

The emerging importance of phytoestrogens in Australia and Europe

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Phytoestrogens have been implicated in a number of disease states. The increasing amount of research in the field of phytoestrogens is bringing with it new markets for food products and phytopharmaceuticals. Gives a brief review of potential health implications of phytoestrogens, as well as a discussion of the commercial and consumer changes that are currently occurring in Australia and Europe.

Introduction

The last two decades have seen a rapid growth in the area of plant estrogen (phytoestrogen) research. Studies ranging from epidemiological, cell, along with animal and human intervention trials, illustrate the effects of these intriguing compounds. This increase in research has prompted companies to release a number of new products containing high levels of phytoestrogens. The effects of phytoestrogens on health are now affecting public health and clinical strategies in Australia and Europe.

What are phytoestrogens?

Compounds with phytoestrogenic actions may actually have multiple actions. Phytoestrogens, or plant estrogens have a structure similar to that of estrogen and hence have both estrogenic and anti-estrogenic effects in various systems as they compete with estrogen for its receptor (Martin, 1978). There are four categories of phytoestrogens:

- 1 isoflavonoids (isoflavones and coumestans);
- 2 flavonoids.
- 3 resorcylic acid lactones; and
- 4 lignans.

The majority of work is currently concentrating on the isoflavones and the lignans (Setchell, 1985). The important dietary sources of phytoestrogens include various legumes, grains and fruits. Soy and linseed are food sources receiving much attention due to their high content of isoflavones and lignans respectively (Mazur, 1996).

Phytoestrogens and cancer

The epidemiological evidence suggests that phytoestrogens may protect against the development of certain forms of cancer, particularly the hormone-dependent cancers

of the breast and prostate. Asian populations, who have a high consumption of phytoestrogens, have low rates of these cancers (Rose, 1986). There have been a number of reviews assessing the role of phytoestrogens *in vitro* and in animal cancer models (Adlercreutz, 1995; Messina, 1994). The data obtained support a protective mechanism, even though there have been some reports of phytoestrogens promoting cancer (Mousavi, 1992; Welshons, 1987). Human data on the effects of soy on breast tissue have been shown to promote cell division and, more recently, a phytoestrogen tablet given to a prostate cancer patient caused marked apoptosis, suggestive of tumour regression (McMichael-Phillips *et al.*, 1996; Stephens, 1997).

Phytoestrogens and cardiovascular disease

A number of studies have looked at the effects of soy consumption on cardiovascular disease risk factors such as serum cholesterol. A change in diet based on animal protein to one based on soy protein decreases serum cholesterol, especially in patients who have elevated cholesterol. This was highlighted by a meta-analysis of 38 studies looking at the effects of soy protein intake on serum lipids (Anderson, 1995). The question remains, though, as to which component of soy is responsible for this change; is it the phytoestrogens or is it the protein fraction of soy? Studies by Sirtori *et al.* (1997), have illustrated decreases in cholesterol in Italian hypercholesterolemic patients using soy which was low in phytoestrogen. In contrast, animal studies have illustrated that phytoestrogens could be the factor responsible in decreasing cholesterol. Anthony *et al.* (1996) have published research in monkeys fed soy diets with and without phytoestrogens and demonstrated various improvements in blood lipids in monkeys on the soy with phytoestrogens diet. Recently, Eden (1996) demonstrated a

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22 percent increase in HDL cholesterol in postmenopausal women consuming an isoflavone-rich tablet. Another area of interest is that of blood vessel reactivity and phytoestrogens. Arterial elasticity decreases as we get older and is an important biomarker of cardiovascular health. Data from monkeys indicate that phytoestrogens enhance vasodilatation (Honore, 1997). In postmenopausal women consuming an isoflavone-rich tablet, an improvement of 26 percent in systemic arterial compliance – a measure of arterial elasticity – has been observed (Nestel, 1997).

Phytoestrogens and women's health

Interest in this field focuses principally on menopausal women. Epidemiological evidence suggests that Japanese women suffer less from menopausal symptoms compared to their Western counterparts (Boulet, 1995). The hypothesis is that a high intake of phytoestrogen acts in a similar fashion to HRT, alleviating menopausal symptoms (Adlercreutz, 1991). In 1990, Wilcox *et al.* (1990) demonstrated that a diet high in phytoestrogen (soy, linseed and red clover) improved the vaginal cytology maturation index (an estrogen-dependent marker) in menopausal women (Wilcox, 1990). Since then a number of studies have looked at diets high in phytoestrogens and their effects on menopausal symptoms. Due to large inter-patient variability in measuring the primary symptom of menopause, hot flushes, there has been no definite answer, even though there seems to be more of an effect in phytoestrogen-rich groups compared to a control (Baird, 1995; Brzezinski, 1997; Burke, 1996; Dalais, 1996; Eden, 1996; Harding, 1996; Murkies, 1995; Woods, 1996). There are, however, data on improvement in vaginal health and also evidence on bone loss protection (Brzezinski, 1997; Dalais, 1996). Also, soy diets protect against bone loss in the rat model (Arjmandi, 1996). Longer-term human studies are still needed. In premenopausal women, menstrual cycle length has been demonstrated to increase as a result of diets high in phytoestrogens (Cassidy, 1994; Phipps, 1992). The hypothesis is that, over a lifetime, a longer cycle length would decrease the estrogen exposure time and therefore decrease the risk of breast cancer.

Research and commercial changes in Australia

Since the late 1980s, phytoestrogen research has grown rapidly in Australia. This growth has not only occurred in the scientific community, but has also occurred in the

commercial sector. There are currently about 11 institutions involved in phytoestrogen research compared to about two in the late 1980s, covering a wide range of topics with the majority being human-based research.

A clinical trial from our group on the effects of phytoestrogen-rich bread (high in soy and linseed) on menopausal symptoms, with Tip Top Bakeries, one of the major bakeries in Australia, led to its release on to the Australian market. The consumer response was incredible, with Tip Top Bakeries having trouble keeping up with demand and all other major bakeries releasing similar breads. The Australian public is now well informed of the potential benefits of consuming phytoestrogens due to aggressive marketing strategies and it is only a matter of time until other major food companies release more food products rich in phytoestrogens in order to claim their share of the phytoestrogen-aware consumer market. Given that these products are soy based, this has also offered the vegetarian consumer market a rapid growth in product diversity. The current expansion in the food industry is not without difficulties. Our food phytoestrogen content analysis data indicate that there is great variation in the levels of isoflavones; not only between the various brands of breads, but also within the same brand of bread. These data suggest that the various bread companies and other food manufacturers need to implement routine quality control to minimize this variation.

Recent interest in phytoestrogen has also prompted the involvement of the phytopharmaceutical group, Novogen Ltd. Formerly known as Norvet Ltd, its research in the field of phytoestrogens, originally based on a red clover extract tablet, has now also advanced to a soy-based tablet. The clinical trials conducted to date are encouraging, demonstrating potential usage in cancer, and cardiovascular disease. Novogen are about to release their tablet, known as Promensil, as an over-the-counter product. The USA, where the product has been granted patent protection, and Australia are the two countries where the product will be initially released for use by menopausal women.

Research and commercial changes in Europe

The situation in the UK and Europe is very similar to that already outlined for Australia. In England, Scotland and Wales, research institutions are investigating soya and linseed products in relation to prostate and breast cancer, postmenopausal health and cardiovascular disease. The Ministry of

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Agriculture, Fisheries and Food (MAFF) currently supports 23 studies on phytoestrogens. The funding is well in excess of £2.8 million. The World Cancer Fund, a charity which specifically funds research relating to diet and cancer, is also currently funding several projects on phytoestrogens and cancer, particularly in relation to cancer of the prostate.

Early in 1997, a food supplement Prevacan was commercially launched in Germany. The product, which is manufactured in the USA, is marketed in this form in the UK by Energiser Plc. Prevacan is a cereal bar and contains soya, linseed and rye bran and is intended as a daily food supplement. The product is also available in North America and will soon be launched in the UK, France and Portugal. The company has several other soya-based products in advanced stages of development. These newer products are being manufactured for specific markets, such as women's health.

Both food manufacturers and phytopharmaceutical companies are using epidemiological evidence and scientific studies, some of which involve their products, to promote them. Both have certain advantages: the food companies are able to use the epidemiological studies involving the benefits of consuming high phytoestrogen-containing foods to emphasize their consumption; the scientific evidence is consistent with the isoflavones as the active components associated with health benefits. This is where phytopharmaceutical companies are able to target specific phytoestrogens to help in various disease states. We must be aware, however, that isolating these components from whole foods may not be appropriate. There may be other compounds in soy that act synergistically with the phytoestrogens, modulate their effects or have effects of their own.

The potential beneficial effects of phytoestrogens are exciting. There is an obvious need for more longer-term, large-scale studies to determine the role of these compounds in our lives as well as an assessment of the effects of new phytoestrogen-rich products on public health.

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