Soy Connection Fact Sheet

SOY+ WOMEN'S HEALTH

Soy foods offer health benefits for all consumers, but studies show that postmenopausal women may reap particular benefits. This fact sheet discusses recent research into the benefits and safety of soy for women, from heart disease to hot flashes.

INTRODUCTION

Traditional soy foods such as tofu and miso have been widely consumed for centuries in many Asian countries. Health-conscious individuals in Western countries have consumed these foods for decades. Over the past 25 years, increasing numbers of non-Asians have incorporated soy into their diets because of purported health benefits. Soy foods hold particular appeal for postmenopausal women because they are uniquely rich sources of isoflavones, one type of phytoestrogen.

Isoflavones exhibit estrogen-like effects under certain experimental conditions and are posited to reduce the risk of coronary heart disease (CHD),[1] osteoporosis,[2] certain forms of cancer,[3] and alleviate menopause-related hot flashes.[4] Consequently, many women view soy foods as natural alternatives to conventional hormone therapy. Women who use alternative therapies express a desire to have control over their symptoms and the way in which their menopause is treated.[5]

However, despite interest in the health benefits of isoflavones, these soybean constituents are not without controversy. Their estrogen-like effects have raised concern that they possess some of the same undesirable properties as hormone therapy. Most notable in this regard is the concern that

soy foods may adversely impact the prognosis of women with breast cancer and increase the risk of high-risk women developing breast cancer.[6] This concern is without scientific support and will be discussed in this brochure. Soy foods are a unique dietary source of isoflavones, a phytoestrogen that may offer heart health benefits and may help alleviate hot flashes during menopause.

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OVERFLOW OF ISOFLAVONES

Isoflavones have a limited distribution in nature, such that diets that do not include soy foods are almost devoid of these compounds.[7] Isoflavone intake among older individuals in Japan[8] and Shanghai[8] is about 30 to 50 milligrams per day (mg/d), whereas intake is less than 3 mg/d in the United States, Canada, and Europe.[9-15] Isoflavones primarily occur in soybeans as glycosides[16], but upon ingestion, the sugar is hydrolyzed thereby allowing for absorption to occur.[17] In fermented soy foods such as miso, tempeh, and natto, substantial amounts of the isoflavones occur as aglycones due to bacterial hydrolysis. The three isoflavones, genistein, daidzein, and glycitein, and their respective glycosides account for approximately 50, 40, and 10%, respectively, of the total isoflavone content of the soybean.[16]

Each gram of soy protein in soybeans and traditional Asian soy foods is associated with approximately 3.5 mg of isoflavones.[8] Consequently, one serving of a traditional soy food, such as 3 to 4 ounces of tofu or 1 cup of soy milk, typically provides about 25 mg of isoflavones. Isoflavones bind to both estrogen receptors (ER) - ERα and ERβ[18,19] - and are able to exert estrogen-like effects under certain experimental conditions; hence, their classification as phytoestrogens. However, whereas estrogen binds to and activates ERα and ERβ equally, isoflavones preferentially bind to and activate ERB.[20-23] This difference in binding and activation between isoflavones and estrogen is important because the two ERs have different tissue distributions, and when activated, can have different and sometimes even opposite physiological effects. This appears to be the case in the breast, where ERβ activation is thought to inhibit the proliferative effects of ERα activation.[34,25] In fact, recent findings implicate ERβ-specific agonists with having growth-inhibitor effects in several cancer models.[26]

The preference of isoflavones for ERβ is the primary reason that isoflavones are viewed as capable of exerting tissue-specific effects and classified as selective estrogen receptor modulators (SERMs).[27-29] In tissues that possess ERs, SERMs exert estrogen-like effects in some tissues but no effects or antiestrogenic effects in others.

HOT FLASHES

Hot flashes are the most common reason given by women seeking treatment for menopausal symptoms. For most women who experience them, hot flashes begin prior to menopause. Ten to 15 percent of these women experience hot flashes that are severe and frequent.[30]

The low incidence of hot flashes among native Japanese women helped raise initial speculation that isoflavones could be useful in their prevention.[31] Since 1995, more than 50 clinical trials have examined the impact of isoflavones from different sources on the alleviation of menopause-related hot flashes. Most studies intervened with supplements rather than soy foods to enhance compliance and to reduce the complexity of study design. The results of these trials have produced inconsistent results. However, with one exception, analyses of the clinical research have failed to consider the importance of sub-analyzing the data according to the type of isoflavone supplement employed based on genistein content, which is the isoflavone considered to be most potent.[32]

This exception is a systematic review and meta-analysis published in 2012, which included 17 and 19 trials, respectively, all of which intervened with isoflavone supplements derived from soy.[32] The meta-analysis of the data on hot flash frequency, which included 13 studies involving 1,196 women, found that isoflavones were consistently efficacious, reducing the number of hot flashes per day by about 21 percent more than the reduction in the placebo group ($p < 0.00001$). Similarly, in the nine trials involving 988 women that evaluated hot flash severity, isoflavones reduced symptoms by about 26 percent more than the reduction in the placebo group ($p<0.001$). When considering the combined effect of the placebo and isoflavones, the overall reduction in frequency and severity was approximately 50 percent.

Isoflavine Content of Soy Foods

SOY FOOD	SERVING SIZE	TOTAL (MG) ISOFLAVONE/ SERVING
Miso	1 tbsp	7
Soybeans, Green, Cooked	1/2 cup	50
Soybeans, Black, Cooked	1/2 cup	40
Soybeans, Yellow, Cooked	1/2 cup	78
Soybeans, Roasted, Plain	1/4 cup	78
Soymilk, Plain, Unfortified	1 cup	10
Soy, Plain, Fortified	1 cup	43
Soy Flour, Defatted	1/4 cup	42
Soy Flour, Full-Fat	1/4 cup	33
Soy Flour, Low-Fat	1/4 cup	50
Soy Crumbles	1/2 cup	9
Soy Protein Isolate Powder, Plain	1/3 cup	53
Textured Soy Protein, Dry	1/4 cup	33
Tempeh	1/2 cup	53
Tofu	1/2 cup	25

Source: United States Department of Agriculture Nutrient Database.

Sub-analysis of the data revealed three interesting findings. First, baseline hot flash frequency did not impact efficacy. That is, the percent reduction in hot flash frequency was similar regardless of whether women had two hot flashes per day at baseline or 10 hot flashes per day. Second, hot flashes were reduced more in studies >12 weeks in duration versus shorter-term studies. This finding indicates that the effects of isoflavones are not transient. Third, and most important, supplements that provided higher amounts of genistein were considerably more efficacious than supplements low in this isoflavone. This finding is important because the two primary types of supplements that are commercially available and that have been used in the clinical trials have markedly different isoflavone profiles. One is high in genistein and daidzein but low in glycitein, which is similar to the isoflavone profile of soy foods, whereas the other one is very low in genistein and high in daidzein and glycitein.

In studies that intervened with supplements providing ≥18.8 mg genistein (the median for all studies), hot flash frequency was reduced by almost 27% beyond the placebo effect, whereas in trials providing less than this amount, frequency was reduced by only about 12.5% (difference between groups, P = 0.03). The greater reduction in response to genistein-rich supplements is consistent with several lines of evidence indicating that genistein is more potent than the other two soybean isoflavones.[33,34]

Collectively, the data make a convincing case that isoflavones can be of help to women who experience hot flashes. Several trials published subsequent to the 2012 meta-analysis are supportive of efficacy.[35-37] The one notable unsupportive trial employed an experimental design inconsistent with guidelines for conducting trials evaluating hot flashes.[38]

The level of relief provided by isoflavones is consistent with the degree of benefit deemed satisfactory by women seeking non-hormonal treatments for hot flashes.[39] The amount of isoflavones (~50 mg) providing symptom relief is found in approximately two servings of traditional soy foods.

OSTEOPOROSIS

In response to declining estrogen levels, women can lose substantial amounts of bone mass in the decade following menopause, which markedly increases their fracture risk.[40] Estrogen therapy reduces postmenopausal bone loss and hip fracture risk by approximately one-third.[41] Data shows that the protective effects against hip fracture are lost within two years of cessation of estrogen therapy.[42] Initial speculation that soy foods might promote bone health in postmenopausal women was based on the estrogen-like effects of isoflavones and early research showing that the synthetic isoflavone, ipriflavone, exerted skeletal benefits.[43]

Two prospective Asian epidemiologic studies have evaluated the relationship between soy intake and fracture risk. In both, risk was reduced by approximately one-third when women in the highest soy intake category were compared to women in the lowest. This degree of protection is similar to that noted for estrogen therapy.[41] In one of the studies, approximately 1,800 fractures of all types occurred in the 24,000 postmenopausal Shanghai women who were followed for 4.5 years.[44] In the other study, there were almost 700 hip fractures (the only site studied) among the 35,000 postmenopausal Singaporean women during the 7-year follow-up period.[45]

In a third prospective epidemiologic study, which involved U.S. Seventh-day Adventists, soy milk intake was significantly inversely related to risk of osteoporosis.[46] However, evidence suggests the beneficial effect of soy milk was due to its calcium content rather than its isoflavone content since dairy product intake was similarly protective. Although the results of this study[46] and the two previously discussed Asian studies[44,45] are intriguing, definitive conclusions about the skeletal effects of soy foods can only be based on the results from appropriately designed clinical studies.

Danish researchers recently meta-analyzed the results of 26 randomized controlled trials involving 2,652 peri-or postmenopausal women that evaluated the effect of isoflavone eynosure on bone mineral density (BMD).[47] They found that at both the lumbar spine and the femoral neck, in comparison to the control/placebo, isoflavone treatment was associated with a significantly higher weighted mean difference of BMD change. However, when sub-analyzing the data, the benefit of treatment was enhanced when limiting the analysis to trials intervening with isoflavones in aglycone form, whereas the benefit disappeared when only studies with formulations comprising predominantly isoflavone glycosides were included.

Of the many intervention trials, four stand out for their size and duration (≥2 years duration). Two were conducted in the U.S.,[38,48] one in Italy,[49] and one in Taiwan. Three of the four trials failed to show favorable effects on BMD. The one trial that did, found that in osteopenic Italian women consuming 54 mg/d genistein, BMD at the spine and hip increased markedly over a three-year period, whereas in the placebo group, there were marked decreases.[49] This trial intervened with genistein in aglycone form.

The failure of three of the four large trials to show skeletal benefits of isoflavones certainly casts doubt upon the efficacy of isoflavones. That being said, research from Purdue University using novel methodology highlights the potential skeletal benefits of isoflavones and possibly provides at least a partial explanation for the lack of effect in the longer-term clinical trials.[51] For this crossover study, 24 healthy postmenopausal women were administered daily either different isoflavone supplements or risedronate, a bisphosphonate anti-osteoporotic drug, for 50 days.[51] Prior to the intervention, each woman was injected with 41Ca, a rare isotope of calcium that has an exceptionally long half-life, which makes it possible to precisely detect changes in bone calcium content. Risedronate increased bone calcium content by a statistically significant 15.3 percent. Hence, the methodology employed in this study identified the bone-protective effects of this drug. Risedronate is known to reduce the risk of developing both vertebral and hip fractures by approximately 50 percent.[52]

In response to a daily supplement containing 105 mg of isoflavones, bone calcium content significantly increased by 7.6 percent. Thus, at this dose level, isoflavones were about half as potent as a well-established drug used to treat osteoporosis. The authors of this study concluded that "…the use of soy isoflavones presents minimal to negligible risk to postmenopausal women…and can be used long term for some protection against postmenopausal bone loss." This trial also showed that isoflavone doses much higher than the 105 mg dose were actually much less efficacious. Two of the three previously cited clinical trials used very large doses, which might explain why they failed to show that isoflavones affect BMD.[38,50]

Regardless of the effects of isoflavones, soy foods may support bone health because they provide high-quality protein.[53-56] In addition, some soy foods are good sources of calcium as well as vitamin D.[57] Importantly, the absorption of calcium from calcium-set tofu and calcium-fortified soy milk[57,59] is comparable to the absorption of this mineral from cow's milk. Therefore, for several reasons, soy foods can contribute to a bone-healthful diet.

Fortified soy milk is a good source of isoflavones and also contains calcium, vitamin D and protein, which offer additional bone health benefits.

HEART HEALTH

Soy foods potentially offer protection against heart disease through several mechanisms. For example, soy foods are low in saturated fat and high in polyunsaturated fat.[60] When soy foods replace common sources of protein in the U.S. diet, as a result of the favorable change in fatty acid intake, estimates are that circulating LDL-cholesterol concentrations may be reduced by as much as 4 percent.[61] There is also evidence indicating that when unsaturated fat replaces saturated fat, endothelial function[62] and cholesterol efflux capacity[63] will be enhanced.

Independent of fat content, soy protein directly lowers blood cholesterol levels, an attribute that was formally recognized by the U.S. Food and Drug Administration (FDA) in 1999.[64] Although the FDA is currently reevaluating evidence in support of the claim, meta-analyses of the clinical data show that soy protein lowers LDL-cholesterol approximately 4 percent.[61,65-73] So protein may also modestly lower blood pressure.[71,74-76]

Finally, there is evidence that isoflavones improve endothelial function in postmenopausal women.[52,53] For a more extensive discussion on heart health, see the Soy Connection *Soy & Heart Health* fact sheet.

Soy foods may offer protection against heart disease, as they are low in saturated fat and high in polyunsaturated fats.

BREAST CANCER

The role of soy foods in reducing breast cancer risk has been rigorously investigated for more than two decades. A meta-analysis of epidemiologic studies published in 2013 that included 12 studies from Asia found that higher soy intake was associated with a statistically significant 29 percent reduction in the risk of developing breast cancer.[3] However, there is intriguing evidence indicating that to derive this benefit, soy consumption must occur during childhood and/or adolescence.[77-79]

Despite the results of the epidemiologic research noted above and the low breast cancer mortality rates in Japan,[80] the relationship between soy foods and breast cancer has been controversial. This controversy is due to concern, based almost exclusively on in vitro and rodent data, that isoflavones may be contraindicated for women with breast cancer and women at high risk of developing this disease.[81] However, as discussed, the clinical and epidemiologic data show that soy foods are safe for women with breast cancer and may even benefit them.

Although no clinical trials evaluating the effects of soy or isoflavones on breast cancer recurrence have been conducted, many studies have shown that isoflavone exposure does not adversely affect markers of breast cancer risk, including mammographic density[82,83] and in vivo breast cell proliferation.[84-89] Furthermore, prospective epidemiologic data show that post-diagnosis soy intake improves prognosis. Results of a meta-analysis of five prospective studies are in support of this statement, two from the U.S. and three from China, involving more than 11,000 women with breast cancer, which found post-diagnosis soy intake was associated with reductions in both breast cancer recurrence (hazard ratio, 0.84; 95% confidence interval: 0.71, 0.99) and mortality (hazard ratio, 0.74; 95% confidence interval: 0.64, 0.85). Importantly, soy consumption was similarly beneficial in Asian and non-Asian women. In contrast to studies in mice, the epidemiologic data suggest that soy consumption may enhance the efficacy of chemotherapeutic agents used to treat breast cancer.[90,91]

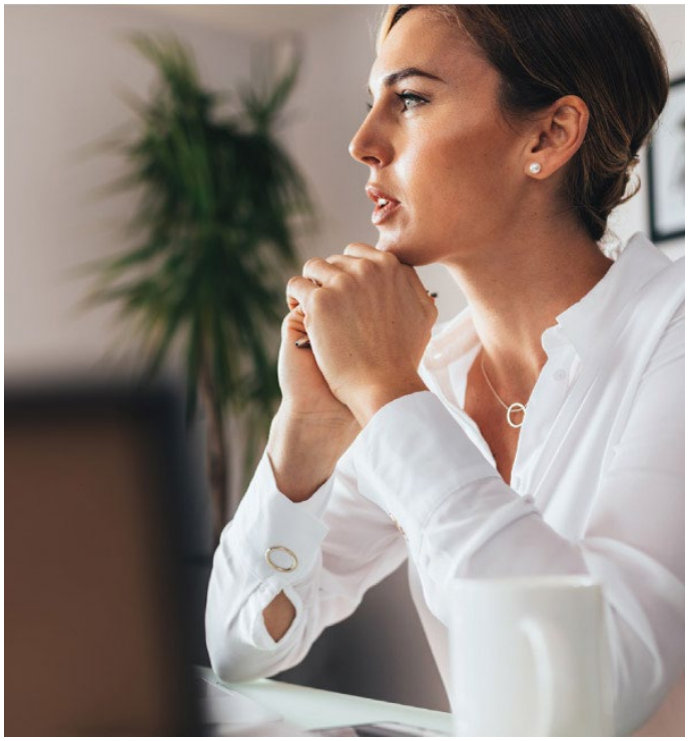
Given the previous data, it is not surprising that after a multi-year comprehensive review of the relevant literature, the European Food Safety Authority concluded that isoflavone supplements do not increase breast cancer risk when taken by postmenopausal women.[92] In 2012, the American Cancer Society[93] and the American Institute for Cancer Research (AICR)[94] concluded that soy foods can be safely consumed by breast cancer patients. In 2018, a combined report from the AIC and the World Cancer Research Fund concluded there is a possible link between consuming soy foods and improved survival from breast cancer.[95]

The American Cancer Society and the American Institute for Cancer Research concluded that soy foods can be safely consumed by breast cancer patients.

In many respects, the scientific perspective has transformed from concern regarding women with breast cancer consuming soy foods to recognition of the potential benefits. For a more a extensive discussion on heart health, see the Soy Connection *Soy & the Breast Cancer Patient* fact sheet.

SKIN HEALTH

Interest in the effects of soy on overall skin health is not surprising given that isoflavones bind to ERs, which are present in the skin,[96,97] and that estrogen therapy is thought to improve a number of skin parameters[98-101], including skin elasticity,[102] water-holding capacity,[103] pigmentation,[104] and vascularity.[105] Skin appendages, such as hair follicles, are also influenced by estrogens.[106]



Several trials suggest that isoflavones help to reduce wrinkles. For example, in one study, two groups of 20 healthy postmenopausal women aged 50 to 65 years were instructed to consume their usual diet with or without 20 g/d of an isoflavone-rich soy protein for three months.[107] There were statistically significant improvements in facial-skin wrinkling, discoloration and overall appearance in the supplement group. In another study involving 26 Japanese women in their late 30s and 40s, over a three- month period, use of supplements that provided 40 mg/d isoflavones led to a statistically significant decrease in fine wrinkles, whereas no change occurred in the placebo group.[108]

A 14-week trial conducted by Jenkins et al.[109] involving 159 postmenopausal women found that a beverage containing isoflavones statistically significantly reduced wrinkles by on average of 10 percent. There was also a positive correlation between baseline wrinkle depth and the response to the isoflavone-containing beverage; that is, the greater the wrinkle depth at baseline, the greater the improvement. In addition to the effect on wrinkles, there was also a statistically significant increase in collagen synthesis.

Finally, Japanese researchers recently examined the effect of soy milk consumption on subjective and objective measures of skin health in 60 women.[110] In this 8-week study, when compared to baseline, soy milk improved skin condition as subjectively assessed from scores of overall satisfaction, dryness, moisture, elasticity, coarseness, and pigmentation. In addition, skin biopsies showed significant improvement in the stratum corneum morphology.

ENDOMETRIAL TISSUE

Endometrial cancer, cancer of the corpus uteri, represents the most common gynecological malignancy in the industrialized world and is the seventh most common cancer among females. Although incidence and mortality rates vary markedly among geographical regions and countries.[80] The highest rates are in the U.S. and Europe, and the lowest in Asia and Africa.[111] There is concern that because of the presence of isoflavones, soy foods could increase the risk of developing endometrial cancer and stimulate the growth of existing endometrial tumors. Ever users of unopposed estrogen therapy are about two to three times more likely to develop endometrial cancer than never users.[112-114]

After reviewing 25 clinical studies that measured endometrial thickness and nine that measured histopathological changes, the European Food Safety Authority concluded that isoflavones do not adversely affect the endometrium.[115]

Interestingly, a recently published meta-analysis of the clinical data found that when all studies (N=23; 2,167 participants) were included in the analysis, there was no effect of isoflavones on endometrial thickness; however, there was a significant (P=0.04) decrease in thickness when considering only the seven North American trials, which involved 726 women.[116] In contrast, there was a small increase in thickness among women involved in the three Asian trials, but none of these studies actually intervened with soybean-derived isoflavones.

A recent meta-analysis of 10 observational studies, eight case-control and two prospective, found soy intake was inversely associated with endometrial cancer risk with an overall risk estimate (RE) of 0.81 (95% confidence interval: 0.72, 0.91).[117] Subgroup analyses found statistically significant protective effects for both Asian (RE: 0.79, 95% CI: 0.66, 0.95) and non-Asian (RE: 0.83, 95% CI: 0.71, 0.96) populations. Finally, Bitto et al.[118] found that in a group of premenopausal women with non-atypical endometrial hyperplasia, genistein (54 mg/d) improved symptoms after six months to approximately the same degree as norethisterone. Hence, the authors concluded that genistein might be useful for the management of endometrial hyperplasia without atypia in women who cannot be treated with progestin.[118]

FERTILITY

There are a number of issues involving soyfoods that have given rise to quite lively discussions in the peer-reviewed literature. One of these somewhat ironically, given the large populations of Asian countries that have historically consumed soy, is the impact of soy on fertility. n women, soy foods appear to increase the length of the menstrual cycle; although ovulation is not prevented, it is simply delayed by one day.[119] According to limited epidemiologic data, this minor effect on menstrual cycle length could help to decrease breast cancer risk.[120]

There is some evidence that isoflavones aid fertility. A prospective study found that among 315 women who collectively underwent 520 assisted reproductive technology cycles, soy isoflavone intake was positively related to live birth rates.[121] Similarly, among women undergoing in vitro fertilization, soy consumption appeared to negate the adverse reproductive effects of the endocrine disruptor bisphenol A (BPA).[122] Although the low isoflavone intake among the soy-consumers (mean intake, 3.4 mg/d) in this study raise doubt about the plausibility of these findings, they do agree with animal data.[123,124]

SUMMARY AND CONCLUSIONS

Soy foods are uniquely rich dietary sources of isoflavones, compounds classified as phytoestrogens but that differ from the hormone estrogen. Epidemiologic and clinical data suggest that soy foods can make important contributions to the health of women, particularly postmenopausal women. Soy foods potentially reduce CHD through multiple mechanisms. Clinical research indicates that isoflavones alleviate hot flashes, although the evidence that they reduce bone loss is mixed. Irrespective of the skeletal effects of isoflavones, soy foods can be part of a bone-healthy diet as they provide high-quality protein and many are good sources of well-absorbed calcium.

Adult soy intake does not appear to reduce breast cancer risk although evidence suggests that soy consumption during childhood and adolescence does. Claims that soy foods are contraindicated for breast cancer patients are unsupported by the clinical and epidemiologic evidence; the former shows neither soy nor isoflavones adversely affect markers of breast cancer risk, and the latter shows that post-diagnosis soy intake reduces breast cancer recurrence and mortality. Soy consumption may decrease the risk of developing endometrial cancer, and preliminary clinical research indicates that isoflavones may improve skin health. Finally, soy food consumption does not adversely affect reproduction in women.

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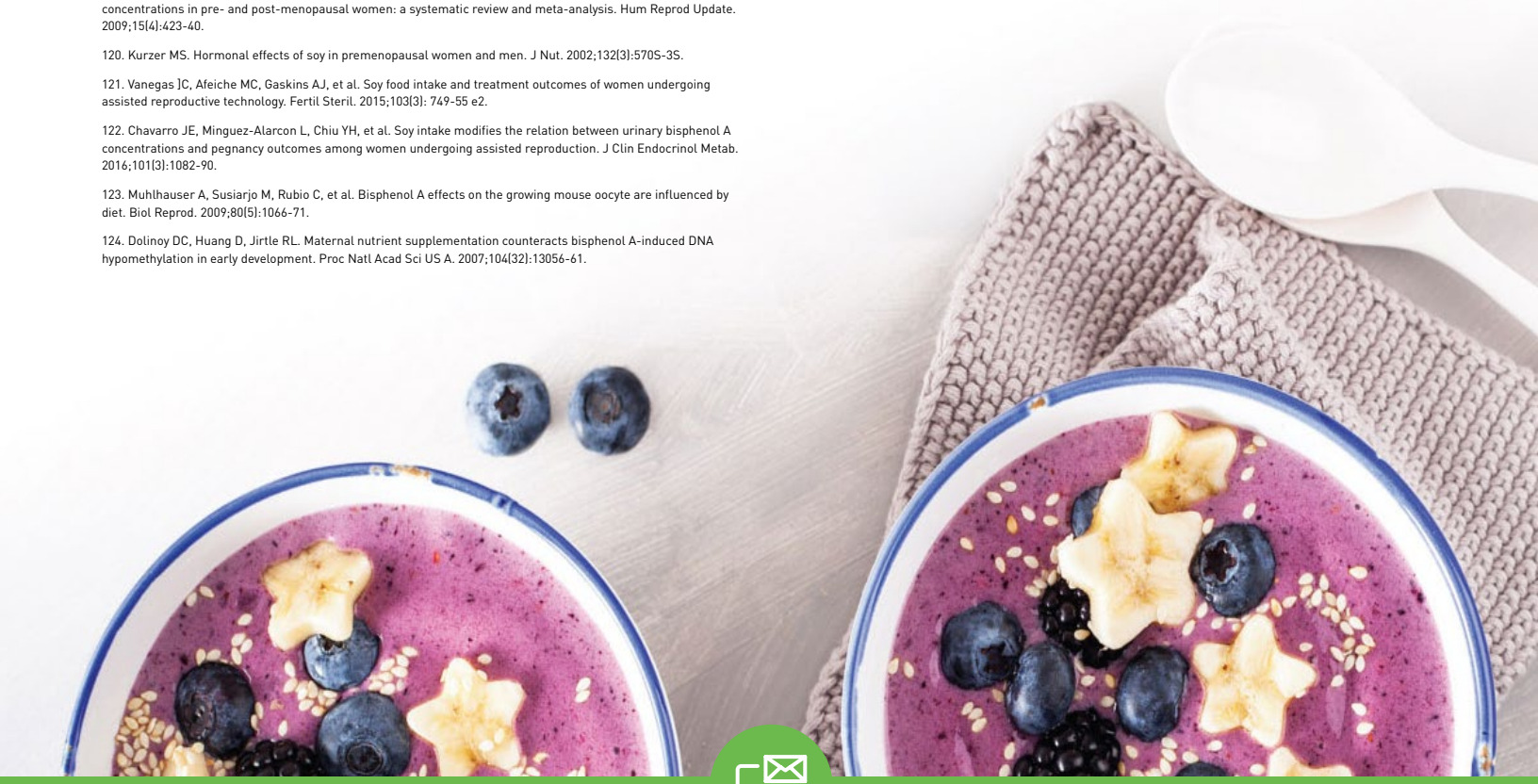

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