

# **Soy, From Poor Man's Meat to Functional Food**

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## **The rise of soyfoods**

The soybean, once considered “the poor man’s meat” because of perceived poor protein quality at that time, has had a spectacular rise in popularity as a food source in Western countries and over recent years soyfoods have been in the vanguard of the emerging “Functional Foods” market (1).

In the United States sales of soy products have increased in value from less than \$US 1b in 1992 to approximately \$US 2.29b in 1999 and \$US 2.77b in 2000 (2). US sales were projected to further increase to \$US 3.7b in 2002 (2). In the US, more than 300 new soy-based food and beverage products were launched in 1999 alone (3). In Australia the soymilk and soy-based drink market, which is a major segment, increased 60% in value from \$A 75.0m in 1996 to \$A 120.0m in 1999, before declining slightly in 2000 (4). In 1999 almost a quarter of adult male and female respondents to a survey in Australia reported consumption of a soyfood at least once weekly or more frequently (G Russell personal communication). Similar figures have been reported in the US (5).

## **Drivers of market growth**

The strong growth in the soyfood market in the West outlined above has had a number of drivers, and these are briefly discussed below.

### Technological innovations and “Westernisation” of soyfoods

Traditional soyfoods include soymilk, tofu, miso, natto and tempeh, the last three being fermented foods generally unattractive to Western tastes. Traditional soymilks made from whole beans have a strong “beany taste”, which is a positive attribute in some Asian countries, but generally negative in the West. Reduction of beany taste by, for example, the use of refined ingredients such as isolated soy protein, or by the use of proprietary taste masking or neutralising agents (3) has made soymilks much more acceptable to Western palates. New manufacturing processes and new soy ingredients have been developed to enable the manufacture of a broader range of products acceptable in the West, such as soy cheeses, soy yoghurts, soy breakfast cereals (3) and soy breads (in which Australia led the world (6)). New processes have also allowed the production of a large range of meat alternatives more acceptable to the consumer. New soybean varieties with specific nutritional characteristics (eg high oleic acid, low saturated fat, low stachyose, low lipoxigenase) and new applications have also been or are being developed (7).

## Incorporation of soyfoods into the product ranges of major food companies

The incorporation of soyfoods into the product ranges of large food companies has enabled major mass media marketing campaigns and increased consumer awareness as well as greater exposure in major supermarket chains. These product categories were mentioned above and include breakfast cereals, soy breads and dairy and meat substitutes. Linked to this has been the formation of a number of strategic alliances. For example, between Kraft Foods and Boca Burger which manufactures and markets soy-based meat alternatives in the US and between Dean Foods, a major US dairy company, and Silk a major soymilk manufacturer (3). In Australia, National Foods formed a joint venture with the Hong Kong company Vitasoy to manufacture soymilk in Australia (8). In the UK, Protein Technologies International, a major world soy protein company, has formed a joint venture with the Australian company Sanitarium aimed at building the European soymilk market (8). (9)

## Consumer awareness of possible soy-health links

Another driver for market growth has been public interest in possible health benefits associated with consumption of soyfoods. Consumer surveys conducted for the US United Soybean Board report that the fraction of consumers who perceived soy and soy products as being healthy increased from 59% in 1997 to 69% in 2001 (5). Acceptance of a soy-health link was boosted in 1999 by approval by the USFDA of a health claim relating soy protein consumption to reduced risk of heart disease (10), and in 2002 UK authorities approved a similar claim (11). In a similar vein, in 2000 the US Department of Agriculture, which had previously limited substitution of animal proteins by vegetable proteins (including soy) in the US Federal School Lunch Program to 30%, issued a ruling allowing their complete replacement and signalling recognition that soy protein was no longer considered a poor quality protein (12). To this extent, soy has moved from being considered merely a poor man's meat to be considered a true functional food. Whilst health claims are not yet permitted in Australia, soyfood manufacturers and ingredient suppliers have leveraged from the US claim to promote their products.

## Research of health benefits

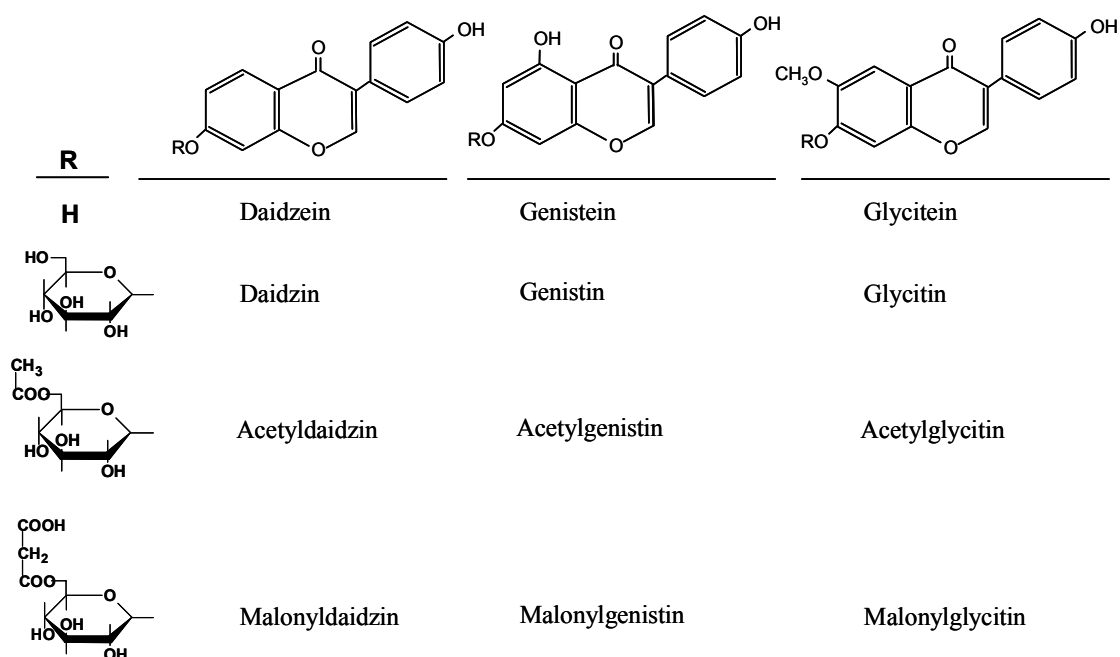
As indicated above, research into links between soy consumption and disease prevention has underpinned much of the promotion of soyfoods to the public. Scientific research was critical to the acceptance of the US and UK health claims. Over the last decade there has been an explosion of research into the role of soyfoods in human health. This research has focussed on a number of diseases and conditions (for reviews see (12-15), including cardiovascular disease; various cancers, most notably breast cancer and, more recently, prostate cancer, osteoporosis, and menopausal symptoms. The roles of a number of soy components that may contribute to possible health benefits have been studied and these include protein, saponins, phytosterols, fibre, phytate, protease inhibitors, oligosaccharides and isoflavones, but by far most studied in the last 1-2 decades have been the isoflavones. Some of the major areas of this soy and isoflavone research are summarised below.

## **Soy as a potent source of isoflavones and the nature of soy isoflavones**

In attempting to understand the effects of soyfoods and soy isoflavones on human health it is important to understand factors affecting the content and nature of isoflavones in soybeans and soyfoods, and this understanding has increased substantially in recent years.

## Soy isoflavones

Soybeans and soyfoods can contain up to twelve major isoflavone “species” belonging to three families – daidzein and its three glucoside conjugates, genistein and its three glucoside conjugates, and glycitein and its glucoside conjugates (16). The structures of these twelve species are shown in Figure 1. Glycitein and its glucosides are present in soybeans at much lower concentrations than the daidzein and genistein families (17), but they are present in very high concentrations in the hypocotyl (or “soy germ”) (18,19) commercial soy hypocotyl preparations are now used to boost the isoflavone content of foods (20).



**Figure 1.** Chemical structures of the twelve soy isoflavones

## Isoflavone content of soyfoods

Although most legumes contain isoflavones, soybeans are a uniquely rich dietary source, with levels some two orders of magnitude higher than those found in other commonly consumed legumes such as peas (*pisum sativum*) and other beans (21). Concentrations of isoflavones in soybeans depend upon the cultivar of soybean and the environmental conditions under which it is grown, but they are usually in the range 0.5-2 mg/g (16,21). Green soybeans (also called vegetable soybeans or edamame) consumed in some Asian countries (although not much in the West (22)) also contain significant levels of isoflavones but less than those of mature beans (23).

## Effect of processing on the content and nature of isoflavones

There is a huge range of soy products, both traditional and non-traditional, on the market today and these have been subjected to various manufacturing processes. These processes include fermentation (eg. miso, natto and tempeh), crushing and extraction with water (soymilk made from whole beans), precipitation (tofu) and extrusion (eg. textured vegetable protein). Heat is also often involved. A number of studies have examined the effects of these various manufacturing processes on the content and forms of isoflavones in processed soyfoods (23-27). In soybeans and non-fermented soy products, isoflavones are present

almost entirely in the glucosidic conjugate forms (16) (Fig 1). Fermentation converts a high proportion of these glucosides to the “aglycone” (ie. “without sugar”) forms, that is genistein, daidzein and glycitein, whilst non-fermented foods, such as soymilk and tofu, contain mainly the nine glucosides (16,16). Moist heat tends to convert the malonyl forms to acetyl- and simple glucoside forms, but, importantly, there is no major destruction of the core aglucone structures (16,23-30). Extrusion, which involves substantial pressures, shear forces and heat, may result in some losses, but again these do not appear to be major (28,29,29,30). Substantial proportions of isoflavones can be lost in processes involving aqueous solutions in which the aqueous phase is mostly discarded or lost, such as in the preparation of tofu (25-27). Losses can also potentially occur during the manufacture of soy protein concentrates and soy isolates (17,26) although proprietary processes have now been developed to largely overcome this (see for example (31)).

The typical content of isoflavones in some soyfoods on the Australian market are summarised in the table below. In addition, a number of databases of the isoflavone content of various soy foods have been published and an extensive one is available on the internet at <http://www.nal.usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html>. Not surprisingly, the content of isoflavones per unit weight and the content per serving of different soyfoods differ over a wide range.

<b>Soy food category</b>	<b>Isoflavone content (mg/100g)</b>	<b>Approx. mg isoflavones per serve</b>
Soybeans - dry	123-305	25-60
Soy flour	183-276	35-55
Textured vegetable protein	142-245	35-60
Soy grits	166	35
Soybeans - canned	80	40
Tofu	11-30	5-15
Soy & linseed bread	9-19	5-10
Soymilk	6-24	10-50
Soy sauce	0.2-1.2	Trace-0.1

An important point to note is that the values in the table are expressed as so-called ‘aglycone’ units (the term ‘aglycone’ means ‘without sugar’). In most soy foods the isoflavones are present joined, or ‘conjugated’, to a sugar molecule. This means that for every milligram of isoflavone in the form joined to a sugar only about one half of this is the ‘active ingredient’ – the aglycone. Foods labelled with isoflavone content may be expressed in either way.

### **Absorption and metabolism of isoflavones**

It is beyond the scope of this paper to summarise our present understanding of this topic in detail. It has however been reviewed extensively recently (32) and the reader is referred to that review and references therein for detailed information. Briefly however, the major points are, 1) absorption of isoflavones from the gastrointestinal tract occurs predominantly from the large bowel, although limited absorption also probably occurs from the distal small intestine, 2) essentially no absorption of the isoflavones as intact glucosides occurs; they must be first

hydrolysed to their aglycone forms by hydrolases in the intestinal wall or by enzymes of bacteria resident in the large bowel, 3) during passage through the intestinal wall, as well as in the liver and other organs, the isoflavones are largely conjugated to form glucuronides and sulphates, 4) isoflavones (mainly as glucuronides and sulphates) are excreted from the body mainly in urine, with only small amounts appearing in feces, 5) peak plasma concentrations of isoflavones appear approximately 6-9 hours after ingestion in humans, and essentially all are eliminated by 24-36 hours, 6) extensive bacterial metabolism of isoflavones occurs in the large bowel; equol and *O*-desmethylangolensin are major metabolites, but a large number of other bacterial metabolites have been identified and the contribution of these (especially equol) to the biological effects of isoflavones is a subject of considerable interest (33).

## **Health benefits of soy**

Interest in the possible health benefits associated with eating soy foods has focused in three main areas - cardiovascular disease, cancer, and postmenopausal symptoms and consequences, although other diseases and conditions have been examined. This paper provides a brief overview of these three areas; the reader is referred to the reviews referred to earlier (12-15) for a more comprehensive treatment of the topic.

### Cardiovascular disease

This is probably the area where there is strongest evidence for a health benefit. In October 1999 the Food and Drug Administration (FDA) in the USA accepted that there was sufficient evidence that soy foods reduce cholesterol for it to allow food manufacturers to label foods which meet certain guidelines with a health claim to indicate that they may assist in reducing cardiovascular disease (10). This was supported by an official statement from the American Heart Association in 2000 (34), and a similar health claim was approved in the UK in 2002 (11). The FDA concluded that “based on the totality of the publicly available scientific evidence, that there is significant scientific agreement that soy protein, included at a level of 25 g/day in a diet low in saturated fat and cholesterol, can help reduce total and LDL-cholesterol levels, and that such reductions may reduce the risk of CHD”.

A cornerstone of the case for approval of this health claim was a meta-analysis of approximately forty relevant human studies published in 1995 (35). This showed an ability of soy to significantly reduce LDL (“bad”) cholesterol in plasma, especially in individuals who had high initial levels. More recent well-controlled studies however have tended to show less reduction in LDL than those of the meta-analysis (see for example (36)). Interestingly, the FDA did not accept that the isoflavones in soy foods were directly involved in cholesterol reduction. Certainly, it appears clear that consumption of isoflavones alone does not reduce cholesterol (37-42). However, some have argued that whilst isoflavones alone are ineffective, there may be a synergistic effect of the soy protein or other components and the isoflavones (43,44). This is still an area of significant debate (45).

Distinct from effects on cholesterol, the effects of soy or isoflavones on a number of other processes or risk factors of relevance to cardiovascular disease have also been studied. For example, recent research, including some studies in Australia, has suggested that the isoflavones may assist in maintaining healthy arteries (37,46-49) although not all studies have been able to demonstrate an effect (40). The effect of soy or isoflavones on blood pressure, has also been examined in humans. Some have provided support (50-54) whilst others have been unable to demonstrate a significant reduction (37,40,55), or have shown a slight increase

under some circumstances (55). The reason for these differences is not clear, but does not seem to relate to differences in starting blood pressure.

Oxidised LDL is an important early initiator of formation of precursors of atherosclerotic plaques in the walls of blood vessels (56). Substances that inhibit the oxidation of LDL may therefore protect against plaque formation. Many studies have shown the ability of genistein to inhibit oxidation of LDL in the test tube (see for example (57-59)), but concentrations employed are often much higher than are likely to be reached in the body. In order to obtain more physiologically relevant results, a number of studies have tested the ability of consumption of soy or isoflavone extracts by humans to inhibit LDL oxidation *ex vivo*. The results from these studies have been mixed. Some studies have been unable to demonstrate any beneficial changes (37,41), whereas others have demonstrated small, but statistically significant effects (60-62). It is possible that the processes involved in isolating LDL from plasma in order to conduct the tests may lead in some cases to the loss of factors that may be operative in vivo. In order to overcome this difficulty, Hodgson and colleagues (55) measured urinary excretion of the isoprostane 8-Epi-PGF2 $\alpha$ , a recently identified biomarker of free radical-induced lipid oxidation, following the daily consumption for eight weeks of a clover isoflavone supplement that supplied 55 mg isoflavones per day. They were unable to show any significant effect of the supplement. On the other hand, Wiseman and colleagues (63) showed that plasma 8-Epi-PGF2 $\alpha$  levels in subjects who consumed a soy diet high in isoflavones were 20% lower than when they consumed a soy diet low in isoflavones ( $p < 0.05$ ), indicating protection of lipids (although not necessarily LDL lipids) from oxidation. Consistent with this study, the conjugated diene content of LDL isolated from individuals consuming a soy diet was significantly lower than when consuming a control diet (51,64). There are a number of possible reasons for the different results, but it may be significant that Hodgson et al used an isoflavone supplement, whereas the other studies used whole soy, suggesting the possible involvement of components other than the isoflavones. Clearly, further studies are required to clarify effects in humans.

## Cancer

Possible anticancer effects of soy and soy isoflavones were an initial strong focus for soy research and, probably, more papers have been published in this area than in any other. The major focus has been on breast cancer (see (65-71) for example), but other cancers have been studied (72-74) and there has been recent increased interest in prostate cancer (for reviews see (75-79) for example). Because of this extensive literature on soy and cancer it is not possible to review this entire area in a paper of this nature. Rather I will provide a brief overview of some of the key aspects of breast cancer research and the reader is referred to the literature noted for reviews of other cancers.

Studies of soy foods and breast cancer fall into four main categories. The first involve comparisons of the incidence of breast cancer in different countries that have differences in the consumption of soyfoods (eg. Japan compared to Australia), as well as comparisons between high and low soy consumers within countries. Some of these epidemiological studies suggest that soyfoods may be protective (80-89), but not all studies support a link (90-93). There is also evidence that exposure to isoflavones before puberty is important to endow a protective effect (81,87,94,95) and that protection may be more effective premenopausally than postmenopausally (see (82) for example). The second type of studies involve the use of animals in which cancers are induced by some means and the incidence of tumours in those that were fed soy is compared to animals that were fed a control non-soy diet. These studies generally suggest that soy and isoflavones are protective (see for example (65,71,96-99)),

although this is not always the case (100-102). The third type of studies involve the use of cancer cells grown in test tubes in which the effect of isoflavones on their growth is tested. These types of studies generally show a biphasic effect. At genistein concentrations above about 10 $\mu$ M inhibition of growth has been uniformly reported; however at lower concentrations, around 1 $\mu$ M, (which are closer to plasma concentrations found in soy consumers *in vivo*) slight stimulation of growth occurs under some conditions (68). The final type of studies involve administration of isoflavones or soy to women and the determination of the effect on biomarkers that may relate to cancer risk, and some of these have shown increased levels of risk markers in nipple aspirate (103,104) and biopsy samples (105). The cautionary results from some of these studies have led to concerns in some quarters, particularly regarding use of isoflavone supplements (as apposed to soyfoods), and particularly with regard to use by breast cancer sufferers (68,106-108). In summary, the outcomes of studies that have examined the link between soy or isoflavones and breast cancer risk are inconclusive, and any relationship can only be proved with long-term prospective studies in humans.

### Post-menopausal symptoms

The consequences of menopause include hot flushes, night sweats, vaginal dryness, mood swings and osteoporosis and they affect approximately 80-85% of postmenopausal women in Western countries and can be quite debilitating (109,110). Conventional estrogen replacement therapy (HRT) is very effective, leading to a reduction of about 70% in hot flushes (110). However, for a number of reasons, including concerns about cancer, many women are seeking alternative, or so-called “natural”, therapies to treat menopausal symptoms (111). Soy and isoflavones are one class of natural therapy (112) and there have been a number of studies to determine their efficacy, particularly with regard to hot flushes.

### Hot flushes

In a consensus statement published in 2000 (14) based on review of nine studies (two reported in abstract form) published at that time, the North American Menopause Society concluded that with regard to hot flushes the effect of soy and isoflavones was inconclusive. There have now been at least 15 studies published. These have varied significantly in a number of respects. Seven studies used soy foods (54,113-118), five used a soy isoflavone extract (119-123) and three used a clover isoflavone extract (124-126). Dosages of isoflavones ranged from 30 to 150 mg per day, and period of treatment from 4 to 12 weeks. Most studies have been double blind placebo controlled and two have been multi-centre studies (120,122). Uncertainty and controversy however remain (127,128) and it is clear that more research will be required to resolve this uncertainty.

### Osteoporosis

Osteoporosis is a serious and potentially debilitating consequence of the menopause in many women, particularly in the West (129). Whilst HRT is effective in preventing bone loss in early menopause, there may be side effects (130) and as with other menopausal symptoms women are therefore seeking other treatments for this condition.

A synthetic isoflavone, ipriflavone (which interestingly gives rise to the soy isoflavone daidzein as one of a number of intermediates upon metabolism) has been studied for at least thirty years (131). It has been marketed since the late 1980s in at least twenty countries for the clinical treatment of osteoporosis (131) with generally positive results (132). Doses are high,

in the range 500 - 1000 mg/d (132) and whilst these are not achievable for isoflavones from soy foods, they may be relevant if daidzein is a major active metabolite of ipriflavone.

Studies of the effects of soy and isoflavones have used *in vitro* methods, animal models and human studies (133). The animal studies have generally used ovariectomised rodents (134-142), or in some cases ovariectomised primates (143) and these have provided some supportive evidence, however isoflavone doses are often in the range 5-50 mg/Kg body weight per day, much higher than could be achieved in humans by normal dietary intake. The human studies have generally involved postmenopausal women and have been epidemiological (144-152), as well as clinical intervention (62,153-158) in design and have used bone mineral density and/or urinary or plasma markers of bone metabolism as end points. They have been conducted in both Western (62,144,151,153-156,158) and Asian countries (145-150,152,157). The results have been mixed – some have provided support (62,145,146,148,152,154-157) whilst others have not (144,147,149-151,153,158). The reasons for these differences are not clear, but is perhaps not altogether surprising when study times have ranged from a few weeks to several years; isoflavone and soy doses have varied, the sites for testing bone mineral density have varied, as have the biomarkers measured.

The North American Menopause Society concluded that at the time of their review there was insufficient evidence about effects of isoflavones on bone health to draw firm conclusions (14). That was also the conclusion of a recent extensive review commissioned by the UK Food Standards Authority (see <http://www.food.gov.uk/multimedia/pdfs/phytoestrogenreport.pdf>). As with breast cancer, most researchers agree that more research is needed.

## Conclusion

In this review I have attempted to provide an overview of the growth of soy's recent acceptance in the West and the drivers of this growth. In particular I have reviewed the major areas of research related to possible health benefits of soyfoods. In the last decade there has been substantial progress in our understanding of this area. There is however still a long way to go before the level of substantiation required for additional health claims will be achieved.

## References

1. Riaz,M.N. (1999) Soybeans as functional foods, *Cereal Foods World* 44, 88-92.
2. Liu,K.S. (2000) Expanding soybean food utilization, *Food Tech.* 54, 46.
3. Pszczola,D.E. (2000) Soy: Why it's moving into the mainstream, *Food Tech.* 54, 76-85.
4. Anonymous. International trends, *Retail World* (July 22 - August 2, 2002), p 18.
5. National report 2001-2002: Consumer attitudes about nutrition. 2002. United Soybean Board.
6. Jorgensen,K., Suter,D.A.I., Thompson,W.K., Dalais,F.S., Wahlqvist,M.L., and Rice,G.E. (1999) Burgen soy-lin: Development of an innovative functional staple food, *Functional Foods* 2, 22-24.
7. Designer soybeans. 2001. American Soybean Association and United Soybean Board.

8. Spence,K. (2000) National Food's new soy beverage plant, Food Aust. 52, 303.
9. Mellentin,J. and Heasman,M. (2001) The land of soy milk and money, Dairy Ind.Int. 66, 11.
10. Dotzel,M.M. (1999) Food labeling: Health claims; Soy protein and coronary heart disease; final rule, Federal Register 64, 57700-57733.
11. Gayer,J. (2002) New heart health claim for soy protein, Food Aust. 54, 490.
12. Messina,M., Gardner,C., and Barnes,S. (2002) Gaining insight into the health effects of soy but a long way still to go: Commentary on the Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, J.Nutr. 132, 547S-551S.
13. Gilani,G.S.; Anderson,J.J.B (eds). (2002) Phytoestrogens and health. AOCS Press.
14. Greenwood,S., Barnes,S., Clarkson,T.B., Eden,J., Helferich,W.G., Hughes,C., Messina,M., and Setchell,K.D.R. (2000) The role of isoflavones in menopausal health: Consensus opinion of the North American Menopause Society, Menopause 7, 215-229.
15. Setchell,K.D.R. and Cassidy,A. (1999) Dietary isoflavones: Biological effects and relevance to human health, J.Nutr. 129, 758S-767S.
16. King,R.A. and Bignell,C.M. (2000) Concentrations of isoflavone phytoestrgens and their glucosides in Australian soya beans and soya foods, Aust.J.Nutr.Diet. 57, 70-78.
17. Wang,H.-J. and Murphy,P.A. (1994) Isoflavone content in commercial soybean foods, J.Agric.Food Chem. 42, 1666-1673.
18. Eldridge,A.C. and Kwolek,W.F. (1983) Soybean isoflavones: effect of environment and variety on composition, J.Agric.Food Chem. 31, 394-396.
19. Kudou,S., Fleury,D., Welti,D., Magnolato,T., Uchida,K., Kitamura,K., and Okubo,K. (1991) Malonyl isoflavone glycosides in soybeans seeds (*Glycine max* Merrill), Agric.Biol.Chem. 55, 2227-2233.
20. Rigg,D. (1999) Soy isoflavone for new products, Food Aust. 51, 68.
21. Mazur,W. and Adlercreutz,H. (1998) Naturally occurring oestrogens in food, Pure And Applied Chemistry 70, 1759-1776.
22. Simonne,A.H., Weaver,D.B., and Wei,C.-I. (2001) Immature soybean seeds as a vegetable or snack food: acceptability by American consumers, Innovative Food Science and Emerging Technologies 1, 289-296.
23. Simonne,A.H., Smith,M., Weaver,D.B., Vail,T., Barnes,S., and Wei,C.I. (2000) Retention and changes of soy isoflavones and carotenoids in immature soybean seeds (Edamame) during processing, J.Agric.Food Chem. 48, 6061-6069.
24. Coward,L., Smith,M., Kirk,M., and Barnes,S. (1998) Chemical modification of isoflavones in soyfoods during cooking and processing, Am.J.Clin.Nutr. 68, 1486S-1491S.

25. Wang,H.-J. and Murphy,P.A. (1996) Mass balance study of isoflavones during soybean processing, *J.Agric.Food Chem.* 44, 2377-2383.
26. Wang,C., Ma,Q., Pagadala,S., Sherrard,M.S., and Krishnan,P.G. (1998) Changes of isoflavones during processing of soy protein isolates, *J.Am.Oil Chem.Soc.* 75, 337-341.
27. Grun,I.U., Adhikari,K., Li,C.Q., Li,Y., Lin,B., Zhang,J.L., and Fernando,L.N. (2001) Changes in the profile of genistein, daidzein, and their conjugates during thermal processing of tofu, *J.Agric.Food Chem.* 49, 2839-2843.
28. Singletary,K., Faller,J., Li,J.Y., and Mahungu,S. (2000) Effect of extrusion on isoflavone content and antiproliferative bioactivity of soy/corn mixtures, *J.Agric.Food Chem.* 48, 3566-3571.
29. Rinaldi,V.E.A., Ng,P.K.W., and Bennink,M.R. (2000) Effects of extrusion on dietary fiber and isoflavone contents of wheat extrudates enriched with wet okara, *Cereal Chemistry* 77, 237-240.
30. Mahungu,S.M., Diaz-Mercado,S., Li,J., Schwenk,M., Singletary,K., and Faller,J. (1999) Stability of isoflavones during extrusion processing of corn/soy mixture, *J.Agric.Food Chem.* 47, 279-284.
31. Crank, D. L. and Kerr, P. S. US5858449: Isoflavone-enriched soy protein product and method for its manufacture, US1997000913180. 12-1-1999.
32. King,R.A. (2002) Digestion, absorption and metabolism of isoflavones. In: *Phytoestrogens and health*, Editors: G.S.Gilani and J.J.B.Anderson. AOCS Press.
33. Setchell,K.D., Brown,N.M., and Lydeking-Olsen,E. (2002) The clinical importance of the metabolite equol-a clue to the effectiveness of soy and its isoflavones, *J.Nutr.* 132, 3577-3584.
34. Erdman,J.W. (2000) Soy protein and cardiovascular disease - A statement for healthcare professionals from the Nutrition Committee of the AHA, *Circulation* 102, 2555-2559.
35. Anderson,J.W., Johnstone,B.M., and Cook-Newell,M.E. (1995) Meta-analysis of the effects of soy protein intake on serum lipids, *N.Engl.J.Med.* 333, 276-282.
36. Nestel,P. (2002) Role of soy protein in cholesterol-lowering - How good is it?, *Atheroscler.Thromb.Vasc.Biol.* 22, 1743-1744.
37. Nestel,P.J., Yamashita,T., Sasahara,T., Pomeroy,S., Dart,A., Komesaroff,P., Owen,A., and Abbey,M. (1997) Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women, *Atheroscler.Thromb.Vasc.Biol.* 17, 3392-3398.
38. Greaves,K.A., Parks,J.S., Williams,J.K., and Wagner,J.D. (1999) Intact dietary soy protein, but not adding an isoflavone-rich soy extract to casein, improves plasma lipids in ovariectomized cynomolgus monkeys, *J.Nutr.* 129, 1585-1592.

39. Hodgson, J.M., Puddey, I.B., Beilin, L.J., Mori, T.A., and Croft, K.D. (1998) Supplementation with isoflavonoid phytoestrogens does not alter serum lipid concentrations - a randomized controlled trial in humans, *J.Nutr.* 128, 728-732.
40. Simons, L.A., von Konigsmark, M., Simons, J., and Celermajer, D.S. (2000) Phytoestrogens do not influence lipoprotein levels or endothelial function in healthy postmenopausal women, *Am.J.Cardiol.* 85, 1297-1301.
41. Samman, S., Wall, P.M.L., Chan, G.S.M., Smith, S.J., and Petocz, P. (1999) The effect of supplementation with isoflavones on plasma lipids and oxidisability of low density lipoprotein in premenopausal women, *Atherosclerosis* 147, 277-283.
42. Howes, J.B., Sullivan, D., Lai, N., Nestel, P., Pomeroy, S., West, L., Eden, J.A., and Howes, L.G. (2000) The effects of dietary supplementation with isoflavones from red clover on the lipoprotein profiles of post menopausal women with mild to moderate hypercholesterolaemia, *Atherosclerosis* 152, 143-147.
43. Crouse, J.R., Morgan, T., Terry, J.G., Ellis, J., Vitolins, M., and Burke, G.L. (1999) A randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins, *Arch.Intern.Med.* 159, 2070-2076.
44. Clarkson, T.B. (2002) Soy, soy phytoestrogens and cardiovascular disease, *J.Nutr.* 132, 566S-569S.
45. Sirtori, C.R., Lovati, M.R., Manzoni, C., Gianazza, E., Bondioli, A., Staels, B., and Auwerx, J. (1998) Reduction of serum cholesterol by soy proteins: clinical experience and potential molecular mechanisms, *Nutr.Metab.Cardiovasc.Dis.* 8, 334-340.
46. Honore, E.K., Williams, J.K., Anthony, M.S., and Clarkson, T.B. (1997) Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques, *Fert.Steril.* 67, 148-154.
47. van der Schouw, Y.T., Pijpe, A., Lebrun, C.E.I., Bots, M.L., Peeters, P.H.M., van Staveren, W.A., Lamberts, S.W.J., and Grobbee, D.E. (2002) Higher usual dietary intake of phytoestrogens is associated with lower aortic stiffness in postmenopausal women, *Atheroscler.Thromb.Vasc.Biol.* 22, 1316-1322.
48. Yildirim, A., Tokgozoglu, S.L., Oduncu, T., Oto, A., Haznedaroglu, I., Akinci, D., Koksali, G., Sade, E., Kirazli, S., and Kes, S. (2001) Soy protein diet significantly improves endothelial function and lipid parameters, *ClinCardiol.* 24, 711-716.
49. Walker, H.A., Dean, T.S., Sanders, T.A.B., Jackson, G., Ritter, J.M., and Chowienzyk, P.J. (2001) The phytoestrogen genistein produces acute nitric oxide-dependent dilation of human forearm vasculature with similar potency to 17 beta-estradiol, *Circulation* 103, 258-262.
50. Burke, V., Hodgson, J.M., Beilin, L.J., Giangiulio, N., Rogers, P., and Puddey, I.B. (2001) Dietary protein and soluble fiber reduce ambulatory blood pressure in treated hypertensives, *Hypertension* 38, 821-826.
51. Jenkins, D.J.A., Kendall, C.W.C., Jackson, C.J.C., Connelly, P.W., Parker, T., Faulkner, D., Vidgen, E., Cunnane, S.C., Leiter, L.A., and Josse, R.G. (2002) Effects of

- high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women, *Am.J.Clin.Nutr.* 76, 365-372.
52. Rivas,M., Garay,R.P., Escanero,J.F., Cia,P., Cia,P., and Alda,J.O. (2002) Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension, *J.Nutr.* 132, 1900-1902.
  53. Teede,H.J., Dalais,F.S., Kotsopoulos,D., Liang,Y.L., Davis,S., and Mcgrath,B.P. (2001) Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women, *J.Clin.Endocrinol.Metab.* 86, 3053-3060.
  54. Washburn,S., Burke,G.L., Morgan,T., and Anthony,M. (1999) Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women, *Menopause* 6, 7-13.
  55. Hodgson,J.M., Puddey,I.B., Croft,K.D., Mori,T.A., Rivera,J., and Beilin,L.J. (1999) Isoflavonoids do not inhibit in vivo lipid peroxidation in subjects with high-normal blood pressure, *Atherosclerosis* 145, 167-172.
  56. Griffin,B.A. (1999) Lipoprotein atherogenicity: an overview of current mechanisms, *Proc.Nutr.Soc.* 58, 163-169.
  57. Kerry,N. and Abbey,M. (1998) The isoflavone genistein inhibits copper and peroxy radical mediated low density lipoprotein oxidation in vitro, *Atherosclerosis* 140, 341-347.
  58. Hodgson,J.M., Croft,K.D., Puddey,I.B., Mori,T.A., and Beilin,L.J. (1996) Soybean isoflavonoids and their metabolic products inhibit in vitro lipoprotein oxidation in serum, *J.Nutr.Biochem.* 7, 664-669.
  59. Kapiotis,S., Hermann,M., Held,I., Seelos,C., Ehringer,H., and Gmeiner,B.M.K. (1997) Genistein, the dietary-derived angiogenesis inhibitor, prevents LDL oxidation and protects endothelial cells from damage by atherogenic LDL, *Atheroscler.Thromb.Vasc.Biol.* 17, 2868-2874.
  60. Tikkanen,M.J., Wahala,K., Ojala,S., Vihma,V., and Adlercreutz,H. (1998) Effect of soybean phytoestrogen intake on low density lipoprotein oxidation resistance, *Proc.Natl.Acad.Sci.U.S.A.* 95, 3106-3110.
  61. Ashton,E.L., Dalais,F.S., and Ball,M.J. (2000) Effect of meat replacement by tofu on CHD risk factors including copper induced LDL oxidation, *J.Am.Coll.Nutr.* 19, 761-767.
  62. Scheiber,M.D., Liu,J.H., Subbiah,M.T.R., Rebar,R.W., and Setchell,K.D.R. (2001) Dietary inclusion of whole soy foods results in significant reductions in clinical risk factors for osteoporosis and cardiovascular disease in normal postmenopausal women, *Menopause* 8, 384-392.
  63. Wiseman,H., O'Reilly,J.D., Adlercreutz,H., Mallet,A.I., Bowey,E.A., Rowland,I.R., and Sanders,T.A.B. (2000) Isoflavone phytoestrogens consumed in soy decrease F-2-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans, *Am.J.Clin.Nutr.* 72, 395-400.

64. Jenkins,D.J.A., Kendall,C.W.C., Garsetti,M., Rosenberg-Zand,R.S., Jackson,C.J., Agarwal,S., Rao,A.V., Diamandis,E.P., Parker,T., Faulkner,D., Vuksan,V., and Vidgen,E. (2000) Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity - A controlled crossover trial, *Metabolism* 49, 537-543.
65. Barnes,S., Grubbs,C., Setchell,K.D., and Carlson,J. (1990) Soybeans inhibit mammary tumors in models of breast cancer, *Prog.Clin.Biol.Res.* 347, 239-253.
66. Adlercreutz,H., Mazur,W., Heinonen,S.M., and Stumpf,K. (2002) Phytoestrogens and breast cancer. In: *Breast cancer: Prognosis, treatment, and prevention*, pp. 527-554. Editor: J.R.Pasqualini. Marcel Dekker.
67. Hilakivi-Clarke,L., Cho,E., daAssis,S., Olivo,S., Ealley,E., Bouker,K.B., Welch,J.N., Khan,G., Clarke,R., and Cabanes,A. (2001) Maternal and prepubertal diet, mammary development and breast cancer risk, *J.Nutr.* 131, 154S-157S.
68. Messina,M.J. and Loprinzi,C.L. (2001) Soy for breast cancer survivors: A critical review of the literature, *J.Nutr.* 131, 3095S-3108S.
69. Messina,M., Barnes,S., and Setchell,K.D. (1997) Phyto-oestrogens and breast cancer, *Lancet* 350, 971-972.
70. Barnes,S. (1998) Phytoestrogens and breast cancer, *Baillieres Clin.Endocrinol.Metab.* 12, 559-579.
71. Barnes,S. (2001) Soy, Isoflavones and cancer, *Soy and Health* 2000 49-53.
72. Seow,A., Poh,W.T., Teh,M., Eng,P., Wang,Y.T., Tan,W.C., Chia,K.S., Yu,M.C., and Lee,H.P. (2002) Diet, reproductive factors and lung cancer risk among Chinese women in Singapore: Evidence for a protective effect of soy in nonsmokers, *Int.J.Cancer* 97, 365-371.
73. Li,D.H., Yee,J.A., McGuire,M.H., Murphy,P.A., and Yan,L. (1999) Soybean isoflavones reduce experimental metastasis in mice, *J.Nutr.* 129, 1075-1078.
74. Messina,M. and Bennink,M. (1998) Soyfoods, isoflavones and risk of colonic cancer: a review of the in vitro and in vivo data, *Baillieres Clin.Endocrinol.Metab.* 12, 707-728.
75. Adlercreutz,H., Bartels,P., Elomaa,V.V., and Kang,C. (2001) Phytoestrogens and prostate cancer, *Soy and Health* 2000 61-71.
76. Castle,E.P. and Thrasher,J.B. (2002) The role of soy phytoestrogens in prostate cancer, *Urologic Clinics of North America* 29, 71-81.
77. Griffiths,K., Denis,L., Turkes,A., and Morton,M.S. (1998) Phytoestrogens and diseases of the prostate gland, *Baillieres Clin.Endocrinol.Metab.* 12, 625-647.
78. Rosenthal,M.A., Taneja,S., and Bosland,M.C. (1998) Phytoestrogens and prostate cancer: possible preventive role, *Med.J.Aust.* 168, 467.
79. Barnes,S. (2001) Role of phytochemicals in prevention and treatment of prostate cancer, *Epidemiologic Reviews* 23, 102-105.

80. Wu,A.H., Ziegler,R.G., Nomura,A.M.Y., West,D.W., Kolonel,L.N., Horn-Ross,P.L., Hoover,R.N., and Pike,M.C. (1998) Soy intake and risk of breast cancer in Asians and Asian Americans, *Am.J.Clin.Nutr.* 68, 1437S-1443S.
81. Shu,X.O., Jin,F., Dai,Q., Wen,W.Q., Potter,J.D., Kushi,L.H., Ruan,Z.X., Gao,Y.T., and Zheng,W. (2001) Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women, *Cancer Epidemiol.Biomarkers Prev.* 10, 483-488.
82. Lee,H.P., Gourley,L., Duffy,S.W., Esteve,J., Lee,J., and Day,N.E. (1991) Dietary effects on breast-cancer risk in Singapore, *Lancet* 337, 1197-1200.
83. Witte,J.S., Ursin,G., Siemiatycki,J., Thompson,W.D., Paganini-Hill,A., and Haile,R.W. (1997) Diet and premenopausal bilateral breast cancer - a case-control study, *Breast Cancer Res.Treat.* 42, 243-251.
84. Zheng,W., Dai,Q., Custer,L.J., Shu,X.-O., Wen,W.-Q., Jin,F., and Franke,A.A. (1999) Urinary excretion of isoflavonoids and the risk of breast cancer, *Cancer Epidemiol.Biomarkers Prev.* 8, 35-40.
85. Dai,Q., Shu,X.O., Jin,F., Potter,J.D., Kushi,L.H., Teas,J., Gao,Y.T., and Zheng,W. (2001) Population-based case-control study of soyfood intake and breast cancer risk in Shanghai, *Br.J.Cancer* 85, 372-378.
86. Jakes,R.W., Duffy,S.W., Ng,F.C., Gao,F., Ng,E.H., Seow,A., Lee,H.P., and Yu,M.C. (2002) Mammographic parenchymal patterns and self-reported soy intake in Singapore Chinese women, *Cancer Epidemiol.Biomarkers Prev.* 11, 608-613.
87. Wu,A.H., Wan,P., Hankin,J., Tseng,C.C., Yu,M.C., and Pike,M.C. (2002) Adolescent and adult soy intake and risk of breast cancer in Asian-Americans, *Carcinogenesis* 23, 1491-1496.
88. Dai,Q., Franke,A.A., Jin,F., Shu,X.O., Hebert,J.R., Custer,L.J., Cheng,J.R., Gan,Y.T., and Zheng,W. (2002) Urinary excretion of phytoestrogens and risk of breast cancer among Chinese women in Shanghai, *Cancer Epidemiol.Biomarkers Prev.* 11, 815-821.
89. Ingram,D., Sanders,K., Kolybaba,M., and Lopez,D. (1997) Case-control study of phyto-oestrogens and breast cancer, *Lancet* 350, 990-994.
90. Key,T.J., Sharp,G.B., Appleby,P.N., Beral,V., Goodman,M.T., Soda,M., and Mabuchi,K. (1999) Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan, *Br.J.Cancer* 81, 1248-1256.
91. den Tonkelaar,I., Keinan-Boker,L., Van't Veer,P., Arts,C.J.M., Adlercreutz,H., Thijssen,J.H.H., and Peeters,P.H.M. (2001) Urinary phytoestrogens and postmenopausal breast cancer risk, *Cancer Epidemiol.Biomarkers Prev.* 10, 223-228.
92. Horn-Ross,P.L., John,E.M., Lee,M., Stewart,S.L., Koo,J., Sakoda,L.C., Shiau,A.G., Goldstein,J., Davis,P., and Perez-Stable,E.J. (2001) Phytoestrogen consumption and breast cancer risk in a multiethnic population - The Bay Area Breast Cancer Study, *Am.J.Epidemiol.* 154, 434-441.
93. Yuan,J.M., Wang,Q.S., Ross,R.K., Henderson,B.E., and Yu,M.C. (1995) Diet and breast cancer in Shanghai and Tianjin, China, *Br.J.Cancer* 71, 1353-1358.

94. Lamartiniere,C.A., Murrill,W.B., Manzollilo,P.A., Zhang,J.X., Barnes,S., Zhang,X.S., Wei,H.C., and Brown,N.M. (1998) Genistein alters the ontogeny of mammary gland development and protects against chemically-induced mammary cancer in rats, *Proc.Soc.Exp.Biol.Med.* 217, 358-364.
95. Murrill,W.B., Brown,N.M., Zhang,J.X., Manzollilo,P.A., Barnes,S., and Lamartiniere,C.A. (1996) Prepubertal genistein exposure suppresses mammary cancer and enhances gland differentiation in rats, *Carcinogenesis* 17, 1451-1457.
96. Lamartiniere,C.A., Moore,J.B., Brown,N.M., Thompson,R., Hardin,M.J., and Barnes,S. (1995) Genistein suppresses mammary cancer in rats, *Carcinogenesis* 16, 2833-2840.
97. Constantinou,A.I., Mehta,R.G., and Vaughan,A. (1996) Inhibition of N-methyl-N-nitrosourea-induced mammary tumors in rats by the soybean isoflavones, *Anticancer.Res.* 16, 3293-3298.
98. Gallo,D., Giacomelli,S., Cantelmo,F., Zannoni,G.F., Ferrandina,G., Fruscella,E., Riva,A., Morazzoni,P., Bombardelli,E., Mancuso,S., and Scambia,G. (2001) Chemoprevention of DMBA-induced mammary cancer in rats by dietary soy, *Breast Cancer Res.Treat.* 69, 153-164.
99. Constantinou,A.I., Lantvit,D., Hawthorne,M., Xu,X.Y., vanBreemen,R.B., and Pezzuto,J.M. (2001) Chemopreventive effects of soy protein and purified soy isoflavones on DMBA-induced mammary tumors in female Sprague-Dawley rats, *Nutr.Cancer* 41, 75-81.
100. Ju,Y.H., Doerge,D.R., Allred,K.F., Allred,C.D., and Helferich,W.G. (2002) Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice, *Cancer Res.* 62, 2474-2477.
101. Allred,C.D., Ju,Y.H., Allred,K.F., Chang,J., and Helferich,W.G. (2001) Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein, *Carcinogenesis* 22, 1667-1673.
102. Cohen,L.A., Zhao,Z., Pittman,B., and Scimeca,J.A. (2000) Effect of intact and isoflavone-depleted soy protein on NMU-induced rat mammary tumorigenesis, *Carcinogenesis* 21, 929-935.
103. Hargreaves,D.F., Potten,C.S., Harding,C., Shaw,L.E., Morton,M.S., Roberts,S.A., Howell,A., and Bundred,N.J. (1999) Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast, *J.Clin.Endocrinol.Metab.* 84, 4017-4024.
104. Petrakis,N.L., Barnes,S., King,E.B., Lowenstein,J., Wiencke,J., Lee,M.M., Miike,R., Kirk,M., and Coward,L. (1996) Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women, *Cancer Epidemiol.Biomarkers Prev.* 5, 785-794.
105. McMichael-Phillips,D.F., Harding,C., Morton,M., Roberts,S.A., Howell,A., Potten,C.S., and Bundred,N.J. (1998) Effects of soy-protein supplementation on

- epithelial proliferation in the histologically normal human breast, *Am.J.Clin.Nutr.* 68, 1431S-1436S.
106. Bouker, K.B. and Hilakivi-Clarke, L. (2000) Genistein: Does it prevent or promote breast cancer?, *Environ.Health Perspect.* 108, 701-708.
  107. This, P., DelaRocheFordiere, A., Clough, K., Fourquet, A., and Magdelenat, H. (2001) Phytoestrogens after breast cancer, *Endocrine-Related Cancer* 8, 129-134.
  108. de Lemos, M. (2002) Safety issues of soy phytoestrogens in breast cancer patients, *Journal of Clinical Oncology* 20, 3040-3041.
  109. Eden, J.A. (2001) Managing the menopause: phyto-oestrogens or hormone replacement therapy?, *Annals Of Medicine* 33, 4-6.
  110. Elkind-Hirsch, K. (2001) Effect of dietary phytoestrogens on hot flashes: can soy-based proteins substitute for traditional estrogen replacement therapy?, *Menopause* 8, 154-156.
  111. Newton, K.M., Buist, D.S.M., Keenan, N.L., Anderson, L.A., and LaCroix, A.Z. (2002) Use of alternative therapies for menopause symptoms: Results of a population-based survey, *Obstet.Gynecol.* 100, 18-25.
  112. Warren, M.P., Shortle, B., and Dominguez, J.E. (2002) Use of alternative therapies in menopause, *Best Prac.Res.Clin.Obstet.Gynaecol.* 16, 411-448.
  113. Murkies, A.L., Lombard, C., Strauss, B.J.G., Wilcox, G., Burger, H.G., and Morton, M.S. (1995) Dietary flour supplementation decreases post-menopausal hot flashes - effect of soy and wheat, *Maturitas* 21, 189-195.
  114. Dalais, F.S., Rice, G.E., Wahlqvist, M.L., Grehan, M., Murkies, A.L., Medley, G., Ayton, R., and Strauss, B.J. (1998) Effects of dietary phytoestrogens in postmenopausal women, *Climacteric* 1, 124-129.
  115. Brzezinski, A., Adlercreutz, H., Shaoul, R., Rosler, A., Shmueli, A., Tanos, V., and Schenker, J.G. (1997) Short-term effects of phytoestrogen-rich diet on postmenopausal women, *Menopause* 4, 89-94.
  116. Albertazzi, P., Pansini, F., Bonaccorsi, G., Zanotti, L., Forini, E., and DeAloysio, D. (1998) The effect of dietary soy supplementation on hot flashes, *Obstet.Gynecol.* 91, 6-11.
  117. Kotsopoulos, D., Dalais, F.S., Liang, Y.L., Mcgrath, B.P., and Teede, H.J. (2000) The effects of soy protein containing phytoestrogens on menopausal symptoms in postmenopausal women, *Climacteric* 3, 161-167.
  118. St.Germain, A., Peterson, C.T., Robinson, J.G., and Alekel, L. (2001) Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment, *Menopause* 8, 17-26.
  119. Scambia, G., Mango, D., Signorile, P.G., Angeli, R.A., Palena, C., Gallo, D., Bombardelli, E., Morazzoni, P., Riva, A., and Mancuso, S. (2000) Clinical effects of a standardized soy extract in postmenopausal women: A pilot study, *Menopause* 7, 105-111.

120. Upmalis,D.H., Lobo,R., Bradley,L., Warren,M., Cone,F.L., and Lamia,C.A. (2000) Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: A multicenter, double-blind, randomized, placebo-controlled study, *Menopause* 7, 236-242.
121. Quella,S.K., Loprinzi,C.L., Barton,D.L., Knost,J.A., Sloan,J.A., LaVasseur,B.I., Swan,D., Krupp,K.R., Miller,K.D., and Novotny,P.J. (2000) Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial, *J.Clin.Oncol.* 18, 1068-1074.
122. Faure,E.D., Chantre,P., and Mares,P. (2002) Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study, *Menopause* 9, 329-334.
123. Han,K.K., Soares,J.M., Haidar,M.A., de Lima,G.R., and Baracat,E.C. (2002) Benefits of soy isoflavone therapeutic regimen on menopausal symptoms, *Obstet.Gynecol.* 99, 389-394.
124. Baber,R.J., Templeman,C., Morton,T., Kelly,G.E., and West,L. (1999) Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women, *Climacteric* 2, 85-92.
125. van de Weijer,P.H.M. and Barentsen,R. (2002) Isoflavones from red clover (Promensil<sup>(R)</sup>) significantly reduce menopausal hot flush symptoms compared with placebo, *Maturitas* 42, 187-193.
126. Knight,D.C., Howes,J.B., and Eden,J.A. (1999) The effect of Promensil<sup>TM</sup>, an isoflavone extract, on menopausal symptoms, *Climacteric* 2, 79-84.
127. Husband,A.J. (2002) Phytoestrogens and menopause - Published evidence supports a role for phytoestrogens in menopause, *Br.Med.J.* 324, 52.
128. Davis,S.R. (2001) Phytoestrogen therapy for menopausal symptoms? There's no good evidence that it's any better than placebo, *Br.Med.J.* 323, 354-355.
129. Cooper,C., Champion,G., and Melton,L.J., III (1992) Hip fractures in the elderly: a world-wide projection, *Osteoporos.Int.* 2, 285-289.
130. Morabito,N., Crisafulli,A., Vergara,C., Gaudio,A., Lasco,A., Frisina,N., Danna,R., Corrado,F., Pizzoleo,M.A., Cincotta,M., Altavilla,D., Ientile,R., and Squadrito,F. (2002) Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: A randomized double-blind placebo-controlled study, *J.Bone Min.Res.* 17, 1904-1912.
131. Gennari,C. (1997) Ipriflavone: Background, *Calcif.Tissue Int.* 61, S3-S4.
132. Maugeri,D., Panebianco,P., Russo,M.S., Motta,M., Tropea,S., Motta,L., Garozzo,C., Lomeo,E., Barbagallo Sangiorgi,G., Scuderi,G., Carozzo,M., Cantatore,F.P., Perpignano,G., Ferraraccio,A., and Ennas,F. (1994) Ipriflavone-treatment of senile osteoporosis: Results of a multicenter, double-blind clinical trial of 2 years, *Arch.Gerontol.Geriatr.* 19, 253-263.
133. Anderson,J.J.B. and Garner,S.C. (1998) Phytoestrogens and bone, *Baillieres Clin.Endocrinol.Metab.* 12, 543-557.

134. Arjmandi,B.H., Birnbaum,R., Goyal,N.V., Getlinger,M.J., Juma,S., Alekel,L., Hasler,C.M., Drum,M.L., Hollis,B.W., and Kukreja,S.C. (1998) Bone-sparing effect of soy protein in ovarian hormone-deficient rats is related to its isoflavone content, *Am.J.Clin.Nutr.* 68, 1364S-1368S.
135. Ishida,H., Uesugi,T., Hirai,K., Toda,T., Nukaya,H., Yokotsuka,K., and Tsuji,K. (1998) Preventive effects of the plant isoflavones, daidzin and genistin, on bone loss in ovariectomized rats fed a calcium- deficient diet, *Biol.Pharm.Bull.* 21, 62-66.
136. Picherit,C., Coxam,V., Bennetau-Pelissero,C., Kati-Coulibaly,S., Davicco,M.J., Lebecque,P., and Barlet,J.P. (2000) Daidzein is more efficient than genistein in preventing ovariectomy-induced bone loss in rats, *J.Nutr.* 130, 1675-1681.
137. Picherit,C., Bennetau-Pelissero,C., Chanteranne,B., Lebecque,P., Davicco,M.J., Barlet,J.P., and Coxam,V. (2001) Soybean isoflavones dose-dependently reduce bone turnover but do not reverse established osteopenia in adult ovariectomized rats, *J.Nutr.* 131, 723-728.
138. Notoya,K., Yoshida,K., Tsukuda,R., Taketomi,S., and Tsuda,M. (1996) Increase in femoral bone mass by ipriflavone alone and in combination with 1- $\alpha$ -hydroxyvitamin D-3 in growing rats with skeletal unloading, *Calcif.Tissue Int.* 58, 88-94.
139. Ohta,A., Uehara,M., Sakai,K., Takasaki,M., Adlercreutz,H., Morohashi,T., and Ishimi,Y. (2002) A combination of dietary fructooligosaccharides and isoflavone conjugates increases femoral bone mineral density and equol production in ovariectomized mice, *J.Nutr.* 132, 2048-2054.
140. Wu,J., Wang,X.X., Takasaki,M., Ohta,A., Higuchi,M., and Ishimi,Y. (2001) Cooperative effects of exercise training and genistein administration on bone mass in ovariectomized mice, *J.Bone Min.Res.* 16, 1829-1836.
141. Picherit,C., Chanteranne,B., Bennetau-Pelissero,C., Davicco,M.J., Lebecque,P., Barlet,J.P., and Coxam,V. (2001) Dose-dependent bone-sparing effects of dietary isoflavones in the ovariectomised rat, *Br.J.Nutr.* 85, 307-316.
142. Uesugi,T., Toda,T., Tsuji,K., and Ishida,H. (2001) Comparative study on reduction of bone loss and lipid metabolism abnormality in ovariectomized rats by soy isoflavones, daidzin, genistin, and glycitin, *Biol.Pharm.Bull.* 24, 368-372.
143. Lees,C.J. and Ginn,T.A. (1998) Soy protein isolate diet does not prevent increased cortical bone turnover in ovariectomized macaques, *Calcif.Tissue Int.* 62, 557-558.
144. Kardinaal,A.F.M., Morton,M.S., Bruggemann-Rotgans,I.E.M., and van Beresteijn,E.C.H. (1998) Phyto-oestrogen excretion and rate of bone loss in postmenopausal women, *Eur.J.Clin.Nutr.* 52, 850-855.
145. Horiuchi,T., Onouchi,T., Takahashi,M., Ito,H., and Orimo,H. (2000) Effect of soy protein on bone metabolism in postmenopausal Japanese women, *Osteoporos.Int.* 11, 721-724.
146. Ho,S.C., Chan,S.G., Yi,Q.L., Wong,E., and Leung,P.C. (2001) Soy intake and the maintenance of peak bone mass in Hong Kong Chinese women, *J.Bone Min.Res.* 16, 1363-1369.

147. Hsu,C.S., Shen,W.W., Hsueh,Y.M., and Yeh,S.L. (2001) Soy isoflavone supplementation in postmenopausal women - Effects on plasma lipids, antioxidant enzyme activities and bone density, *Journal of Reproductive Medicine* 46, 221-226.
148. Mei,J., Yeung,S.S.C., and Kung,A.W.C. (2001) High dietary phytoestrogen intake is associated with higher bone mineral density in postmenopausal but not premenopausal women, *J.Clin.Endocrinol.Metab.* 86, 5217-5221.
149. Kim,M.K., Chung,B.C., Yu,V.Y., Nam,J.H., Lee,H.C., Huh,K.B., and Lim,S.K. (2002) Relationships of urinary phyto-oestrogen excretion to BMD in postmenopausal women, *Clinical Endocrinology* 56, 321-328.
150. Nagata,C., Shimizu,H., Takami,R., Hayashi,M., Takeda,N., and Yasuda,K. (2002) Soy product intake and serum isoflavonoid and estradiol concentrations in relation to bone mineral density in postmenopausal Japanese women, *Osteoporos.Int.* 13, 200-204.
151. Kritz-Silverstein,D. and Goodman-Gruen,D.L. (2002) Usual dietary isoflavone intake, bone mineral density, and bone metabolism in postmenopausal women, *Journal of Womens Health Gender-Based Medicine* 11, 69-78.
152. Greendale,G.A., FitzGerald,G., Huang,M.H., Sternfeld,B., Gold,E., Seeman,T., Sherman,S., and Sowers,M. (2002) Dietary soy isoflavones and bone mineral density: Results from the Study of Women's Health Across the Nation, *Am.J.Epidemiol.* 155, 746-754.
153. Wangen,K.E., Duncan,A.M., Merz-Demlow,B.E., Xu,X., Marcus,R., Phipps,W.R., and Kurzer,M.S. (2000) Effects of soy isoflavones on markers of bone turnover in premenopausal and postmenopausal women, *J.Clin.Endocrinol.Metab.* 85, 3043-3048.
154. Alekel,D.L., StGermain,A., Pererson,C.T., Hanson,K.B., Stewart,J.W., and Toda,T. (2000) Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women, *Am.J.Clin.Nutr.* 72, 844-852.
155. Potter,S.M., Baum,J.A., Teng,H.Y., Stillman,R.J., Shay,N.F., and Erdman,J.W. (1998) Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women, *Am.J.Clin.Nutr.* 68, 1375S-1379S.
156. Clifton-Bligh,P.B., Baber,R.J., Fulcher,G.R., Nery,M.L., and Moreton,T. (2001) The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism, *Menopause* 8, 259-265.
157. Uesugi,T., Fukui,Y., and Yamori,Y. (2002) Beneficial effects of soybean isoflavone supplementation on bone metabolism and serum lipids in postmenopausal Japanese women: A four-week study, *J.Am.Coll.Nutr.* 21, 97-102.
158. Chiechi,L.M., Secreto,G., D'Amore,M., Fanelli,M., Venturelli,E., Cantatore,F., Valerio,T., Laselva,G., and Loizzi,P. (2002) Efficacy of a soy rich diet in preventing postmenopausal osteoporosis: the Menfis randomized trial, *Maturitas* 42, 295-300.