Phytoestrogens Definition and Origin

Subjects: Endocrinology & Metabolism

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Phytoestrogens are literally estrogenic substances of plant origin. Although these substances are useful for plants in many aspects, their estrogenic properties are essentially relevant to their predators. As such, phytoestrogens can be considered to be substances potentially dedicated to plant–predator interaction.

phytoestrogens nutrition health cardiovascular isoflavones coumestrol resorcylic acid lactone enterolignans prenylflavanone reproduction

1. Definition and Relative Potencies

Phytoestrogens have estrogenic potencies due to their structure, which mimics that of estradiol. The common feature of all phytoestrogens, as is seen in **Figure 1**, is basically the presence of at least two hydroxyl functions in opposite positions on the molecule and usually at a distance of 10 angstroms, as in estradiol.

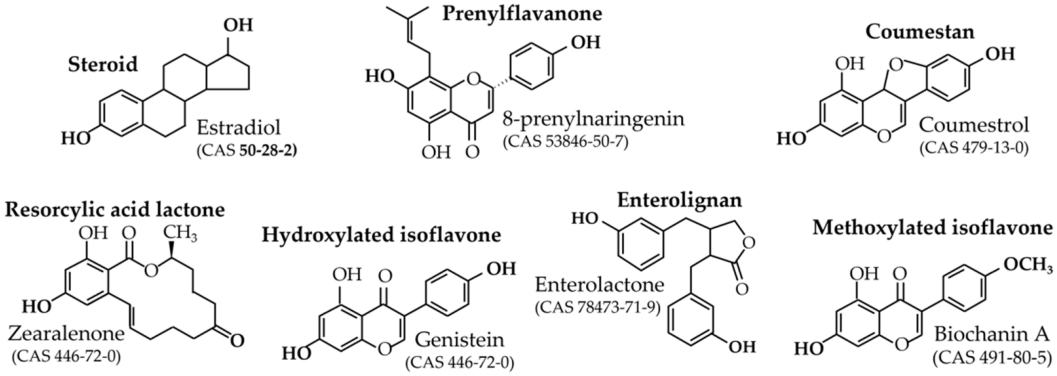

Figure 1. Chemical structures of the main phytoestrogens and their precursors beside the molecular structure of estradiol.

These hydroxyl groups are responsible for the interaction of phytoestrogens with the ligand binding domain of estradiol receptors [1]. Currently, three estradiol receptors are considered. The first two receptors are canonical estradiol receptors ERα and ERβ, which act mainly via a nuclear interaction with a DNA palindromic sequence called ERE [2]. However, thanks to a palmitoylation at C451A-ERα site [3], ERα can also be present just below the cell membrane, bound to caveolin, and is able to react to low concentrations of lipophilic xenoestrogens. At this location, ERα activates intracellular phosphorylation pathways that are stimulated within a few seconds, contrarily to the nuclear pathway. Several pathways have been described so far, including PI3K/Akt, Src/ERK1/2, and NFκB [4]. See **Figure 2**.

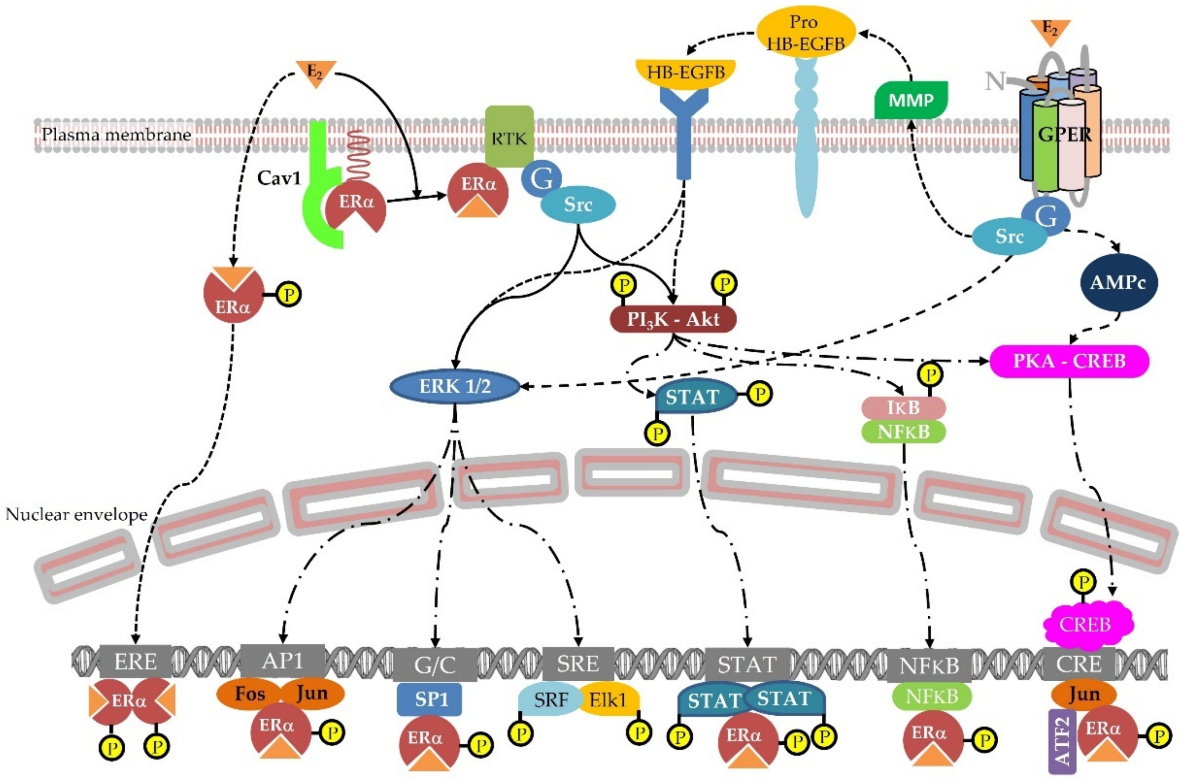

Figure 2. Cellular pathways triggered by estradiol via the nuclear ER, Membrane ER, and membrane GPER.

The third estrogen receptor is called GPER (previously GPR-30) and belongs to the rhodopsin receptor family, counting seven transmembrane domains. It is associated with G proteins bridging molecules, and it activates at least three different pathways depending on the ligand concentrations. One pathway is cAMP-dependent and reacts to 1 µM of the agonist G1, while another relies on the Src/EGFR pathways and responds to 0.01 µM of G1 [5]. Considering these different receptors, their different affinities for estrogens, their different cell locations, their different activation modes, and, finally, their different tissue distributions, it can easily be understood that the effects of estradiol—and also estrogen mimetics—can be very complex and do not follow a linear dose–response curve. Indeed, according to their specific affinities for the different receptors, some xenoestrogens exhibit bell-shaped dose–response curves, such as soy isoflavones, or U-shaped dose–response curves, such as bisphenol A. These effects can be observed at either the cell levels or the individual levels, i.e., *in vivo* [6]. Likewise, genistein (soy isoflavone) epigenetic effects are different according to the dose tested. *In vivo*, at dietary dosage in agouti mice models, genistein is a methylation activator [7], while *in vitro* at pharmacological doses it exerts demethylation effects [8].

Here, only compounds with an estrogenic effect possibly observed in humans at plausible exposure are taken into account. This means that the present document deals with the prenyl-flavanone 8-prenylnaringenin and its precursor isoxanthohumol, coumestrol, the resorcylic acid lactones zearalenol and zearalenone, hydroxylated isoflavones genistein, daidzein, glycitein, the metabolite equol, and the enterolignans enterodiol and enterolactone. Finally, this research also concerns the methoxylated isoflavones that can be hydrolyzed into hydroxylated parent

compounds. See **Figure 1** for the structures of these main compounds and **Figure 3** for their in vitro estrogenic potencies, sorted from the highest to the lowest.

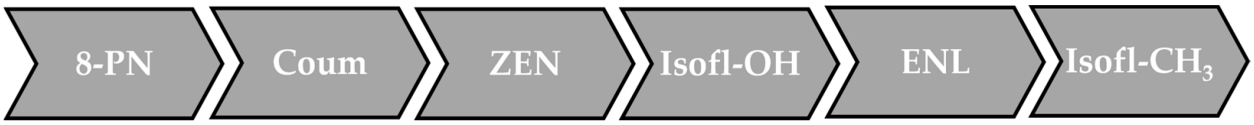

Figure 3. *In vitro* relative potencies of phytoestrogens. The scale does not take into account the metabolism and the bioavailability of the compounds. 8-PN: 8-prenylnaringenin; Coum: coumestrol; ZEN: zearalenone and zearalenol; Isofl-OH: hydroxylated isoflavones (C4′ position), *i.e.*, genistein, daidzein, equol and glycitein; ENL: enterolignans, *i.e.*, enterodiol and enterolactone; Isofl-CH3: methoxylated isoflavones (C4′ position), *i.e.*, biochanin A and formononetin.

In addition to these compounds, others have been shown to exhibit estrogenic effects *in vitro* or in animals when tested at pharmacological doses. These include apigenin, naringenin, quercetin, and resveratrol, etc. This research will not treat these substances.

Estradiol is essential for many different physiological functions such as reproduction, growth, food digestion and metabolism, mood expression, energy balance, core temperature management, and bone accretion, etc. Therefore, estrogens can have beneficial effects in certain physiological statuses and are used as drug-replacement therapies in several menopausal disorders. In parallel, the over-dosing of estradiol or estradiol analogues (ethynyl-estradiol, for instance) are used medically as contraceptive treatments. Therefore, the duration and the dose of estrogen exposure are crucial to consider for avoiding potential adverse effects, especially on reproduction or reproductive tissues. Finally, if Asian populations are nowadays largely exposed to some phytoestrogens, the lack of strict control populations does not allow for the deciphering of the precise consequences of such exposures.

2. Origin and Role in Plants

The different phytoestrogen compounds considered in this research can be classified into three groups:

- Mycotoxins;
- Phytoalexins;
- Non-estrogenic native compounds requiring gut-flora metabolism to become active.

This late category includes equol and enterolignans, which are estrogenic but are generated by the cooperation of human gut-bacteria clusters [9][10]. Given that not all consumers harbour the relevant bacteria species, these compounds will not be present and active in all consumers. The origin of their precursors can be named (and will be mentioned later), but ingesting these plant sources will never guarantee an exposure to estrogenic metabolites.

- Prenyl-flavanones

The prenyl-flavanones 8-prenylnaringenin, 6-prenylnaringenin, and isoxanthohumol are secreted by the lupulin glands of hops' inflorescences. Their role in plants seems to be poorly documented, while their estrogenic activities, which are essentially provided by 8-prenylnaringenin, are often cited. However, Yan et al., [11] recently reported a significant anti-fungal activity of isoxanthohumol on *Botritis cinerea*. This means that the prenylflavanones can act as phytoalexins in hops.

- Coumestrol

Coumestrol is essentially produced in alfalfa, *Medicago sativa* (up to 36 mg/100 g Dry Mater (DM) in a Stamina 5 cultivar), and clover (14.079 mg/100 g DM), where it acts as a phytoalexin. To a lesser extent, it can also be found in mungo beans (0.932 mg/100 g DM), pinto beans (1.805 mg/100 g DM), kala chana seeds (6.130 mg/100 g DM), and in split beans (0.812 mg/100 g DM) [12]. In all cases, the pulses are considered raw, and cooking in water removes the glycosidic forms of coumestrol which are majoritarian. Such a treatment was previously used to reduce the toxic effects of alfalfa extracts on livestock reproduction [13]. In alfalfa, coumestrol is produced in response to an infestation by *Pseudopeziza medicaginis* or by *Stemphylium vesicarium* [14]. In clover, it may be present in some white clover cultivars such as Sonja, and its concentration increases when the fungus *Pythium ultimum* is inoculated [15]. It may also be present in soy; however, according to the literature, its presence is not systematic and may also be linked to a pathogenic fungus infestation. In clover and alfalfa, it is thought to play a role in the plant symbiosis with arbuscular mycorrhizae and rhizobium bacteria, which colonize plant roots to form nitrogen-fixing nodules [12][15].

- Resorcylic acid lactones

The estrogenic resorcylic acid lactones are the mycotoxins zearalenone and zearalenol types α and β. All are produced by fungi of the *Fusarium* family and develop on maturing corn, wheat, barley, rye oats, soybeans, sorghum, peanuts, and other food and feed crops, both in the field and on grains during transportation or storage. Zearalenone and zearalenol are mainly produced by *Fusarium graminearum* and *F. semitectum* [12]. Due to its structural similarity to naturally occurring estrogens, zearalenone is an estrogenic mycotoxin that induces obvious estrogenic effects in animals [16]. Zearalenone and zearalenol productions are favoured by high-humidity and low-temperature conditions. Zearalenone is stable in food under regular cooking temperature; however, it can be reduced under intense heating. In a human diet, the main sources are grain milling products, *e.g.*, breakfast cereals, breads, and rolls. These mycotoxins are carefully managed at harvest and human exposure remains low. Efsa monitors the zearalenone and zearalenol levels in cereals and food. A tolerable daily intake (TDI) has been fixed at 0.25 µg/kg/day. This level includes zearalenone, zearalenol, and their metabolites, *i.e.*, their glucuro- and sulfo-conjugates.

- Isoflavones

Isoflavones are present in several legumes at different concentrations. Soybeans, alfalfa, clover, and kudzu root (*Pueraria* sp.) are those containing the highest amounts of hydroxylated isoflavones or their precursors: the

methoxylated isoflavones on the 4′-carbon (biochanin A and formononetin). Moreover, lentils, chickpeas, mungo beans, and broad beans contain an amount of 10 to 100 times less of isoflavones. Kudzu (*Pueraria lobata* or *P. mirifica*), a Chinese medicinal plant, also contains high amounts of genistein and daidzein in combination with puerarin. The ratio of genistein and daidzein are inverted in kudzu when compared to soy. This will be discussed later. Isoflavones also play as an attractant of arbuscular mycorrhizae and rhizobium bacteria in several pulses, including soy [12]. The contamination of a soy strain with the fungus *Diaporthe phaseolorum* f. sp. *meridionalis* induced the accumulation of isoflavones (genistein and daidzein), pterocarpans (glyceolins), and flavones (apigenin and luteolin) via the nitric oxide synthase pathway [17]. According to some authors, isoflavones also play a role as phytoalexins, preventing insect attacks in combination with UV resistance in the plant [18].

- Enterolignans

Finally, enterolactone and enterodiol are produced from seccoisolariciresinol diglucoside (SDG) by the gut flora of certain consumers [9]. Other lignans were shown to lead to estrogenic-enterolignan formation, namely, seccoisolariciresinol, lariciresinol, matairesinol, pinoresinol, syringaresinol, sesamin, sesamolin, and medioresinol [12]. Lignans are considered moieties of lignin, whose role is to provide a rigid structure to many plants, including cereals. These compounds are also present in seeds. Although lignans are known to be present in fruits and vegetables, the main source of SDG is known to be linseeds, also called flaxseeds [19].

- 3. Aromatic and Medicinal Plants

Certain aromatic or medicinal plants (herbal teas or essential oils) also exert endocrine effects, in particular on metabolic functions and reproductive functions. In 1975, Farnsworth reported a long list of plants that had long been used in Western countries as anti-fertility agents [20][21], and 60% of them contained phytoestrogens, isoflavone-type phytoestrogens, or coumestrol. Experimental studies have identified preovulatory, pre-implantation, and post-implantation anti-fertility mechanisms induced by other plant substances affecting the hypothalamic–pituitary and female reproductive organs. Lithospermic acid, m-xylohydroquinone, coronaridine, rutin, and rottlerin also have anti-fertility properties [20][21]. However, certain volatile oils, such as quinine, castor oil, and sparteine, are considered abortifacients with toxic side effects on the foetus independent of an estrogenic mechanism [20][21][22]. Contraceptive plants contain terpenoids, alkaloids, glycosides, phenols, and other compounds which interfere with sex receptors or steroid hormones. Not all mechanisms are related to an estrogen-type mechanism; some are related to an anti-androgen-type effect. Many of them (*Polygonum hydropiper* Linn, *Citrus limonum*, *Piper nigrum* Linn, *Juniperis communis*, *Achyanthes aspera*, *Azadirachta indica*, *Tinospora cordifolia*, and *Barleria prionitis*) act by an anti-zygotic mechanism [23]. As an example, the contraceptive properties of the neem leaf oil (*Azadirachta indica*) is due to an estrogenic compound, Azadirachtin A [24], and an anti-androgenic compound that disrupts spermatogenesis in men [25].

Medicinal plants displaying estrogenic effects are used in the treatment of acute menopausal syndrome: mainly hot flushes, insomnia, vaginal atrophy, and osteoporosis, [26][27] but also mood and anxiety [28]. Estrogenic effects of aromatic or medicinal plants have often been established in clinical observations and demonstrated experimentally on the basis of plant extracts [29][30]. Therefore, further studies are required to reinforce data about their bioactive

compounds beyond isoflavones, lignans, and coumestans. Fennel (*Foeniculum vulgare*), fenugreek (*Trigonella foenum-graecum*), lemon balm (*Melissa officinalis*), sage (*Salvia officinalis*), rosemary (*Rosmarinus officinalis*), and even black cohosh (*Cimifiga racemosa*) owe their estrogenic effects to polyphenols or terpenes. Thus, sage (*Saltiva officinalis*), traditionally used to suppress hot flushes and stimulate cognitive faculties in postmenopausal women, owes its effects to a glycosylated flavonoid (luteoline-7_0-glycoside) also found in other medicinal or aromatic plants (such as oregano, chasteberry *Vitex rotundifolia*, and *Vitex Agnus-castus*). The estrogenicity of terpenes and terpenoids is mediated through alpha estrogen receptors, but it is still poorly investigated [31][32]. Plants containing estrogenic terpenes and terpenoids are also used in traditional medicine in the treatment and prevention of hormonal cancers and in food supplements to correct the symptoms of menopause and/or prevent cardiovascular, immunological and/or inflammatory disorders. These molecules are particularly concentrated in the essential oils of medicinal plants including clary sage, peppermint, chamomile, and niaouli [33][34]. A recent *in vitro* study, having examined the estrogenic potency of several medicinal plants by using a human placenta model, points to anethole as one of the most estrogenic molecules [35]. Anethole is a phenylpropene that confers estrogenic effects to fennel and other Apiaceous plants (such as star anise and cumin) that are widely present in traditional medicine or have culinary uses in many countries as spices or seed teas; they are used for their beneficial effects on digestion, intestinal spasms, and premenstrual symptoms, or to stimulate lactation.

Fennel (*Foeniculum vulgare*) deserves special attention because of its growing consumption in different forms around the world (as a vegetable, herbal tea, or in supplements). Beneficial effects on menopausal syndrome have been established by a clinical study conducted in Iran on ninety postmenopausal women (45–60 years old): a twice-daily intake of fennel (2 × 100 mg, n = 45) for four weeks was sufficient to reduce symptoms of menopause (hot flushes, fatigue, sleep disturbances, vaginal dryness, anxiety, and irritability) *vs*. the placebo group (n = 45) [36]. On the other hand, a regular intake of fennel seed teas in early age in order to soothe intestinal spams occurring in babies may be a cause of premature thelarche or could advance the age of puberty in young girls [37][38][39].

Although the data relating to these plants and the molecules they contain have been expanding in recent years, they are still too incomplete or controversial to allow quantitative indications to be drawn. For this reason, this research will not focus on the phytoestrogens conveyed by medicinal plants. Nevertheless, due to their use as ingredients in dietary supplements, the reader should be warned that the regular intake of these plants, and particularly at high dosages via food supplements, may lead to similar or even superior effects to those induced by the dietary intake of phytoestrogens and hence their therapeutic use [26][40][41].

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