Alpro Foundation

Health & Nutrition Newsletter

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Soy and phytoestrogens

The interest and knowledge on the role of phytoestrogens in man has tremendously increased within the past 10-15 years.

Epidemiological studies suggest that phytoestrogens can play a role in several chronic diseases e.g. coronary heart disease, cancer (breast and prostate), osteoporosis ...
A lot of research in Europe is ongoing to study the possible effects of phytoestrogens.

This newsletter discusses the 'soy and phytoestrogen research' which was an important topic on the International Conference on Polyphenols in Finland.

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Highlights of the XXII International conference on polyphenols

Focus on Soy & Isoflavones

Helsinki Finland (august 2004)
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Tuija Jokela, M.Sc.

Soy is the most important source of plant estrogen in human nutrition, and contains the isoflavones daidzein and genistein. Also red clover is rich in isoflavones, mostly formononetin and biochanin A. Formononetin and biochanin A are converted to daidzein and genistein by human gut microflora and further metabolized to various isoflavonoid structures. The role of plant estrogens in human health has been widely studied during the past few years. According to epidemiological studies, plant estrogen rich diet, as in Southeast Asian countries, has been associated with a considerably diminished number of fatal cases in chronic diseases such as breast and prostate cancers, cardiovascular disease and osteoporosis.[1-3]

Cardiovascular disease

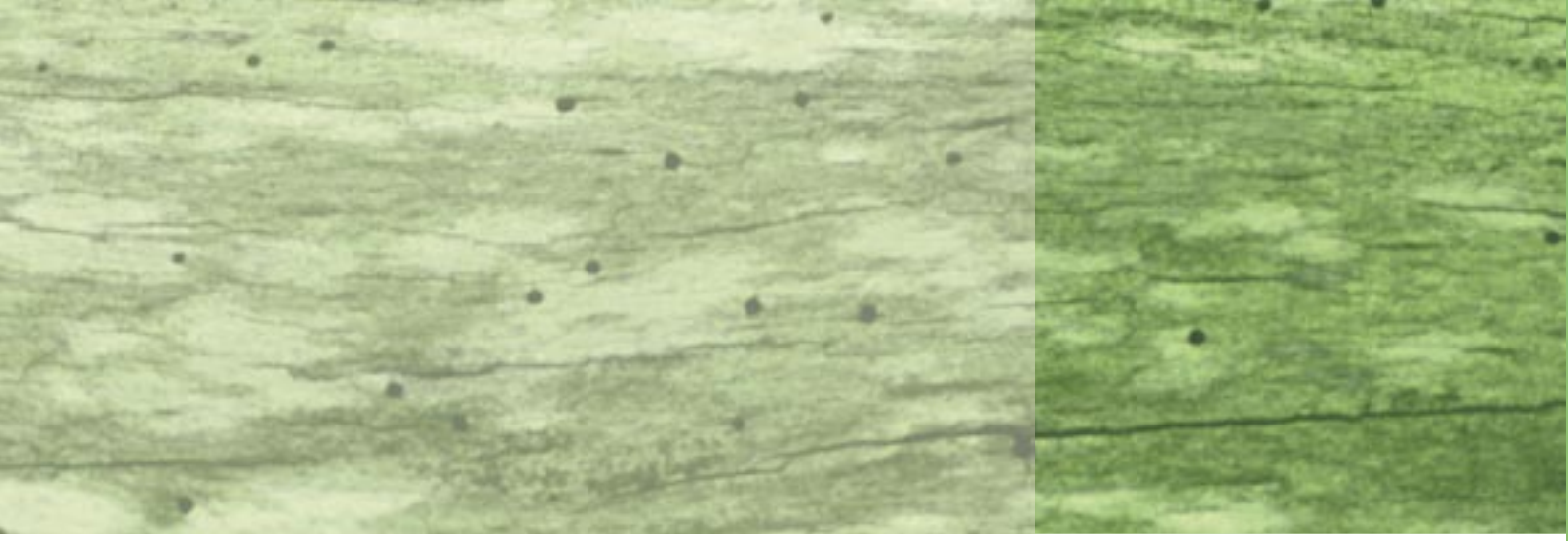
Red clover supplements sold in grocery and health food shops have been found to prevent cardiovascular disease in perimenopausal women[4] in a study involving 177 women at ages between 49 to 65. The most significant positive health effects in cardiovascular disease, decreases in the blood triglyceride and PAI-1 value, were observed in perimenopausal women compared to postmenopausal women. The trial also included a placebo group which did not show these positive blood lipid level changes. Similar results were reported in another red clover supplement study among perimenopausal women.[5] In the trial, women's blood lipid levels were lowered compared to the placebo group indicating a lower risk for cardiovascular disease. This 12 week trial was conducted on 252 women from 45 to 60 years of age.

Prostate & breast cancer

Genistein is found to inhibit the growth of prostate cancer cell lines[6] and angiogenesis[7] in vitro. Soy-containing diet also inhibits breast cancer especially if consumed early in life before puberty or during adolescence, as shown by results of immigrant and epidemiological studies.[8]

Osteoporosis

According to in vitro studies isoflavones may prevent also osteoporosis.[9] Trials were conducted by studying the effect of isoflavones on osteoblasts, which have an positive influence on bone growth and osteoclasts which are responsible for bone loss. Isoflavones, given as



such or as soy milk or soy beans are found to prevent bone loss also in ovariectomised mice as well as after castration.[10] Plant isoflavones are reported to inhibit bone loss also in postmenopausal women.[11] Most relevant molecular actions of isoflavones are those mediated by oestrogen receptors alpha and beta (α & β). Especially ERβ is important in bone metabolism. Isoflavones are able to bind to ER receptors, but isoflavone metabolites such as equol, which is an isoflavan in chemical structure, may bind with an even higher affinity and thus have stronger biological effects than the parent compound daidzein.[12] Therefore the metabolites are presumed to have a more important role in human health than their precursor isoflavones.

Isoflavone metabolism

Isoflavone metabolism in man was studied by giving red clover supplements in food.[13] In the trial isoflavones were found to be converted to equol type compounds and further to other similar polyhydroxy isoflavans and α-methyldeoxybenzoins such as angolensin and *O*-DMA. Similar metabolites were found in urine of people who consumed soy diet.[14] In the same trial also some new isoflavonoid structures, new plant estrogen metabolites, were found. To investigate soy isoflavone metabolism in man, fecal bacteria were isolated and used to ferment soy isoflavones in vitro. Several new metabolic structures of isoflavones were discovered in this study.[15] The biological activity of these metabolites has not yet been studied.

The metabolism in man of plant estrogens differs from that of other mammals in the sense that only 30 to 50% of the human population can convert isoflavones to further metabolic compounds such as equol and/or *O*-DMA.[16] For example all rats convert the soy isoflavone daidzein to equol.

To conclude, isoflavones have not been studied extensively in man and much further research is needed. So far only 3 isoflavans other than equol have been discovered (3'-methoxy-, 3'-hydroxy- and 6-methoxyequol).

Three α-methyldeoxybenzoins angolensin, *O*-DMA and 6'-hydroxy-*O*-DMA have been identified using authentic synthetic reference compounds by a GC-MS method.13-15 Three other compounds similar to *O*-DMA have been tentatively identified and reference compounds are under preparation to verify these results. So far isoflavones have been found in human breast milk, urine and blood after the consumption of isoflavone rich foodstuffs.[17,18,19]

The highly topical isoflavones were one of the central themes in the ICP2004 (International Conference on Polyphenols) meeting held in August 2004 in Helsinki with ca. 500 participants. A postsymposium involving phytoestrogens was also organized in Helsinki as a PHYTOHEALTH (Improving Health Through Dietary Phytoestrogens) Thematic Network Industrial Platform meeting.

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A thematic network for phytoestrogen research in Europe

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Cardiovascular disease, cancer, osteoporosis and neurodegenerative diseases constitute the greatest burden for European social systems. Several EU funded projects are investigating the role of phytoestrogens on those diseases.

Phystoestrogen intake in Europe (much lower than in South East Asia) might be promoted by increasing the intake of phytoestrogen rich foods present in European diets and/or promoting the consumption of enriched foods.

The Thematic Network PHYTOHEALTH (www.phytohealth.org) has been funded by EU to meet the need to extend the exchanges and collaboration among European research groups, so that the benefits of the synergy can be extended to a wider audience. The network will circulate information on phytoestrogen research, will develop consensus documents on research methodology and on public health implications, will analyse consumers' attitudes concerning the use of phytoestrogens and other phytoprotectants, will communicate to the public and to regulators.

Phytoestrogens

Phytoestrogens are naturally occurring plant-derived phytochemicals, whose common biological roles are to protect plants from stress or to act as part of a plant's defence mechanism. Although composed by a wide group of nonsteroidal compounds of diverse structure, phytoestrogens have been shown to bind estrogen receptors and to behave as weak agonist/antagonist in both animals and humans. Phytoestrogens include mainly isoflavones, coumestans, and lignans. These compounds are known to be present in fruits, vegetables, and whole grains commonly consumed by humans as staple foods. Isoflavones are mainly found in legumes-soybeans, in particular-whereas flaxseed are a major source of lignans, and coumestans are significantly present in clover, alfalfa and soybean sprouts.

Several epidemiological studies correlated high dose consumptions of soy isoflavones with multiple beneficial effects on breast and prostate cancers, menopausal symptoms, osteoporosis, atherosclerosis and stroke, neurodegeneration. For the relief of menopausal symptoms, a consumption of 60 mg aglycones/day has been suggested since some reduction was already seen at about 50 mg aglycones/day. For cancer prevention, a consumption between 50 to 110 mg aglycones/day is considered beneficial to reduce risks of breast, colon and prostate cancer. To decrease serum LDL-cholesterol a minimal intake of about 40-60 mg aglycones/day, depending on prior cholesterol status, is suggested to be used together with about 25 grams of soy protein that is absolutely necessary at the level of LDL metabolism. For improvement in bone mineral density (BMD), 60-100 mg aglycones/day for a period of at least 6-12 months should determine significant advantage. The safety profile of isoflavones is difficult to be drawn due to limited sample sizes and short periods of investigation.

Objectives and methods

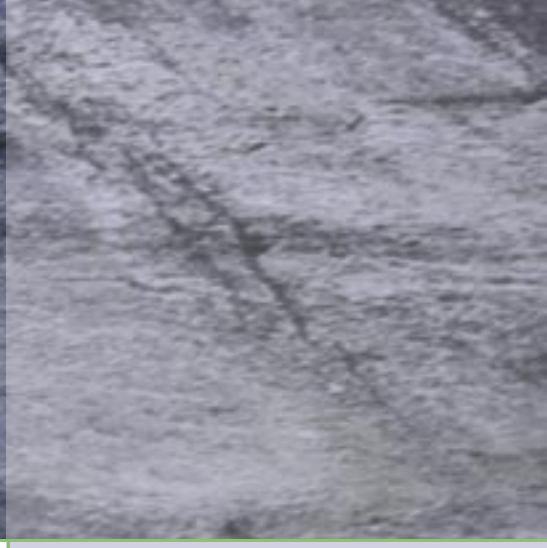
PHYTOHEALTH will lead to the establishment of a pan-European netwerk of institutions dealing with safety and health effects of phytoestrogens (PE), identification of optimal sources and processing technologies. The main objectives are: to circulate existing information on different aspects of phytoestrogen research; to allow co-ordination of existing research programmes on phytoestrogens in Europe; to develop consensus documents on research methodology and on public health implications; to explore consumers attitudes concerning the use of phytoestrogens and other phytoprotectants from supplements and from food; to communicate to the public; to communicate to regulators, including the European Food Authority.

The PHYTOHEALTH network is built around a cluster of three EU funded RTD projects dealing with health effects of phytoestrogens: "Effects of phytoestrogen-rich diets on bone turnover in postmenopausal women" (PHYTOS), "Prevention of prostate cancer and breast cancer" (PHYTOPREVENT) and "Isoflavones for reducing risk of coronary heart disease among post-menopausal women" (ISOHEART). The network involves key nutrition and agro-industrial research Institutes in Europe, academic institutions, leading food manufacturers and SMEs in a total of 11 European countries (Austria, Denmark, France, Finland, Germany, Greece, Italy, Netherlands, Spain, Sweden, United Kingdom) and two associated States (Poland, Switzerlan).

Current achievements and future plans

In the first plenary meeting (Barcelona, 4-7 February 2004) the scope has been extended to include other compounds with estrogenic action, such as prenyl flavonoids, that are common in the southern European diets. A web site has been established (www.phytohealth.org) and a Newsletter is regularly produced with research updates. Three consensus papers have been outlined and will be prepared by the 2nd plenary meeting in Heraklion (27-30th October 2004). The first one is addressing health effects of phytoestrogens in postmenopausal women. The paper will critically evaluate the existing data on phytoestrogen effects on menopausal symptoms, osteoporosis and cardiovascular health and will address practical questions such as: can phytoestrogen be used as an alternative to HRT? What age group can phytoestrogen benefit most? What dose would be appropriate for post-menopausal women? For how long should phytoestrogen be consumed in postmenopausal women?

The second paper is addressing the safety concerns over phytoestrogen intake. The few studies on short term effects have not pointed out the presence of toxic effects. However, issues to be investigated are the long term effects and effects of early exposure. There are methodological points such as discrepancy between tissue levels and plasma levels and the complexity of mechanisms of action. The paper on the assays for the evaluation of estrogenic potency takes off from the understanding that the relative binding affinity is unrelated to the relative transactivation activity and therefore no single simple standard assay can be used. Thus, the estrogen equivalents obtained with yeast models should be taken with caution. A compount cannot be assigned one value ("estrogen equivalent"); but it will vary depending on the endpoint. This evaluation will have to deal with the complexities of the actions of phytoestrogens, such as the interactions with coactivators or corepressors, the role of other nuclear receptors, the modulation of other intracellular signalling systems. Finally, the role of complex mixtures and of the metabolites will have to be considered.



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Am J Clin Nutr. 2004 Nov;80(5):1391-6.

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