Modern soy use consumption and safety Issues

Andrew Price BSc, MASc HFI (ACSM)

Introduction

The role of soy products in western diets cannot be overstated. Soy and soy bean derivatives now permeate the whole food chain from livestock to food processing. The full effect of this large-scale use is unknown and the health implications not fully understood.

Soy has been promoted as an invaluable source vegetable based protein; more land efficient than animal sources in a world with many hungry mouths. Indeed though deficient in methionine (and to a lesser extent lysine) (1) soy is unusual as a plant based source of relatively high quality protein, it is also valued for it's oil content which has become more valuable to the food industry as it has been included in an ever increasing variety of products. To put it in perspective a 27kg bushel of soybeans yields about 21kg of protein-rich meal and 5kg of oil (2).

As well as its use as a cheap source of high quality for soy has also been shown to have heath benefits rather than just counteracting malnutrition. The low rate of oxidative diseases and cancers in Asian populations has long been linked to the consumption and recent epidemiological studies seem to support this view. However the recent developments in food technology and economics have changed the way we use this foodstuff.

Comparing western and Asian consumption habits

Soy products have been readily consumed in Asian diets for many hundreds of years. However whilst important, the view that these were or are relied upon by these communities as a major source of dietary protein or, that soy products form a staple of these diets is largely groundless. While historically the use of soy products tended to rise in times of famine a study conducted into the eating habits of men and women in Takayama city, Japan revealed that the diets of those contained relatively small amounts of soy products. The 1242 male and 3596 female subjects generally consumed soy products tofu (plain, fried or dried), miso paste, fermented soybeans, traditional style soy-milk, and boiled soybeans. The estimated (the study was semi quantative) amount of soy protein consumed from these sources was 8.00 ± 4.95 g/day for men and 6.88 ± 4.06 g/day for women. (3). Another study showed that total legume consumption (not exclusively soy) ranged from 0 to 58 grams per day, with an average of about 13 grams (4).

Soy products historically consumed as part of Asian diets occupy more of a condiment roll and not a staple or major protein source, as sometimes seen in the vegan or vegetarian diets seen in the west. Moreover the production techniques vary greatly for the types of soy product most often seen in the west either as additives (usually associated with bulking of other food technology factors) or as stand-alone products such as tofu.

Economic importance of Soy: Changes in the way soy is used and consumed

The use of soy has changed dramatically in the last 40 years and it is now included in almost all categories of food available to the consumer. It is either added for it's nutritional properties of as a functional ingredient modifying the texture of physical characteristics of the product. It is now involved in many parts of the food production chain and consumption of soy by the west has grown accordingly. Notable uses for soy are as a feedstuff for cattle (processed meal), an emulsifier or stabilizer in processed food (soy lecithin), meat extenders (processed soy proteins) and in infant food (soy protein).

As discussed above soy represents a valuable source of cheap protein. With a growing world population there is a obvious incentive to produce a cheap plant based high quality protein source to compliment other plentiful but protein deficient food energy sources such as grains this, as well as the growth in the use of soy in food processing and as a source of animal feed meant that by the year 2000 soy accounted for 28% of the US plated crop by area making it their second greatest cash crop and the primary export crop (5).

The Chemical make up of Soy;

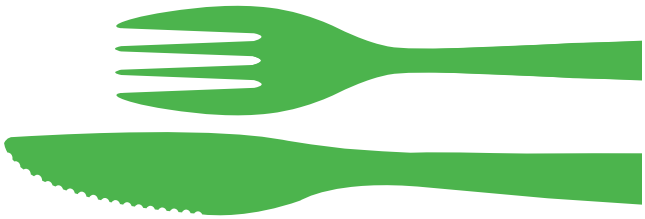
Nutrients

As already mentioned the proportion of protein and lipid in soy in considerable. The following tables were adapted from the USDA food database for standard reference

	Unit	Quantity per 100g
Energy	Kcal	147
Water	g	67.5
Protein	g	12.95
Total Lipid	g	6.8
Carbohydrate	g	11.05
Fiber	g	4.3

Although there is a considerable amount of fat in common with many other similar plants the lipid profile of one of mainly unsaturated or polyunsaturated fats as shown below

	Unit	Quantity per 100g
Saturated fat	g	0.79
Monounsaturated fat	g	1.28
Polyunsaturated fat	g	3.2
Cholesterol	mg	0.0
Phytosterols	mg	50



The abundance of polyunsaturated fats as well as the relatively high concentration of phytosterols may have implications for its value, both having been shown to have a beneficial effect on cardiovascular health so much so that soy products are now used to make 'functional foods' such as cholesterol lowering spreads (6).

The amino acid profile as discussed is, for a plant source, very good. All essential amino acids are present (although the ratio of methionine and lysine are low) as well as eight non essential amino acids.

Amino acid	Quanity per 100g	Amino acid	Quanity per 100g
Arginine	1.042	Valine	0.576
Histidine	0.348	Cystine	0.118
Isoleucine	0.570	Tyrosine	0.464
Leucine	0.926	Alanine	0.582
Lysine	0.775	Aspartic acid	1.508
Methionine	0.157	Glutamic acid	2.433
Phenylalanine	0.586	Glycine	0.539
Threonine	0.516	Proline	0.607
Tryptophan	0.157	Serine	0.721

Isoflavanoids

Isoflavonoids like those found in soy are a subclass of the flavonoid, a type of plant phenolics that have a displaced phenolic ring. The three soy isoflavonoids are

Genistein.
Daidzein.
Genistin.

Structurally these diphenolic compounds are very similar to estradiol and thus can bind to the estrogen receptor site. However their receptor binding affinity is much lower than that of estradiol and their estrogenic effect is weaker than that of the hormone. Isoflavanoids normally occur as glycones, their glucoside-bound forms. This is however not the active forms of the compounds (7), it is the glucoside free form that has the physiological effect. This state is reached by cleavage of the group in the gut by bacterial enzymes. This not only causes them to have stronger antioxidant properties but also makes them more readily absorbed by the body (8)

'Antinutrients'

Phytic Acid

Phytic acid (phytates) is present in the outer portion of the soy bean and many other legumes. These bind to minerals making them unavailable for absorbtion in the gut. Phytic acid has been shown to reduce the

assimilation of calcium, copper, iron, magnesium and zinc and has been liked to growth problems in children.

Trypsin Inhibitor

Trypsin inhibitors a class of protein whose structure is very stable. These proteins do not denature when exposed to the heat of cooking. They interfere with protein digestion and may cause pancreatic disorders. In test animals soy containing trypsin inhibitors caused stunted growth and they have also been connected with pancreatic nodeual formation and an hyperplasia in animal models (9).

Goitrogenic compounds

Isoflavones such as genistein seem to reduce thryroid function, reducing the hormone output by inhibiting the enzyme (thyroid peroxidase) responsible for attaching iodine to the thyroid hormones (10)

Benefits of Soy

Apart from the whole food (gross calorie intake) related benefits mentioned earlier such as it abundant supply of calories in the form of reasonably high quality protein and oil there are certain other factors in soy that make it useful from a therapeutic point of view.

Asian diets containing soy have long been associated with health benefits and supplementation with soy and soy-derivatives has been shown to help a variety of conditions reduce the incidence of others. Chronic conditions such as cardiovascular disease, cancers of prostate colon and breast etc, as well as symptoms associated with postmenopausal women such as osteoporosis (11) have been shown to be less prevalent in Asian countries. This difference in the incidence of these conditions has been associated with the consumption of soy.

Supplementation with soy products has been shown to have a hypocholesterolemic effect on both men and women (both pre and post menopausal) (12, 13, 14, 15). There are more than one class of compounds contained in soy that can have an impact on LDL (as well as HDL) cholesterol levels. The phospholipids contained within whole soy (abacor and abalon) have been shown to have a beneficial effect on both LDL and HDL cholesterol levels as well as tri glyceride levels (16). It has also been shown by meta analysis of existing studies into supplementation with soy protein isolate (SPI) that the level of isoflavone contained within the SPI independent of the amount given elicited the hypocholesterolemic effect in the subjects (12).

Anticancer Effects

As stated above the consumption of soy has been associated with the significantly lower rates of various cancers, there are a number of proposed reasons and modes of action be researched. Estrogens have been shown to regulate the proliferation of cancerous cells in the breast. Genistein has been demonstrated to have a therapeutic effect both in vitro and in vivo possibly by inducing apoptosis in the cancerous cells (17, 18, 19). Genistein has also been shown to have an inhibitory effect upon protein tyrosine kinase in

vitro. Receptors specific for the peptide growth factors, which regulated the growth of cancerous cells, have intrinsic protein tyrosine kinase activity. It is thought that the inhibitory effect of genistein may interfere with signal transduction in the cancerous cells and thus arrest their growth (20).

The anti cancer benefits are not confined by sex. Soy and its derivatives have been demonstrated to have beneficial effects on men as well as women. It has been shown that genistein may also be effective in the treatment of other conditions such as non-specific lymphomas (21). and non-androgen mediated prostate cancer (22). Though in both these examples the mode of action is different they are similar in that the addition of genistein to the treatment protocols boosts the effect of the other modes of treatment used.

Phytoestrogens and menopause

As a women's endogenous hormone status alters at menopause she may experience a range of symptoms that supplementation with isoflavones may help reduce. Indeed whilst the effect of these phytoestrogens is small (possibly in the range of 1/1000 of the power of estradiol) there exists, distinct from multivitamin and herbal formulas formulated for mid and post menopausal women, a range of dietary supplements containing soy products. These usually take the form of soy protein (and the associated isoflavones) or stand alone isoflavone products. Whilst the research on the effect of supplementation of this type on endogenous hormone production is contradictory (23) the mechanisms of action are in many cases yet to be elucidated and effects vary from individual to individual (24)

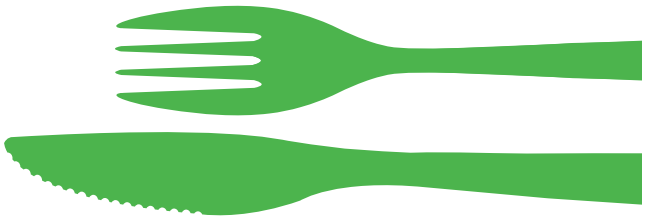
It has been shown that this type of supplementation may be of benefit to some women decreasing symptoms such as hot flushes and having a positive impact on their blood borne lipid profile and may increase estradiol concentration (25). Whilst not immdiatly life threatening treatments such as these can have an effect on the quality of life, they are also examples where soy derivatives can have an impact on the treatment of some of the most common life threatening conditions seen in the west.

Diabetes

One medical condition prevalent in the west is type-two diabetes. This, due to the combination of increasingly sedentary lifestyles and poor nutrition choices form an ever-earlier age is fast on the rise and shows a strong correlation with the ever increasing obese population. Distinct from the medical problems caused by the inability of the body to regulate the concentration of glucose diabetes mellitus can lead to cardiovascular disease, retinopathy), nerve neuropathy), nephropathy. Indeed diabetes mellitus is the most common cause of kidney failure in the US. Soy has been shown to have a beneficial effect on subjects with kidney failure. Moreover subjects who supplemented with soy protein isolate experienced a drop in the urinary serum albumen excretion (in the region of 10%) and also a drop in the HDL/LDL ratio (26)

Possible Problems with processed soy products

With so much statistical data presenting the benefit of soy in the Asian diet the use of growth in the use of soy has been rapid and welcomed. The inclusion of soy in our diet is pervasive, the value of the commodity is great and as such effort should be made to understand the possible implications for health of sustained use or western style soy products (such as soy milk) in our diets. Whilst the health benefits are



encouraging and empirical, anecdotal and epidemiological data suggests many health benefits there are also factors that give cause for concern. Though there is much conflicting data concerning soy's effects upon reproductive/endocrine, brain, thyroid and immune function can't be ignored.

Soy based infant food

Soy protein has been used a base for infant formula as a substitute for the protein from cows milk (namely casein), that has been shown to cause an immune response and to avoid lactose mal absorption both of which are common in infants. Soy has many advantages when used in this way, it is cheap to produce and process so that a suitable macronutrient profile can be achieved. There are a range of chemicals that have to be studied when talking about total nutrition quality including the 'anti nutrient' compounds such a phytic acid and trypsin inhibitors and Aluminium.

Possibly of most significance in the long run is the abundance of isoflavanoids in soy products. It has been shown that infants consuming soy based formula have a concentration of isoflavoids circulating in their blood an order of magnitude higher than that of women who have had physiological reactions to these flavanoids (27). Some go further blaming, at least in part, the increased incidence of early onset puberty, menache and thelarche in girls and delay in the onset of physical maturation and learning difficulties in boys on the consumption of soy formula citing a study on the food intake of the correlation between the incidence of these conditions with the demographic and ethnic based consumption of soy formula (28,29). It has been shown more conclusively however that there is a definite carry over into adult hood. Studies using adult women have shown that subjects who were fed with soy based infant formula have a higher incidence of longer duration and more painful menstruation (30). Whilst these studies are by no means conclusive and in some cases are contradicted by other studies (31,32) they raise an issue that definitely warrants further investigation.

Male infants experience a testosterone surge in the first few months of life which has implication for puberty onset and masculine maturation. During this time circulating testosterone levels may be as high as that of adult males and it is also when male brain characteristics are laid down. It has been shown in primate models that deficiency of male hormones impairs the development of spatial perception (which, in humans, is normally more acute in men than in women), of learning ability and of visual discrimination tasks (such as would be required for reading). Male children exposed, during gestation, to diethylstilbestrol, (a synthetic estrogen that has effects on animals similar to those of phytoestrogens from soy) had testes smaller than normal on manturation. 33,34

Soy and Estrogen Related Cancers

As discussed earlier soy can have a preventative effect with regards to cancer, the isoflavanoids acting as antioxidants, soy can also be of use in cancer therapy. However some types of cancer such as various forms breast and uterine cancer are estrogen sensitive. As discussed the structure of the flavanoids making up the phytoestrogens found in soy have a slightly estrogenic effect. Indeed the treatment of post menopausal women with isoflavones may be connected to a rise in the incidence of these cancers and in vitro studies have shown stimulation of breast cancer cell growth at low concentrations (35) though it was also demonstrated that at higher concentrations genistein could competitively inhibit estrogen, binding to

the receptors and exerting a weaker effect slowing cell proliferation.

Other Evidence for Carcinogenisis and Mutagenisis

While ingestion if soy has been shown to have a positive effect on cancer rates for a given population and the treatment with soy isoflavanoids has been shown to reduce the incidence of cancer and also increase the effectiveness of some cancer treatment protocols these same flavanoids have been shown to possess some limited mutagenic properties.

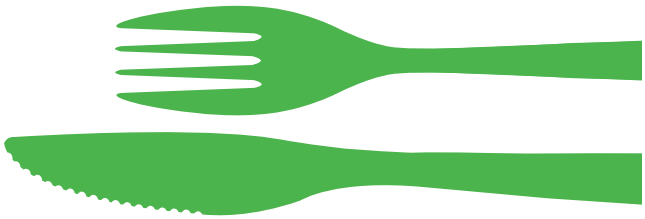
In studies using hamster V79 lung fibroblasts it was reported that genistein induced the formation of micronuclei (36). It has also been shown that in both daidzein and genistien increase the incidence of DNA strand breaks in sperm and peripheral lymphocytes (37). This study is of limited use however due to the lack of a direct evidence of mutagenisis, DNA strand breaking does not directly lead to mutagenic of carcinogenic events. Attention should also be paid to the concentration of isoflavanoids used in these in vitro studies and whether these concentrations are repeatable, attainable and sustainable in vivo considering tissue metabolism, excretion etc.

In vivo studies have been conducted and predominantly involve the use of animal models and are for the most part contradictory. Exposure to genistein whilst in utero has been shown to increase the incidence of mammary tumours in animal studies (38). The type of cancer is induced by dimethyl benz(a)anthracene (DMBA). However postnatal exposure to isoflavones has been shown to result in a protective effect against this same type DMBA of cancer. Injection of neonatal mice with genistein has also been shown to produce several different types of abnormality in the reproductive tissues (39). These included increased uterine weight, uterine adencarcinoma, squamous mataplasia and atypical hypoplasia. These effects where observed after 18 months of administration. Again the method of administration and the concentrations of isoflavanoid attained within the tissues should be considered. Whilst effects were observed that suggest carcinogenic effect these were attained by the sub-cutanious administration of isoflavanoids at relatively high doses (thus high concentrations) and not by the addition of soy products to the diet of the animal model.

Soy and the Nervous System

It has been reported that there is a correlation between the consumption of soy products and the reduction in cognitive function. A study of Japanese-American males linked the mid life consumption of tofu to a reduction in cognitive function (40) however the design of the study being purely observational allied with the possible effects of unknown confounding factors on the results added to the fact that similar results where not observed in a short term dietary intervention study using high soy diets (41).

It has been suggested that if indeed soy consumption did have a negative effect on cognitive function then this would be reflected in epidemiological studies. Studies of this type have shown that although causality in the two populations is different, there is not any statistically significant difference in dementia in elderly population of the United States and Japan. Studies of this type though cannot factor out the many other factors associated with cognitive decline. Also the type of soy products and the method of preparation of



these products can have a significant effect on the chemical make up of the final product.

The levels of aluminium present in some soy-based products have been shown to be comparatively high. It is widely known that increased levels of aluminium can have at detrimental effect on the nervous system and has been implicated in the onset of Alzheimer's. A whole host of 'modern' foodstuffs include soy protein isolate (SPI). SPI is produced by a method involving acid washing. It has been shown that this acid washing can leach the aluminium out of the processing tanks leading to an increased level of aluminium in the final product and studies have been undertaken to asses the levels of Al in SPI in particular the levels in infant formulas using SPI as a base.

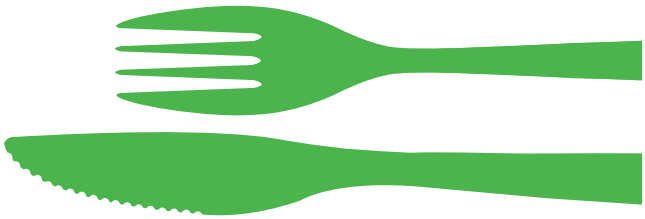
What Conclusions can be drawn?

The consumption of soy is steadily rising and there is no foreseeable change in this trend however, the impact of this increased consumption has clearly not be fully studied and understood. There are many different issues to consider when looking at the safety profile of this resource. The use of soy as a source of food for populations of third world countries may well be its most important use and would, used correctly, improve the diet of many millions of people in for whom quality protein sources are scarce. While there is the issue of the associated health problem with soy this of course would have to be looked at in context and the addition of quality protein to the diets of those in famine stricken areas. The consumption of soy certainly has beneficial effects for some special populations and may become a viable tool in the treatment of various disease states. Chronic diseases such as arteriosclerosis and diabetes associated with obesity are on the rise in the west and soy has been shown to be a useful tool in treating these conditions. Chemicals isolated from soy are starting to be used as supplements such as post menopausal women and are becoming more popular.

However, whilst many of the quoted benefits are real what has to be taken into account is that other therapies exist that in each situation may be just as effective if not more so than using soy products, for example, obesity and it associated diseases. Obesity is one of the greatest challenges to society in the west and soy has been shown to be useful in treating it however, the use of diet manipulation, and without reliance on soy coupled with the use of exercise and supplements such as fish oils etc are extremely effective methods both in the short and long term.

There are many facets to soy and every question needs to be looked at in context. A good analogy for the larger situation is the issue of isoflavones in soy; in some circumstances, such as their concentrations in infant formula, their estrogenic properties are cause for concern, however in other situations the same compounds are utilised for their anti estrogenic properties, such as the used of daidzien to block estrogen receptor sites in supplements aimed at men.

Clearly there are many unanswered questions, which merit further research in particular toxicological, pharmacological, epidemiological and biochemical studies to address each of the questions raised by the significant compounds found in soy. Current research is contradictory but suggests that in the short term occasional and 'normal' use of soy (normal consumption based on physiological not pharmacological limits) should be of little worry but increasingly the use of soy in western diets (such as the consumption of soy milk) is heavy, regular and long term. Consumption of this type is a relatively new behaviour and little



is known about its long-term effect and could not be advised in situations where healthy, viable alternatives exist.

References

1.
Friedman M, Brandon DL.
Nutritional and health benefits of soy proteins.
J Agric Food Chem. 2001 Mar;49(3):1069-86.

2.
United Soya Bean Organisation

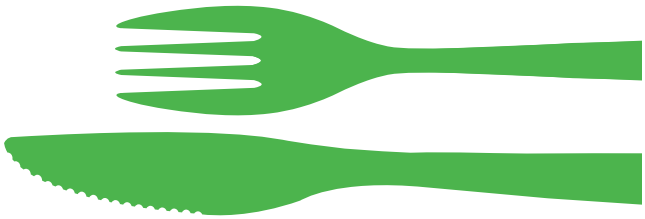
3.
Nagata C, Takatsuka N, Kurisu Y, Shimizu H.
Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women.
J Nutr 1998, 128:209-13

4.
Chen J, Campbell TC, Li J, Peto R.
Diet, Lifestyle and Mortality in China. A study of the characteristics of 65 counties.
Monograph, joint publication of Oxford University Press, Cornell University Press, China People's Medical Publishing House. 1990.

5.
USDA

6.
Westrate JA. Ayesh R, Meijer GW.
Plant sterl-enriched margarines and reduction of plasma total-and LDL-cholesterol concentrations in normocholesterolaemic subjects.
Eur J Clin Nutr. 1998; 52:334-343.

7.
Yuan L, Wagatsuma C, Sun B, Kim JH, Surh YJ.
The role of beta-glucuronidase in induction of apoptosis by genistein combined polysaccharide (GCP) in xenogeneic mice bearing human mammary cancer cells.
Ann N Y Acad Sci. 2003 Dec;1010:347-9.



8.
Murota K, Shimizu S, Miyamoto S, Izumi T, Obata A, Kikuchi M, Terao J.
Unique uptake and transport of isoflavone aglycones by human intestinal caco-2 cells: comparison of isoflavonoids and flavonoids.
J Nutr. 2002 Jul;132(7):1956-61.

9.
Liener IE.
Possible adverse effects of soybean anticarcinogens.
J Nutr. 1995 Mar;125(3 Suppl):744S-750S.

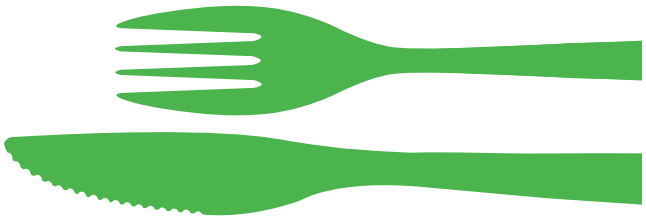
10
Scheiber MD, Liu JH, Subbiah MT, Rebar RW, Setchell KD.
Dietary inclusion of whole soy foods results in significant reductions in clinical risk factors for osteoporosis and cardiovascular disease in normal postmenopausal women.
Menopause. 2001 Sep-Oct;8(5):384-92.

11.
Toda T, Uesugi T, Hirai K, Nukaya H, Tsuji K, Ishida H.
New 6-O-acyl isoflavone glycosides from soybeans fermented with Bacillus subtilis (natto). I. 6-O-succinylated isoflavone glycosides and their preventive effects on bone loss in ovariectomized rats fed a calcium-deficient diet.
Biol Pharm Bull 1999 Nov;22(11):1193-201

12.
Zhuo XG, Melby MK, Watanabe S.
Soy isoflavone intake lowers serum LDL cholesterol: a meta-analysis of 8
randomized controlled trials in humans.
J Nutr. 2004 Sep;134(9):2395-400.

13.
Kerry E Wangen, Alison M Duncan, Xia Xu and Mindy S Kurzer
Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women
American Journal of Clinical Nutrition, Vol. 73, No. 2, 225-231, February 2001

14.
Merz-Demlow BE, Duncan AM, Wangen KE, Xu X, Carr TP, Phipps WR,
Kurzer MS.
Soy isoflavones improve plasma lipids in normocholesterolemic, premenopausal women.
Am J Clin Nutr. 2000 Jun;71(6):1462-9.



15
Puska P, Korpelainen V, Hoie LH, Skovlund E, Smerud KT.
Isolated soya protein with standardised levels of isoflavones, cotyledon soya fibres and soya phospholipids improves plasma lipids in hypercholesterolaemia: a double-blind, placebo-controlled trial of a yoghurt formulation
Br J Nutr. 2004 Mar;91(3):393-401.

16
Hermansen K, Dinesen B, Hoie LH, Morgenstern E, Gruenwald J.
Effects of soy and other natural products on LDL:HDL ratio and other lipid parameters: a literature review
Adv Ther. 2003 Jan-Feb;20(1):50-78

17.
Valachovicova T, Slivova V, Bergman H, Shuherk J, Sliva D
Soy isoflavones suppress invasiveness of breast cancer cells by the inhibition of NF-kappaB/AP-1-dependent and -independent pathways.
Int J Oncol. 2004 Nov;25(5):1389-95.

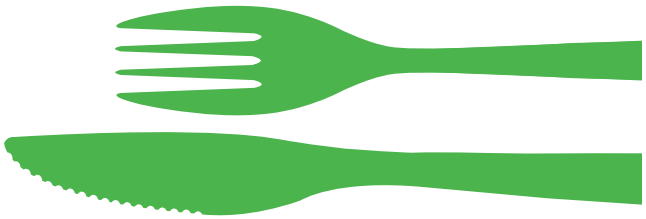
18.
Pagliacci MC, Smacchia M, Migliorati G, Grignani F, Riccardi C, Nicoletti I.
Growth-inhibitory effects of the natural phyto-oestrogen genistein in MCF-7 human breast cancer cells.
Eur J Cancer. 1994;30A(11):1675-82.

19.
Jin Park O, Shin JI.
Proapoptotic potentials of genistein under growth stimulation by estrogen.
Ann N Y Acad Sci. 2004 Dec;1030:410-8.

20
Peterson G, Barnes S.
Genistein inhibits both estrogen and growth factor-stimulated proliferation of human breast cancer cells.
Cell Growth Differ. 1996 Oct;7(10):1345-51.

21
Mansour A, McCarthy B, Schwander SK, Chang V, Kotenko S, Donepudi S, Lee J, Raveche E.
Genistein Induces G2 Arrest in Malignant B Cells by Decreasing IL-10 Secretion.
Cell Cycle. 2004 Dec 08;3(12) [Epub ahead of print]

22.
Yan SX, Ejima Y, Sasaki R, Zheng SS, Demizu Y, Soejima T, Sugimura K
Combination of genistein with ionizing radiation on androgen-independent prostate cancer cells.
Asian J Androl. 2004 Dec;6(4):285-90.



23.
Foth D, Nawroth F.
Effect of soy supplementation on endogenous hormones in postmenopausal women.
Gynecol Obstet Invest. 2003;55(3):135-8.

24.
Petri Nahas E, Nahas Neto J, De Luca L, Traiman P, Pontes A, Dalben I.
Effects of soy consumption on gonadotropin secretion and acute pituitary responses to gonadotropin-releasing hormone in women.
J Nutr. 2002 Apr;132(4):708-14.

25.
Petri Nahas E, Nahas Neto J, De Luca L, Traiman P, Pontes A, Dalben I.
Benefits of soy germ isoflavones in postmenopausal women with contraindication for conventional hormone replacement therapy.
Maturitas. 2004 Aug 20;48(4):372-80.

26
Teixeira SR, Tappenden KA, Carson L, Jones R, Prabhudesai M, Marshall WP, Erdman JW Jr.
Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile in men with type 2 diabetes mellitus and nephropathy.
J Nutr. 2004 Aug;134(8):1874-80.

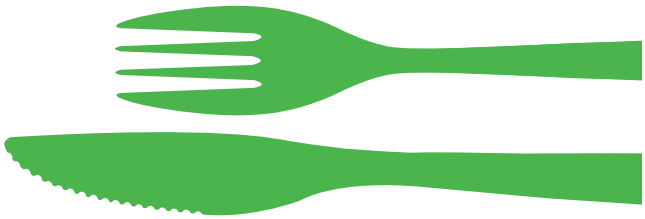
27
Tuohy PG
Soy infant formula and phytoestrogens
J Paediatr Child Health. 2003 Aug;39(6):401-5

28
L W Freni-Titulaer,
Premature Thelarche in Puerto Rico, A search for environmental factors,
American Journal of Diseases of Children, December 1986, Vol 140, No 12, Pages 1263-1267

29
Dr Mary Enig
Weston A Price Foundation

30
Mendez MA, Anthony MS, Arab L.
Soy-based formulae and infant growth and development: a review.
J Nutr. 2002 Aug;132(8):2127-30.

31
Giampietro PG, Bruno G, Furcolo G, Casati A, Brunetti E, Spadoni GL, Galli E.



Soy protein formulas in children: no hormonal effects in long-term feeding.
J Pediatr Endocrinol Metab. 2004 Feb;17(2):191-6.

32
Miniello VL, Moro GE, Tarantino M, Natile M, Granieri L, Armenio L.
Soy-based formulas and phyto-oestrogens: a safety profile.
Acta Paediatr Suppl. 2003 Sep;91(441):93-100.

33
Hagger, C. and J. Bachevalier,
Visual habit formation in 3-month-old monkeys (Macaca mulatta): reversal of sex difference following neo-natal manipulations of androgen,
Behavior and Brain Research (1991) 45:57-63.

34.
Ross, R.K. et al.
Effect of in-utero exposure to diethylstilbestrol on age at onset of puberty and on post-pubertal hormone levels in boys
Canadian Medical Association Journal 128(10):1197-8, May 15, 1983.

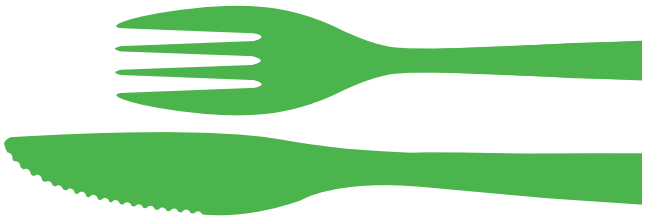
35.
Zava DT et al
Estrogenic and antiproliferative properties of genistein and other flavanoids of human breast cancer cells in virto
Jur Nutr Cancer 1997;27;31-40

36:
Bartholomew RM, Ryan DS,
Lack of mutegenicity of some phytoestrogens in the salmonella/mammalian microsome assay.
Mutat Res 1980;78:317-321

37:
Kulling SE, Metzier M
DNA strand breaks and HPRT mutations in cultured Chinese hamster V79 sells by the phytoestrogen coumoestrol
Food Chem Toxicol 1997; 35:605-613

38:
Hilakivi-Clarke L, Cho E, Onojafe I, Raygada M, Clarke R.
Maternal exposure to genistein during pregnancy increases carcinogen induced mamery tumoriogenisis in female rat offspring.
Oncol Rep.1999;6:1089-1688

39:
Newboid RR, Bancks EP, Bullock B, Jefferson WN.



Unterine adenocarcinoma in mice treated neonataly with genistein.
Cancer Res 2001;61:4325-4328

40:
White LR, Petrovich H, Ross GW.
Brain ageing and midlife tofu consumption.
J Am Coll Nutr. 2000;19:242-255

41:
File SE, Jarrett N, Fluck E, Duffy R, Casey K, Wiseman H,
Eating soya improves human memory.
Physcopharmacology 2001;157:430-436