,92], suggesting that the efficacy of soy isoflavones depends on their presence in the soy protein matrix. Further complicating the relationship between isoflavones and soy protein is evidence from a monkey study showing that, although plasma lipids were lowered by isoflavone-rich soy protein but not by soy protein from which isoflavones had been removed using alcohol, the lipid-lowering effects of soy protein were not restored when the alcohol-extracted isoflavones were returned to the soy protein matrix.[93] This observation raises the possibility that the alcohol extraction process may alter the quality of soy protein in a manner that compromises its lipid-lowering effects.[93]

Intervention studies assessing the effects of lignan-rich flaxseed on CVD risk have been fewer in number but they consistently report reductions in serum lipids. Jenkins et al[94] found that serum concentrations of total and LDL cholesterol, as well as of apolipoproteins B and A-I, were significantly reduced following flaxseed consumption. Most recently, Lucas et al[95] also observed a significant reduction in serum lipids, including total cholesterol and non-high density lipoprotein (non-HDL) cholesterol, apolipoprotein B and apolipoprotein A-I, as a result of flaxseed consumption.

In addition to serum lipids, other potential beneficial effects have been studied that could provide a mechanism for the protection of phyto-oestrogen consumption against CVD.[96] Among these, antioxidant effects have received attention and are evident from intervention studies reporting an increase in LDL resistance to oxidation and a decrease in plasma F_2-isoprostanes following soy consumption[97], as well as a recent observational study reporting a significant negative association between plasma F_2-isoprostanes and serum enterolactone.[98] Also receiving attention have been direct vascular effects, evident from observations of improved systemic arterial

Practice points

- considerable evidence supports a role for soy protein in reducing blood lipids associated with CVD
- food products containing specific amounts of soy protein are authorized in the USA to include a health claim on the label promoting soy protein in the reduction of CVD risk

Research agenda

- further inquiry is necessary to understand why animal and human studies report that isoflavones extracted from the soybean do not exert the same beneficial effects as when isoflavones are part of the soy matrix
- there is a need for further research to clarify the contribution of isoflavones to the lipid-lowering effects of soy protein

compliance following consumption of extracted isoflavones in peri- and post-menopausal women.[91,99]

OSTEOPOROSIS

Concerns regarding bone health and risk of osteoporosis are most relevant to post-menopausal women, since the decline in oestrogen production that occurs with menopause is a major contributing factor.[100] Although hormone replacement therapy (HRT) is able to ameliorate the loss of oestrogen at menopause and thereby address the concerns regarding osteoporosis[101], there remains substantial interest in alternatives, particularly dietary alternatives, to HRT. It is in this regard that phyto-oestrogens have received considerable interest in relation to bone health.[102] Related to isoflavones in particular is research showing that ipriflavone, a synthetic isoflavone, effectively reduces bone loss in post-menopausal women.[103]

Interest in the potential relation between phyto-oestrogens and osteoporosis risk was generated from observations of significantly lower numbers of hip fractures in Asian women, relative to Caucasian women.[104] Numerous observational studies relating soy intake of pre- and post-menopausal women to bone mineral density (BMD) have generally reported significant positive associations[105–107], with only some studies reporting no association.[108,109]

Adding to the evidence from observational studies have been human intervention studies assessing effects of phyto-oestrogen consumption on BMD and/or biomarkers of bone metabolism. Some studies assessing BMD have found positive effects of soy and soy isoflavones specifically on BMD of the lumbar spine.[110,111] Studies assessing markers of bone formation and resorption have been less consistent, with some reporting beneficial effects with respect to bone health[112,113] while others have reported no significant effects[114,115] or effects too small to be of clinical relevance.[116] More recently, a study was completed in which the effect of soy consumption was compared directly with HRT in post-menopausal women, and while soy was not as effective as HRT in reducing bone turnover, it did stimulate osteoblastic activity.[117]

There are fewer data available concerning the relationship between lignans and bone health. Despite results of a recent epidemiological study showing a significant positive association between urinary enterolactone and BMD in Korean post-menopausal women[118], intervention studies have reported that 3 months of flaxseed resulted in no significant effects on markers of bone turnover[95] and a non-significant increase in bone mineral content[119] in healthy post-menopausal American women.

Practice points

- Asian women, who consume increased quantities of soy isoflavones, have lower numbers of fractures than do Western women
- observational studies report that soy consumption is positively related to BMD
- studies evaluating the effect of isoflavones on bone metabolism have been inconsistent

Research agenda

- there is a need for longer-term intervention studies evaluating the effects of isoflavone-rich soy protein and extracted isoflavones on bone health
- human studies exploring the potential role of lignans in bone health are needed

MENOPAUSAL SYMPTOMS

The potential for phyto-oestrogens to alleviate symptoms associated with menopause, particularly hot flushes, is an area of active research and relates to the efficacy of isoflavone-rich soy or isoflavone supplements as a possible dietary alternative to HRT. It is well known that Asian women have considerably fewer menopausal symptoms than Western women, and it has been hypothesized that this difference is due to their high intake of phyto-oestrogen, particularly isoflavones.[120] Soy intake has been significantly negatively correlated with the number of hot flushes in cross-sectional[121] and prospective[122] studies of Japanese women.

Intervention studies in peri- and post-menopausal women have reported decreased hot flushes following consumption of soy; however, in many studies, these were not significantly greater than the decrease observed for the control group.[119,123–125] The apparently strong placebo effect is thought to be due to a true placebo effect and the normal decrease in vasomotor symptoms that naturally occurs over time.[126] Despite this, a few studies have found significant decreases in number[127] or severity[128,129] of hot flushes within the soy treatment group beyond placebo, although the clinical significance of some of the changes observed is debatable. Numerous intervention studies have also used isoflavone extracts and have revealed similarly inconsistent results, with some studies reporting significantly fewer hot flushes[112,130,131], and others reporting no significant effects secondary to an apparent placebo effect.[132–134]

The effect of lignans on hot flushes has not been widely studied. Dalais et al[119] included flaxseed as a treatment group in their intervention study evaluating the effects of phyto-oestrogens and did find that it reduced the frequency of hot flushes; however, it was not significantly different from the soy or wheat groups. Flaxseed was also included as part of the intervention by Brzezinski et al[129] but the modest albeit statistically significant decrease in hot flushes observed could not be attributed directly to the flaxseed as it was consumed in combination with soy products.

Overall, it appears that there is some evidence to support a role for soy isoflavones in the management of menopausal hot flushes but effects specifically due to soy isoflavones are modest in degree.

Practice points

- numerous studies have shown that consumption of isoflavones, both as part of the soybean or extracted from the soybean, reduce menopausal symptoms, but this is largely due to a placebo effect

SAFETY ISSUES

An important area regarding the safety of phyto-oestrogens relates to the widespread use of soy-based infant formula by infants who are intolerant to cow's-milk-based

formula.[135] Isoflavones from soy formula are well absorbed by infants and circulate at concentrations 13 000–22 000-fold higher than oestradiol[136], generating considerable concern regarding their long-term health effects, particularly on endocrinological and reproductive outcomes. The most informative study addressing this issue is that of Strom et al[137], which involved a retrospective cohort design that examined the association between infant exposure to soy formula and numerous endocrinological and reproductive outcomes as adults aged 20–34 years. Results showed no statistically significant differences between exposed and non-exposed groups for more than 30 health outcomes, although women who had consumed soy formula reported slightly longer menstrual bleeding durations and greater discomfort with menstruation.[137] Although these data are encouraging, more research is clearly warranted and, as such, this topic remains an active area of investigation.[138]

An area of increasing interest relevant to the safety of isoflavones is their use in patients who have or have had BC.[139] Much of this concern arises from studies of ovariectomized, athymic mice that have demonstrated the ability of genistein and soy protein to stimulate the growth of BC cells in a dose-dependent manner[140,141], as well as the ability of genistein to antagonize the inhibitory effects of tamoxifen on BC growth[142], both at concentrations achievable by humans. Whether these effects would occur in humans is not clear, although there have been human studies reporting stimulatory[143] effects of isoflavone-rich soy protein on the breast tissue of healthy pre- and post-menopausal women and oestrogenic effects of isoflavone-rich soy protein on the breast tissue of the normal breast of pre-menopausal BC patients.[144] It is noteworthy that these studies were of relatively short duration (2 weeks to 1 month) and one did not include a control group.[143]

A final issue worth discussing is the widespread availability of extracted isoflavones in dietary supplement form. The concerns include not only the ease at which high doses could be consumed using these supplements, but also the lack of data regarding their pharmacokinetics and efficacy.[145] Setchell et al[145] demonstrated that isoflavone extracts are absorbed rapidly and efficiently and that the supplements vary considerably in their pharmacokinetics, dependent on factors such as the starting material, isoflavone profile and isoflavone concentration. Interestingly, de-conjugation of the glucosidic linkages of isoflavones present in the soy matrix appears to be rate-limiting for their absorption[146,147], resulting in a curvilinear relationship between intake of isoflavones in soy foods and their plasma concentrations and apparent bioavailability.[146] This suggests that absorption of isoflavones from food is saturable, possibly making it more difficult to obtain pharmacological blood levels that would raise health concerns.[146,147] Whether this occurs with isoflavone supplements is not as clear, although a recent study assessing the acute pharmacokinetics of one specific formulation of an isoflavone extract reported minimal toxicity of doses up to 16 mg/kg body weight/day in healthy men.[148] Genistein and daidzein were rapidly cleared from the plasma and excreted in the urine, although there were observed elevations of lipoprotein lipase and hypophosphataemia.[148] The long-term effects of consuming high doses of extracted isoflavones are not yet known. In addition to safety, the efficacy of extracted isoflavones is of concern. It appears that extracted isoflavones are able to alleviate menopausal symptoms to a modest degree in some studies[112,130,131]; however, unlike isoflavone-rich soy foods, they do not appear to be able to reduce blood lipids effectively.[91,92] The continual growth of knowledge concerning the safety and efficacy of extracted isoflavone supplements remains a research priority, particularly due to their widespread availability and growing use.[145]

Practice points

- infants consuming soy-based formula have high circulating concentrations of isoflavones
- a large epidemiological trial reported minimal long-term adult health effects of consuming infant formula, but more studies are needed
- soy isoflavones can stimulate the growth of breast cancer cells in ovariectomized athymic mice
- the safety and efficacy of isoflavones extracted from the soybean are not as well understood as isoflavones present in the soy matrix

Research agenda

- continual evaluation of the safety of extracted isoflavones is necessary
- there is a need for evaluation of the efficacy of extracted isoflavones relative to isoflavones present in the soy matrix, with respect to various aspects of human health

SUMMARY

Phyto-oestrogens are important biologically active components present in our diet. Isoflavones, found in highest concentrations in the soybean, and lignans, found in highest concentrations in flaxseed, have received considerable scientific attention regarding their absorption, metabolism and effects on human health. Overall, research has been focused more on isoflavones, although the available data on lignans clearly justifies the need for more. Evidence for a protective role of isoflavone-rich soy in protecting against BC is not entirely consistent and is complicated by the apparent impact of age of phyto-oestrogen exposure. The limited studies regarding phyto-oestrogens and PC precludes consistent conclusions yet they highlight the need for human intervention studies involving both soy isoflavones and lignans. It is apparent that phyto-oestrogens can modulate risks of other cancers, some of which include gastric, colon, rectal and endometrial, underscoring the breadth of their role in human health. A large body of evidence supporting a role of soy protein in reducing CVD risk has led to approval of a health claim for foods in the USA. The role of isoflavones as part of the soybean requires more clarification, and more studies are needed to explore the potential benefits of lignans in cardiovascular health. Osteoporosis is another active area of research in which soy isoflavones appear to exert some benefit, although not similar in magnitude to that of HRT. Also relevant to HRT are reports of reduced hot flushes following consumption of soy isoflavones, although a strong placebo effect is also apparent. Related to all areas of phyto-oestrogen research is the need for more knowledge of the safety and efficacy of isoflavones extracted from the soybean. Overall, the wide depth and breadth of research exploring a role for phyto-oestrogens in human health clearly warrants their major contribution to the relationship between diet and human health. Future research designed to explore the outstanding questions and issues will continue to clarify this exciting relationship.

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