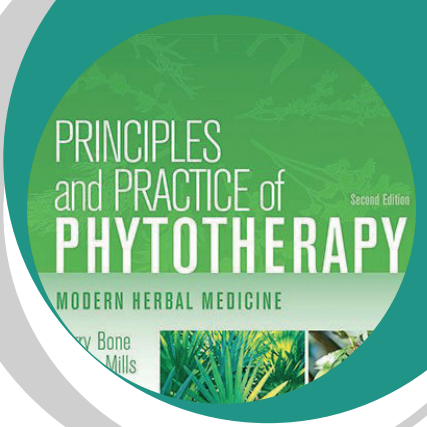
SOCIETY OF WELLNESS
NUTRITIONAL SYSTEMS



Functional Herbal Therapy and Cancer: Module 5

Phyto-oestrogens

An excerpt from Chapter Two: Principles of Herbal Pharmacology Principles and Practice of Phytotherapy, 2nd Edition

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Phyto-oestrogens are phytochemicals that have oestrogenic activity because they bear some structural similarity to 17-beta oestradiol. Compounds belonging to several phytochemical classes interact with oestrogen receptors, but research has focused on the isoflavones and lignans. Oestrogenic isoflavones, which include genistein, daidzein and their glycosides, are mainly found in members of the Leguminosae (pea family) such as soya beans and red clover. Linseed (flaxseed) is the richest source of the oestrogenic lignans enterodiol and enterolactone, which are formed by gut bacterial action on the precursor phytochemical secoisolariciresinol diglucoside (SLDG) found in the seed.

Pharmacodynamics

Interest in the oestrogenic effects of plants first arose in the scientific world when clover disease was identified in Australia in the 1940s. It was observed that infertility developed in sheep after grazing on various species of clover (*Trifolium species*). Research interest at the time focused on understanding the factors that caused clover disease, which were identified as isoflavone glycosides. It was several decades later, when results from epidemiological studies suggested that the dietary consumption of soya products might have a protective role in breast cancer, that interest in the oestrogenic properties of isoflavones was rekindled.[456]

Early studies using various animal tissues demonstrated that, while isoflavones compete strongly with oestradiol at oestrogen receptors, their stimulation of these receptors is much weaker than oestradiol.[457] In other words, they were thought to act as partial oestrogen agonists that could function as oestrogen agonists or antagonists depending on the hormonal milieu. The theory was that in a high-oestrogen environment (such as in the premenopausal woman), their displacement of endogenous oestrogens is postulated to have an antioestrogenic effect. In contrast, in a lower oestrogen environment, as in the postmenopausal woman, they were expected to provide a net oestrogenic effect. While this theory still has some relevance, the situation is now known to be more complex.

There are two isoforms of the (o)estrogen receptor, ERalpha and ERbeta. Their distribution and density varies, depending on the target tissue. The existence of an oestrogen receptor was first reported in the early 1960s. In 1996, an additional ER was discovered. This receptor was designated ERbeta and consequently the originally discovered receptor was renamed ERalpha.[458] Both ERalpha and ERbeta may coexist in a tissue and relevant proportions often vary. ERalpha is the dominant receptor in the adult uterus. ERbeta is expressed in high levels in prostate, salivary glands, testis, ovary, vascular endothelium, bone, smooth muscle, certain neurons in the central and peripheral nervous system and the immune system.[459] Both isoforms are present in the female breast and reproductive tissue.[460]

Each of the oestrogen receptors may influence the function of the other. The effects of substances that interact with receptors when both forms are present are complex.[460] It is hypothesised that ERbeta may modulate, even antagonise, the actions of ERalpha.[461] For example, in the breast ERalpha and ERbeta exhibit opposing functions in cell proliferation: ERalpha promotes epithelial proliferation, whereas ERbeta has a restraining influence.[462] Other studies suggest several possible interactions for the two receptors: antagonistic, synergistic and sequential.[463]

The female sex hormones (the oestrogens) consist of 17beta-oestradiol, oestrone and oestriol. Oestradiol binds to ERalpha and ERbeta with equal affinity.[464] The isoflavone phyto-oestrogen genistein has greater binding affinity for ERbeta than ERalpha. This preferential binding of genistein to ERbeta indicates such isoflavones probably produce pharmacological and clinical effects quite distinct from oestrogens. In particular, they tend to exhibit antiproliferative activity.[464] Other isoflavone phyto-oestrogens also bind more strongly to ERbeta.[465]

Furthermore, isoflavones bind to ERs with a much lower affinity than oestrogens and therefore produce less potent responses.[466,467] However, they initiate greater gene transcription of ERalpha compared to ERbeta.[467]

As noted above, isoflavones and other phyto-oestrogens are thought to compete with oestradiol for binding and activation of ERs,[460] potentially decreasing the effect of oestradiol in vivo in some circumstances. However, there have been some in vitro results to the contrary.[468] The effect depends on the doses (of both phyto-oestrogens and oestradiol). In a pilot study, a soy protein isolate containing isoflavones (120 mg/day) taken for 6 months did not prevent oestradiol-induced endometrial hyperplasia in postmenopausal women.[469] (But interestly, there was also no additive effect.)

Research on selective (o)estrogen receptor modulators (SERMs) such as tamoxifen has provided more insights into how non-steroidal molecules can interact with the oestrogen receptor. A summary of the knowledge thus far is that once a SERM binds to the ER it causes a change in its shape. This allows recruitment of co-activators if it is destined to elicit an oestrogenic response, or co-repressors if its response is anti-oestrogenic. The binding of the coregulatory molecules leads to the activation of the promoter sequence of the oestrogenic responsive gene. Isoflavones have been proposed as natural SERMs.[465]

Studies have found that isoflavones have both agonistic and antagonistic effects, though they are strong ER-beta agonists and weak ER-alpha agonists. The presence of a correctly positioned phenolic ring and also the distance between the two opposing phenolic oxygens in the isoflavones structure is similar to that of 17 beta-oestradiol. This similarity allows the isoflavones to bind to the ER, effectively displacing 17 beta-oestradiol. This action may help explain how phytoestrogens help protect against breast cancer, because ER-beta inhibits mammary cell growth as well as the stimulatory effects of ER-alpha.[465] As with the SERMs, studies have shown that the recruitment of coregulatory molecules may be important in determining the function of phyto-oestrogens. In particular, isoflavones appear to trigger selectively ER-beta transcriptional pathways, especially transcriptional repression.[465]

The in vitro and in vivo studies on phyto-oestrogens can be divided into 3 general categories: chemoprevention, treatment effects and lifetime exposure studies (in vivo only).[465] This literature is so vast that a thorough review is beyond the scope of this primer. However, one aspect worth emphasising is that isoflavones have been shown to prevent cancer or inhibit cancer cell lines in a variety of models.[470,471] Another is that isoflavones exert favourable effects in vivo and in vitro on parameters relevant to cardiovascular risk including insulin resistance, lipid peroxidation, haemostasis and endothelial function.[472] Probably of greater relevance are the many human studies of the impact of phyto-oestrogens on various health outcomes or parameters. Some of the key findings of these studies are outlined below, in a brief review of reviews.

A meta-analysis concluded that soya isoflavone consumption was associated with a reduced risk of breast cancer, but this protective effect has only been observed in studies in Asian populations.[473] Soya isoflavone intake was also inversely associated with the risk of breast cancer recurrence. Moderate consumption of isoflavones in diet does not increase the risk of breast cancer recurrence in Western women who have survived breast cancer, and Asian breast cancer survivors exhibit better prognosis if they continue consuming a soya diet.[474]

Results from Asian epidemiological studies suggest a beneficial impact of isoflavones on bone health.[475] However, clinical trials have yielded conflicting results on bone mineral density and turnover markers that may reflect on differences in study parameters, type and dose of phyto-oestrogen used and the variable metabolism of isoflavones, especially in terms of equol production.[475]

A systematic review and meta-analysis of soya isoflavones versus placebo in the treatment of menopausal vasomotor symptoms concluded that there was a significant tendency in favour of soya.[476] Another meta-analysis found that consumption of 30 mg/day of soya isoflavones (or at least 15 mg genistein) reduced menopausal hot flushes by up to 50%.[477] Individual responses in menopause could be determined by bioavailability and metabolism, especially to equol.[478]

The published effects of isoflavones on circulating hormones in pre- and post-menopausal women were the subject of a systematic review and meta-analysis.[479] In all, 47 studies were included. In pre-menopausal women, meta-analysis suggested that isoflavone consumption did not affect

levels of oestradiol, oestrone or sex hormone binding globulin (SHBG), but did significantly reduce FSH and LH (by about 20%). In post-menopausal women there was no impact of isoflavones on any of these hormones, although there was a 14% non-significant increase in oestradiol.

Epidemiological studies indicate that soya isoflavone consumption is possibly protective against prostate cancer.[480] There is also some suggestion from clinical trials that isoflavones can slow the disease progression.[481]

Isoflavone intake appears to confer cardiovascular benefits that may or may not be related to their phyto-oestrogenic properties. One systematic review identified improvement in arterial stiffness[482] and another used meta-analysis to establish a small reduction in blood pressure.[483] Soya isoflavone intake improved flow mediated dilation (an indicator of cardiovascular health) based on a meta-analysis of randomised, controlled clinical trials.[484]

Intestinal metabolism of isoflavones to their aglycone form is crucial for ensuring bioavailability and therapeutic activity. In other words, the intestinal microflora is pivotal in the metabolism of oestrogenic isoflavones. Individual differences in intestinal microflora have been proposed as a possible reason why there is some inconsistency in the clinical effects of isoflavones.[485] In particular, daidzein is further metabolised by gut microflora to produce equol, a more active oestrogenic compound. There are large individual variances in the capacity to produce equol and hence possibly a therapeutic effect. Dietary fat consumption is known to reduce this capacity.[486] On the other hand, dietary supplementation with fructo-oligosaccharides such as inulin is known to increase equol.[487]

In contrast to the isoflavones, research on the oestrogenic lignans enterolactone and enterodiol has not been as extensive. Initial interest in these compounds resulted from the observation in the early 1980s that their urinary levels in menstruating women exhibited a cyclic pattern during the menstrual cycle, with maximum excretion in the luteal phase.[488] The relatively high concentrations of these new lignans in urine, their cyclic pattern of excretion and their increased excretion in early pregnancy suggested that they were a new class of human hormone. It transpired what had been found was a plant chemical modified by bacteria in the human digestive tract.[488] Selective antibiotic administration to humans suppressed oestrogenic lignan formation.[488]

Enterolactone, like isoflavones, inhibits oestradiol-stimulated breast cancer cell growth in vitro.[489] Lignan ingestion has been associated with increased concentrations of SHBG, but this was not confirmed in clinical studies.[489,490,491] Linseed intake by normal premenopausal women was consistently associated with longer luteal phase (LP) lengths and higher ratios of LP progesterone to oestradiol.[489] These findings may reflect favourably on breast cancer risk. An earlier animal study found that linseed supplementation reduced early risk markers for breast cancer.[492] Dietary studies and assays of urinary lignans in postmenopausal women have found that lignan excretion is significantly lower in the urine of women with breast cancer,[493] although the situation is not as clear from recent prospective cohort studies.[494]

In more recent times, the health effects of linseed and SLDG supplementation have been investigated in a number of clinical trials. Results of trials involving whole linseed are confounded by its content of mucilage and fixed oil (rich in omega-3 fatty acids), especially the trials investigating its impact on blood lipids or glucose.

The following is obviously not a comprehensive review of the clinical data for linseed and its lignans and focuses on hormonal effects. Linseed (25 g/d) altered oestrogen metabolism more than soya (25 g/d), and significantly shifted oestrogen metabolites to less biologically active forms (2-hydroxyoestrone) in post-menopausal women.[495] This was confirmed in other clinical trials at 10 g/d, in pre- and post-menopausal women.[496,497] At 10 g/d linseed decreased endogenous oestrogen levels and increased prolactin in post-menopausal women.[491] Linseed supplementation does not appear to benefit menopausal symptoms, although more studies are necessary.[498]

Adverse reactions and toxicology

Epidemiological studies have not found adverse effects from the dietary consumption of isoflavones or lignans. However, when quantities well above dietary exposure are used in a therapeutic context, adverse events might well ensue. As noted above, the phyto-oestrogens are partial oestrogen agonists similar to the drug tamoxifen. Research has shown that while tamoxifen has potential for preventing breast cancer and cardiovascular disease, its use increases the risk of developing endometrial cancer. Moreover, concurrent intake of phyto-oestrogens and tamoxifen may reduce the therapeutic effects of the drug in breast cancer. For this reason, and because of the observation that phyto-oestrogens can stimulate the growth of oestrogen-dependent tumours in some circumstances, intake of these phytochemicals should be limited to dietary levels in women with oestrogen-sensitive breast cancers until clinical studies suggest otherwise. Such data are beginning to emerge (see the discussion on breast cancer risk below).

Controversy has arisen over the possible adverse effects of soya-based infant milk formulas. One earlier study found that infant exposure to isoflavones from these products was relatively much greater than levels shown to alter reproductive hormones in adults.[499] It was suggested that further studies of possible developmental effects are highly desirable.

On the other hand, studies in males have found no indication of adverse effects. For example, a 2010 review found no evidence from rodent studies and 9 clinical trials that isoflavone intake impacted oestrogen levels in males. Clinical evidence also indicates no impact on sperm and semen parameters in men.[500] In addition, a meta-analysis that included 15 placebo-controlled clinical trials found that neither soya nor isoflavones altered testosterone parameters in men.[501]

While the epidemiological evidence suggests that a lifetime of moderate to high isoflavone intake is protective against breast cancer incidence in women, the impact of such intake commenced later in life is uncertain. Concerns have been raised that a later intake of high levels of phyto-oestrogens might in fact increase the risk of oestrogen-associated cancers. However, these fears are not supported by the available data.

Mammographic density may be a predictor of breast cancer risk. Women with a high percentage of dense tissue are at 4-fold greater risk of breast cancer. Mammographic parenchymal patterns assess the variation between radiological appearances: fat appears dark, epithelium and stroma appear light. Percent density is the ratio of dense area and breast area. A meta-analysis of randomised, controlled, clinical trials on soya and red clover (*Trifolium pratense*) isoflavones found no impact on mammographic breast density in post-menopausal women.[502] However, isoflavones may cause a small increase in breast density in pre-menopausal women, which is of uncertain clinical relevance. An epidemiological study in 3315 Chinese women in Singapore found no significant impact of soya intake on breast density, with the suggestion of a possible reduction.[503]

The results of a case-control study involving nearly 800 participants conducted in New Jersey and published in 2009 suggest a reduction in endometrial cancer risk with intake of foods containing isoflavones (but not lignans) in lean women. Four case-control studies prior to this reported conflicting results for the role of dietary phyto-oestrogens in endometrial cancer risk, although there was a suggestion of a reduced risk for soya foods.[504]

A Cochrane meta-analysis of randomised, controlled clinical trials published to March 2007 investigating relief of menopausal symptoms found no evidence that food or supplements containing phytoestrogens caused estrogenic stimulation of the endometrium when used for up to two years. Trials of women who had breast cancer or a history of breast cancer were excluded.[505] The dosage of isoflavones was 50 to 120 mg/day, with many of the soya products containing soya protein.

One concern is that isoflavones may adversely affect thyroid function and interfere with the absorption of synthetic thyroid hormone. A 2006 review evaluated the relevant literature describing the effects of soya on thyroid function.[506] In total, 14 trials (thyroid function was not the primary health outcome in any trial) were identified where the effects of soya foods or isoflavones on at least one measure of thyroid function was assessed in presumably healthy people. Eight involved women only, four involved men, and two both men and women. With only one exception, no effects or only very modest changes were noted in these trials. Collectively, the findings provide little evidence that soya foods or isoflavones adversely affect thyroid function in euthyroid, iodine-replete individuals. In contrast, some evidence suggests that soya, by inhibiting absorption, may increase the dose of thyroid hormone required by hypothyroid patients. In addition, there remains a theoretical concern based on in vitro and animal data that isoflavone intake by individuals with compromised thyroid function and/or marginal iodine intake may increase the risk of developing clinical hypothyroidism.

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