PHYTOESTROGENS – VALUE AND SIGNIFICANCE DURING MENOPAUSE

A. S. WOLF

The significantly higher life expectancy in Japan has been a reason for science and speculations for a long time. One important reason is the low cancer mortality. People in southeast Asia have a significantly lower incidence of breast-, endometrial-, colon- and prostate cancer and acute myeloic leucemia as well as a lower probability of developing cardiovascular diseases and osteoporosis [1]. The ethnogenetic special features and the different social and cultural background, along with their nutrition of significantly less saturated fat, plenty of vegetables, green tea and the use of soy products containing phytoestrogens seems to play an important role [2]. Migration studies and epidemiological analysis could prove that a certain diet and the involvement of nutritional substances could play a protective role during the development of cancer. Even within Europe there is a unmistakeable difference from north to south of a higher rate of lung and breast cancer in northern Europe (Finnland and Scotland) in comparison to the south (Italy, France and Portugal) [3]. The highly protective part of fruits and vegetables in the mediterranian cuisine is believed to be responsible for this [4]. Cohort and case studies worldwide point out the protective effect of a nutrition with plenty of fruits and vegetables towards a number of different types of cancer [5]. In the meantime there are known estimated 10.000 protective substances in this type of diet, whereas **phytoestrogens**, as secondary plant substances out of the large group of polyphenoles, gained a special meaning.

BIOCHEMICAL CLASSIFICATION OF PHYTOESTROGENES

Phytoestrogens are natural plant substances with a structural and functional similarity to genuine 17β-estradiol. They are mainly absorbed by daily nutrition and are principally categorized in two biochemical classes [6]:

- **Lignans**: Enterolacton and Enterodiol
- **Isoflavones**: Genistein, Daidzein, Biochanin-A, Formononetin and Glycetin

Less significant are: Coumestanes (Coumestrole), Lactones (Ceralenone), Steroles (Sitosterole-A, B).

Very high concentrations are found in the following plants (in decreasing concentration) [7]:

- **Isoflavones**: Soy, red clover, legumes, vegetables
- **Lignans**: Fruits, berries, full grain products, green tea, line seeds, vegetables.

The highest concentration of the phytoestrogens Genistein and Daidzein are found in soy beans as well as other soy products, including for exam-

ple tofu, soymilk, miso, soyflour and refined soyprotein [6, 8, 9].

Metabolism of the Main Phytoestrogens

Phytoestrogens are mainly absorbed as precursor metabolites (Lignanes: Matairesinol, Secoisolariciresinol, Isoflavones: Formononetine, Daidzein, Biochanin A) and metabolized by intestinal bacterias to actual active compounds (fig 1). These effective substances will be either further metabolized or excreted without biochemical alteration in the form of urine or faeces. The catalysis of phytoestrogens from uneffective premetabolites points out the special meaning of the intestinal bacterias as an essential metabolic carrier [10].

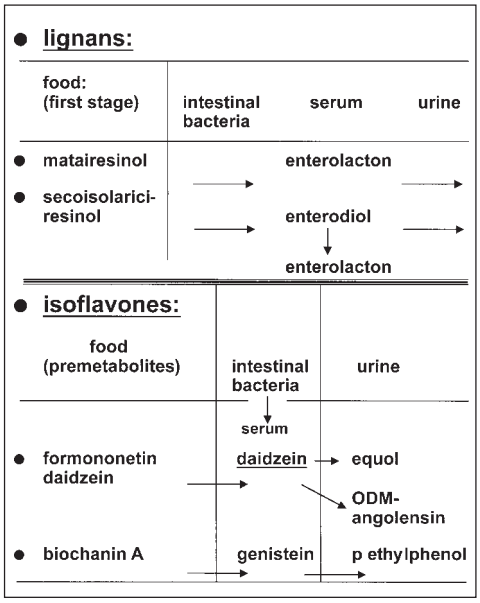

Figure 1. Metabolism of nutritional phytoestrogens

Biochemistry of Phytoestrogens

Due to positioning of both hydroxyl groups in a special dimensional order phytoestrogens have a high sterical identity to 17β-estradiol and are therefore able to bind at the estradiol receptor (fig 2). Moreover, lignans and isoflavones possess a distinct antioxidative capacity through the prevalence of two phenyl groups (radical scavengers).

Phytoestrogens bind with different relative binding affinity (RBA) to the estradiol receptor (ER) with special preference of the estradiol receptor β (ER-β). Opposite to the RBA of 17β-estradiol of 100 the RBA of Genistein is 5 on ER-α and 36 on ER-β [11]. Other phytoestrogens, for example coumestane (coumestrole), will bind even with a significantly higher affinity to the ER-protein (Table 1).

The organ specific distribution of the ER with an even higher concentration of ER-β in prostate gland, ovaries, lung, bladder, kidneys, uterus and testis points to a special local efficacy of phytoestrogens in these organs [11]. The effect of phytoestrogens is only partially based on the relatively good binding of the substances at the estradiol

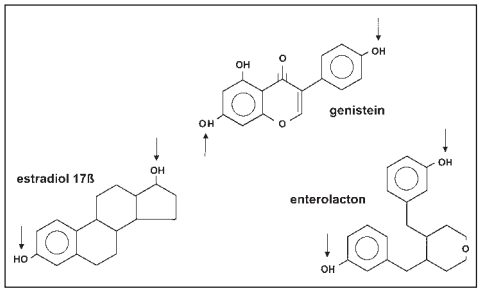

Figure 2. Structures of estradiol 17β and phytoestrogens

receptor. After consumption, the extremely high concentration of isoflavones and lignans is even higher than 17β-estradiol (fig. 3) [12]. ER will be blocked for the genuine estradiol. It is of uttermost meaning, that phytoestrogens after binding on ER, will only develop a relatively weak estrogenic activity [13, 14]. The bioactivity of all phytoestrogens in bioassays with human endometrial carcinoma cells is markedly weak and comes to for example Genistein only 0,08% of the 17β-estradiol [13].

Biological Activity of Phytoestrogens

Lignans and Isoflavones are weak estrogenic and partially antiestrogenic agents [15]. They furthermore possess antimicrobial, anticarcinogenic and anti-inflammatory potentials. The following effects of phytoestrogens are known:

1. Increase of SHBG with consecutive decreases of free steroid hormone concentrations. Primarily this is valid for androgenes, but also for estradiol [16, 17].
2. Blocking of the estradiol receptor as a consequence of high concentrations of phytoestrogens: Despite the weak binding affinity, estradiol will be replaced from the receptor due to a significant mass of substrate. The estradiol receptor will be blocked like a proliferation inhibitor [11].
3. The most essential effect of the phytoestrogens is intracellular enzym inhibition: Genistein is able to inactivate the signal chain of all growth factors of the tyrosinkinase family, for example IGF-1 (Insulin-like growth factor), Insulin, EGF (epidermal growth factor), TGFβ (transforming growth

Table 1. Relative binding affinity (RBA) of different hormones to the estradiol receptor α and β in mice (acc. to [11])

	RBA	
	ERα	ERβ
17β-Estradiol	100	100
Estron	60	37
17α-Estradiol	58	11
Estriol	14	21
Tamoxifene	7	6
Coumestrol	94	185
Genistein	5	36
β-Zearalanol	16	14

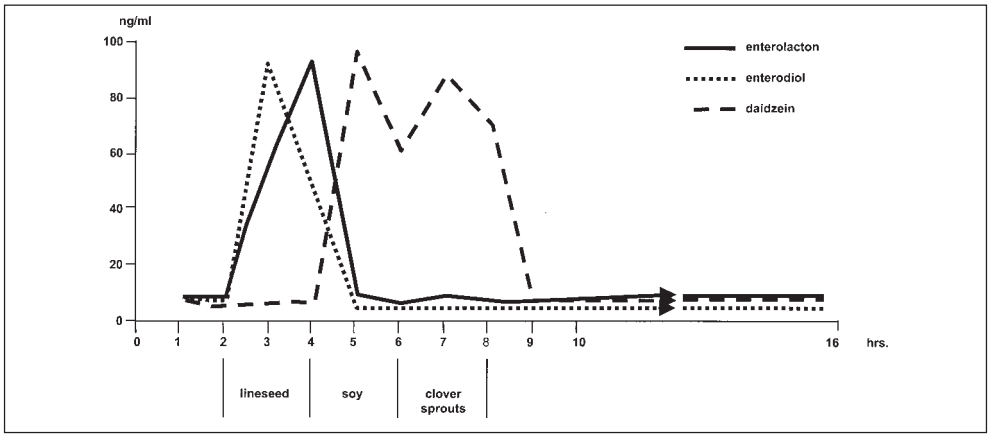

Figure 3. Plasma concentrations of phytoestrogens after different dietary supplements (acc. to [29])

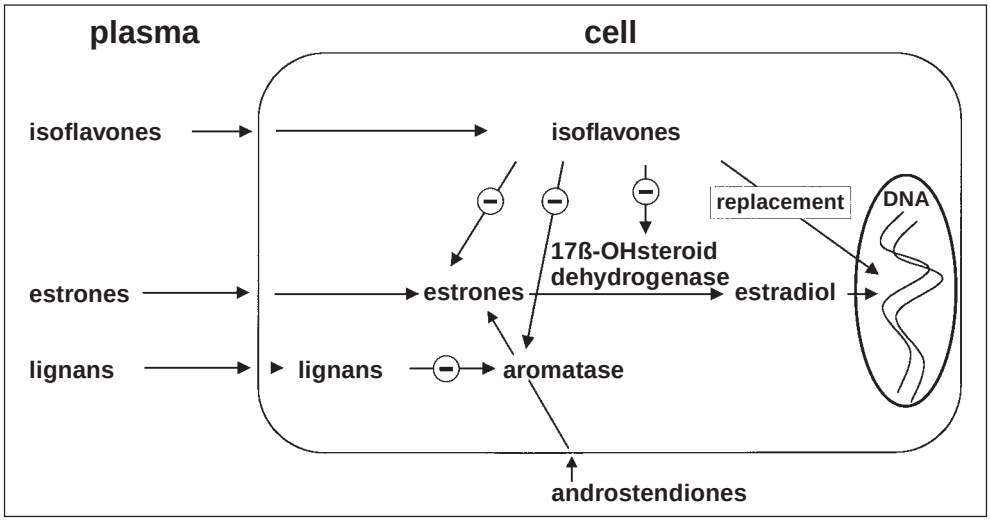

Figure 4. Interaction of phytoestrogens and steroid metabolism

factor) and FGF (fibroblast growth factor) by blocking the tyrosinkinase. Therefore the "second messenger" of the growth hormone signal chain will be established [18, 19]. Furthermore, an inhibitory effect takes place on the aromatase, 17-β-OH-dehydrogenase and 5α-reductase [20, 21].

Clinical Effect of Phytoestrogens

1. Decrease of climacteric complaints

Comparative studies of Japanese women and a comparable group of women from Manitoba (Canada) determined significant differences in the incidence of hot flushes and nocturnal sweatings during pre-, peri- and postmenopausal phases [25]. Many other studies described considerable differences of the rarely and weaker appearance of climacteric complaints (hot flushes, sweating, sleeping disorders, palpitations) in women from Malaysia, South-East China, Singapore, Japan, Hongkong and Thailand compared to women of industrialized countries. It would be too simple to transfer these effects to the activity of phytoestrogenes only. There are remarkable differences in lifestyle, nutrition, family traditions and also a completely different ethnogenetic background and the socio-cultural life of women within their societies. In Japan there is no concrete terminology for "hot flushes". Japanese women involved in their tradition and culture, consider the climacteric complaints of western women more a problem of boredom and abundance as well as a problem of losing the luxury of youth [25]. In fact, phytoestrogens are relatively weak estrogenic substance.

A soy diet lasting 4 weeks resulted in only a minor decrease of FSH. There was no increase of SHBG and only a moderate maturation increase of the vaginal epithelium. Hot flushes significantly decreased by the daily intake of soy and full grain flour [26]. Comparative studies of Japanese-oriental women, American and Finnish women could

prove that the Japanese women had a 60 to 110 times higher amount of isoflavones excreted in the urine while the concentration of estrone and estradiol was nearly identical and the amount of estradiol was slightly less (table 2) [16]. The average age in both groups (Japan and Finnland) was 50.4 years. Both groups came from rural regions, therefore the sociopsychological differences were less than assumed. The measured higher concentrations of isoflavones in Japanese women was caused by the consumption of soy products such as Tofu, Miso, Aburage, Atuage, Koridofu as well as cooked soy beans and was therefore seen as the cause of less climacteric complaints and protective effect against cancer. However, more actual placebo-controlled, randomized, double blind studies resulted no effect of 40–160 mg isoflavones to typical postmenopausal symptoms [9]. Most likely these result could be explained by the obvious effect of the placebos, the lower dosage of phytoestrogens and the intake of isoflavones but unchanged lifestyle.

2. Prevention of Osteoporosis

Asian women, esp. women from Japan and Hongkong, have a lower risk to develop osteoporosis and altogether a lower risk of hip fractures [27]. Comparative studies of hospital data showed an incidence rate of hip fractures per 100,000 U.S. citizens at an average of 2.2 times higher for men and 1.9 times higher for women compared to Hongkong [28]. Animal studies resulted in the conclusion that Genistein and Iproflavones (contain 10% Daidzein) were comparably active to conjugated estrogens in the prevention of osteoporosis [29]. Clinical studies showed an increase in bone mineral density as well as in bone mass of the lumbar spine using 90 mg soy-supplement [30]. Others found a reduction of the bone resorption markers desoxypyridinoline and telopeptide using 60 mg of soy protein per day in a placebo-controlled study over 3 months [31]. The results of all studies including the one with iproflavone showed a remarkable effect in bone resorption as well as in the way of an improvement in bone mass and also a decrease in resorption marker [31].

3. Cardiovascular Protection

Comparative epidemiological studies indicate that the incidence of cardiovascular diseases in Asian countries is 3 times lower than in industrialized countries. As shown in every study, it is certain that soy proteins significantly lower the lipid content of LDL-cholesterol and increase the HDL-cholesterol [32]. Three preparations of soy products per day with more than 30 g soy protein will reduce total-cholesterol,

Table 2. Excretion of isoflavones, phystoestrogens, and endogenous estrogens in Japanese, American and Finnish women (with western nutrition, in ng/24 h, acc. to [16])

Excretion in urine	Japanese	American	Finnish
Genistein	3,440	–	30.1
Daidzein	2,600	216	40.5
Equol	2,600	62.8	44.2
Estron (postmenopausal)	4.48	–	4.48
Estradiol (postmenopausal)	0.76	–	0.94
Estriol (postmenopausal)	4.48	–	4.44

LDL-cholesterol and triglycerides. 60–70% of the total effect is caused by phytoestrogens [24]. Another important protective effect is the reduction of the LDL-oxidation through phytoestrogens as a radical scavenger. A more differentiated view produces the following aspect:

The higher the value of serum-cholesterol, the higher the effect of the decrease of cholesterol by the isoflavones, which varies from +1% to –12% in comparison to the control study. A net decrease of cholesterol from 1–34% could be measured in men and women, as 19 studies showed. The longer the diet lasted, the better the effect [33].

Some facts concerning the clinical effects of phytoestrogens on the fat metabolism: The net effect in hypercholesterolemic women and men was significantly higher than in normocholesterolemic. This effect does not depend on the protein pattern (for example: Typ-II-A, B). The effect of isoflavones is almost equal for men as well as for women and children. There are no co-effects through certain parts of the used amount of proteins (optimum 20%) as well as the used soy preparations concerning texturized soy, fibers and phytoestrogens. All studies resulted countless variables, especially through interaction with nutrition parts and the speciality of the test protocols [34].

4. Prevention of Malignancies through Phytoestrogens

Epidemiological studies between Asian countries, esp. Japan, compared to western industrialized nations indicate a significantly lower incidence of breast-, prostate- and colon-carcinomas. First findings were from Japanese women that immigrated to the U.S., adapting the same risk of their new environment after 10 years up to 1 generation [35, 36]. Many observations pointed out that soy products, as a main source of diphenolic phytoestrogens, have the greatest importance in the malignancy protection. The Japanese consume up to 200 mg soy products per day, which is an amount of 25 to 80 mg Isoflavones daily. In western nations the daily consumption is restricted to less than 5 mg [8, 20].

Breast Cancer

Compared to vegetarians, Finnish women with breast cancer and normal nutrition are excreting a lower content of diphenols as discharge of phytoestrogens through their urine [37]. Besides the lower risk of developing breast cancer, Asian women are also developing cancer types with lower malignancy, lower grading and more noninvasive in situ-carcinomas. They have generally a better prognosis when diagnosed with cancer, less lymphatic metastasis and a lower mortality rate compared to western women [36]. Experimental tests showed specific effects like cell growth arrest of breast cancer-cell lines e.g. MCF-7 and ZR-75-1 by daidzein, genistein and biochanin-A [38–42]. Controlled studies on the subject of phytoestrogens and risk of breast cancer [43–46], mostly based on nutritional protocols, indicated a significant protection of phytoestrogens towards breast cancer.

A study of 144 patients (Table 3) showed the difference in women recently diagnosed with breast cancer and a healthy control group (matched pairs) analyzing the nutrition and also phytoestrogens in urine collected over a time span of 72 hours (measuring daidzein, genistein, equol, lignane) and blood samples (measuring estradiol and FSH) of cases with breast cancer

and healthy patients [43]. There was slightly decreased values for the excreted Isoflavones in women with breast cancer, but significantly decreased values for the lignanes enterodiol and enterolacton in urine (collected over 72 hours) which indicates that women with breast cancer have a significantly lesser nutritional intake of phytoestrogens compared to the healthy control group (see table 3).

Table 3. Phytoestrogens and breast cancer

Phytoestrogens (nmol/24 h)	Median (IQR) cases	Controls
Daidzein	782.9	913–4
Equol	97.2	108–6
Enterodiol	282.0	316.5
Enterolatone	1,973.4	3,097.7

Prostate Cancer

A lower risk of developing prostate cancer for Japanese men compared to western men is described [5, 47]. This is also attributed to phytoestrogens.

The Meaning of Phytoestrogens in Menopause Counselling

Phytoestrogens can be prescribed in different preparations.

1. *In a special diet:* Secondary plant substances are able to block free radicals, which can cause damage to the DNA and play an important role by initiating carcinomas. These secondary plant substances are contained in carotinoids, flavonoids, as colour-, scent- and aromatic substances, highly antioxidative, and more than 10,000 different substances in fruits and vegetables. Phytoestrogens are also contained in a large number of plants. Additional attributes are radical scavengers and inhibition of the carcinoma initiation as well as promotion through blockage of estradiol (Phyto-SERM) and the direct inhibition of growth factors. Especially advised is nutrition with plenty of fresh fruits, fresh vegetables, berries, full grain products and green tea (lifestyle counselling).

2. *Additional prescription of isoflavones as a nutritional substance:* Meanwhile many manufacturers are offering isoflavones, isolated from soy plants in form of a mixture of daidzein and genistein. The capsules mostly contain 17.5 up to 40 mg isoflavones. Moreover, there are preparations with isoflavones, vitamines, carotinoids, minerals and fatty acids or isoflavones with Gelée royale.

3. *Isoflavones from soy products (in health food stores):* The different content of isoflavones per soy preparation must be known and adjusted to the daily dosage.

Indication for the Prescription of Phytoestrogens

- Women with contraindication for an estrogen substitution (after metastasized, estradiol receptor positive breast cancer).
- Intolerance towards estrogens in any form and risk for coronary heart disease or osteoporosis.
- Women with increased personal risk for breast cancer combined with a

special nutrition (for example NPC = Nutritional Cancer Prevention program).

Summary

Phytoestrogens are an actual highlight in the treatment of problems during postmenopause. The outstanding results from Japan point to the sense and the high value of the phytoestrogens. However, a substitution with phytoestrogens is probably less successful without a change in lifestyle and a diet with lesser gourmet food and more physical activity as well as the awareness of a low calorie diet and a spiritually active lifestyle.

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