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Research Studies on Mammary Gland Development and Phytoestrogens

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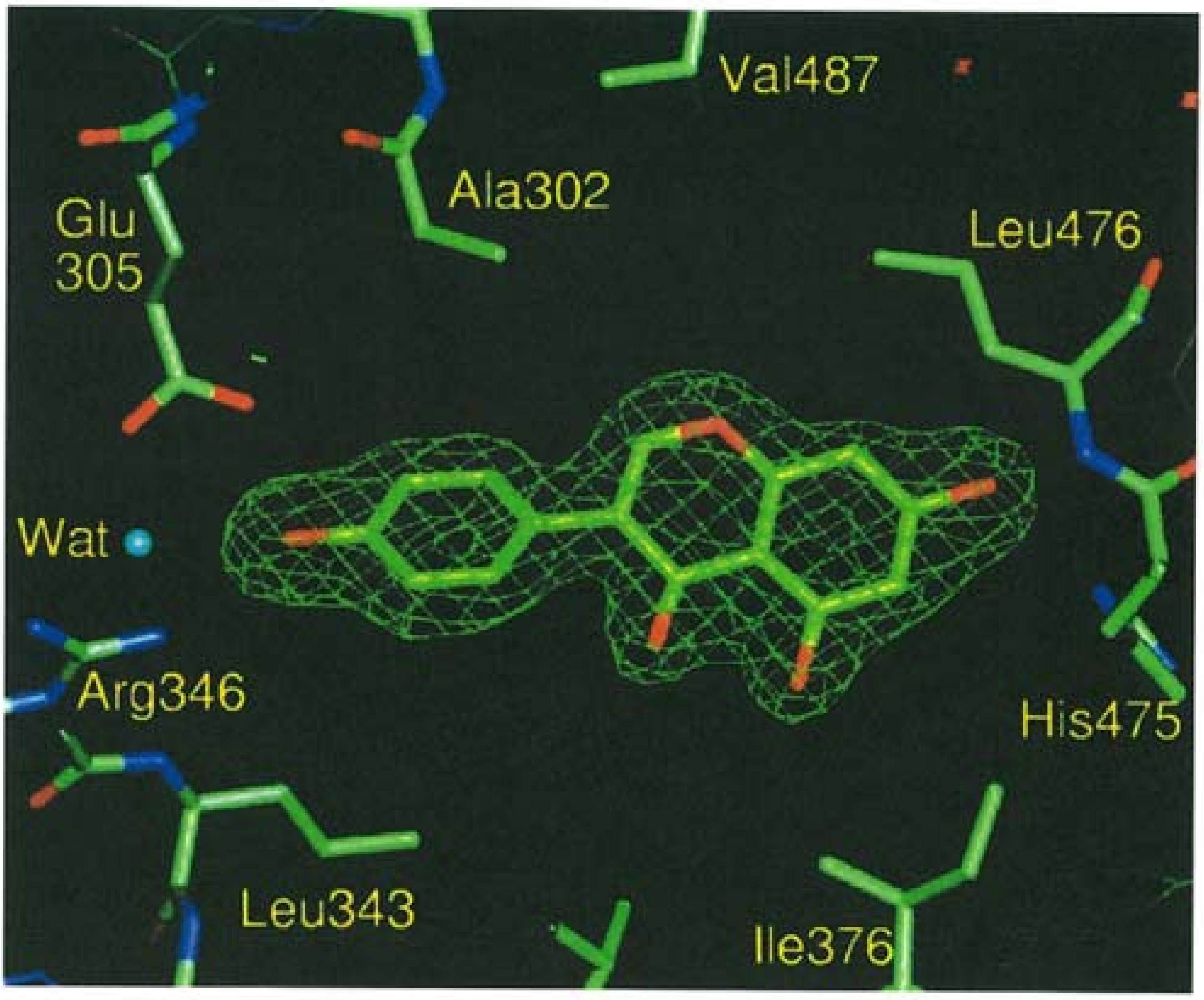
Introduction

In literature no data can be found on the specific effects sorted by phytoestrogen with respect to breast development and enlargement except for the unwanted breast development in male, a phenomenon called gynecomastia. Since phytoestrogen posses significant estrogenic properties and therefore may act like endogenous estrogens this mini review will shortly introduce the natural mammary gland development followed by an introduction on the phytoestrogens themselves.



Artificial representation of genistein in the estrogen receptor

Normal development from foetal life through adolescence [1].

Early in foetal life epithelial cells, derived from the epidermis in the area that will later become the areola, proliferate into the underlying mesenchyme. In the human, 20 or so short cords are formed and eventually develop lumina to become ducts that are connected to the nipple and open to the surface. Surrounding the ducts is a network of myeloepithelial cells, destined ultimately to serve in the expulsion of milk. In the later stages of gestation the blind ends of the ducts bud to form alveolar structures and a small amount of secretory activity occurs. This results in the formation of so called witch's milk, which can be expressed from the breasts of most full term infants for 1 7 weeks thereafter. Subsequently, with the decline of circulating foetal prolactin and in the absence in the infant of estrogen and progesterone of placental origin, the breast regresses to a resting stage composed of a small number of scattered ducts. Such regression may not be complete until months after birth.

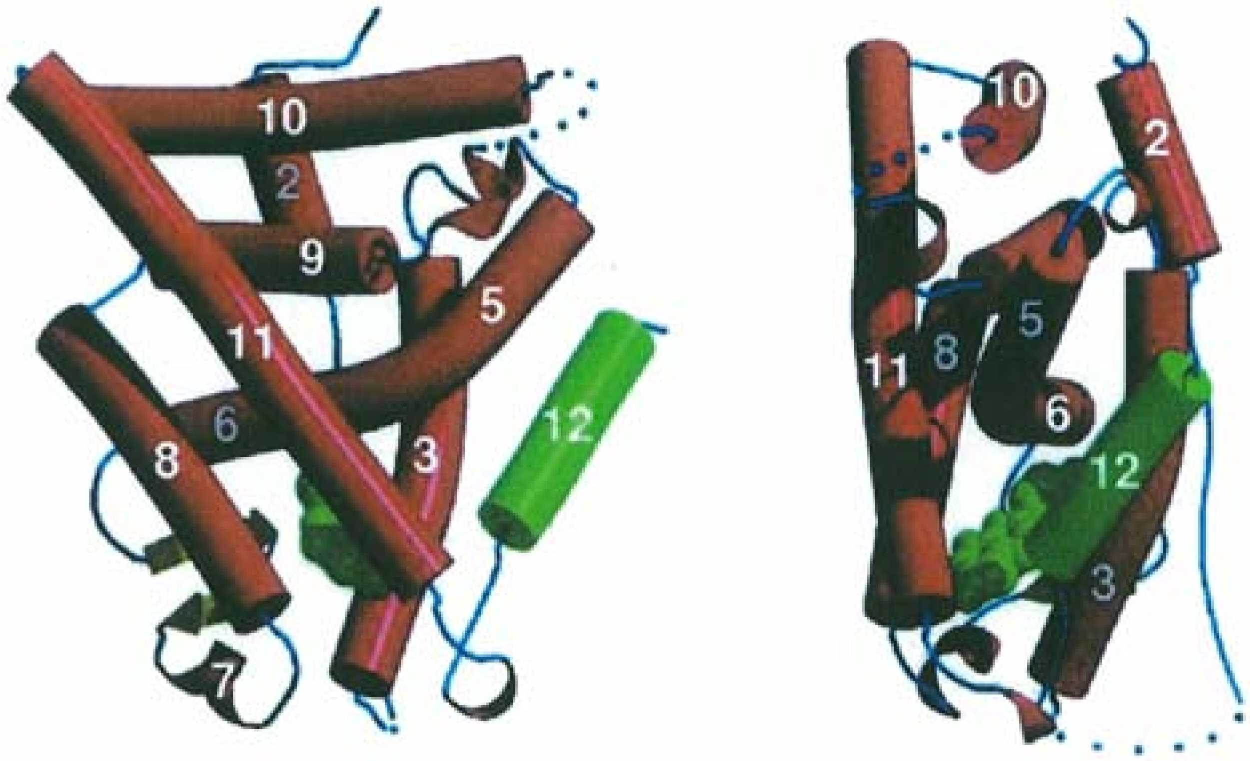
In several species there is sexual dimorphism in the embryogenesis of the excretory duct system. In human beings there does appear to be any histologic or functional difference in the breasts of girls and boys before the onset of puberty. Shortly before human menarche, with increased secretion of ovarian estrogen, lengthening and branching of the ducts begin in the female breast, accompanied by budding of the terminal ends and increased formation of underlying fat and connective tissue. With the onset of menses, further growth takes place in cyclic fashion, some regression occurring at the end of each cycle.

Mammary gland development is under multihormonal control involving functional interplay between ovary and pituitary. The co ordinated action of estrogen, prolactin, progesterone, glucocorticoids, insulin, growth hormone, and thyroid hormone are involved. Classical endocrine ablation / hormone replacement studies demonstrate that ovarian estradiol is critical to the major phases of mammary development; ductal elongation during puberty and lobuloalveolar development during pregnancy. However the effects of estrogens on mammary growth appeared to require a functional pituitary gland. Therefore, estrogens may contribute to mammary development by acting directly on the mammary gland and / or by indirect endocrine action on the hypothalamic / pituitary / gonadal axis. The alveolar development is also controlled by prolactin and progesterone; lactation is mediated by prolactin.

Estrogen, as said before, is ineffective in the absence of anterior pituitary hormones. Administration of estrogens to intact animals promotes the formation if lactotropic cells in the pituitary and increases the secretion of prolactin and growth hormone. In the presence of these two hormones, estrogen acts to promote ductal development in the breast. Although estrogen prepares the breast for eventual milk formation, it also acts to inhibit lactation and in this respect acts as a prolactin antagonist. It is largely because of the high levels of circulating estrogen and progesterone that women do not lactate during pregnancy, and the abrupt withdrawal of these two hormones with the termination of pregnancy triggers the onset of lactation. Estrogen also acts to regulate the number of prolactin receptors in breast tissue.

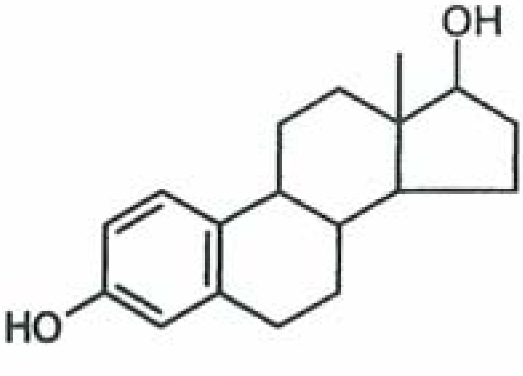
Phytoestrogens

Phytoestrogens are a diverse group of nonsteroidal plant components that can behave as estrogens and occur naturally in most plants, fruits, and vegetables [2]. They were first noted in 1926 to have estrogenic activity [3]. In particular the position and the distance of the hydroxyl substitutes enables the molecule to bind to estrogen receptors. They bind to both receptor types, the estrogenα and the estrogen ß receptor [4].



Artificial representations of the ERß end ERα pockets

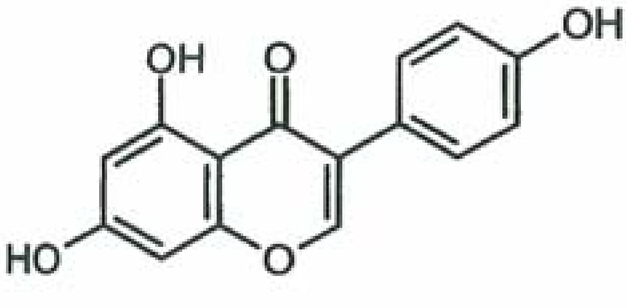
Many phytoestrogens seems to have higher affinity for the ERß receptor than steroidal estrogens, which suggests that they may exert there actions through distinctly different pathways. However, despite their ability to bind to the estrogen receptor, they are much weaker then than human estrogens, with 10^2 to 10^5 times less activity [5]. Phytoestrogens seem to possess both estrogenic as well as antiestrogenic activity. Whether they act primarily as an estrogen or as an antiestrogen seems to depend on the amount of endogenous estrogens the number and type of estrogen receptor and last but not least the tissue type in which the receptors are expressed [6,7]. Phytoestrogens are frequently detected in man in much higher quantities than endogenously produced estrogens [8].



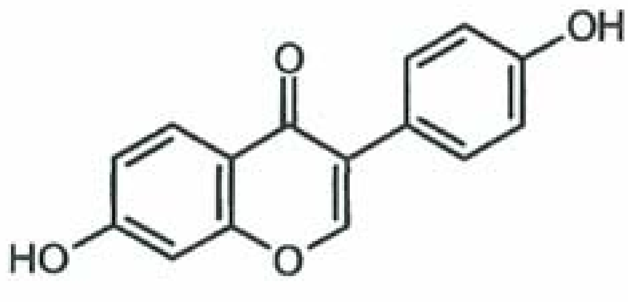
Physiological estrogen 17ß-estradiol

17ß-estradiol

There are three main types of phytoestrogens: the isoflavones (the most potent), coumestans, and lignans. There are more then 1000 types of isoflavones, but the most commonly investigated are genistein and daidzein, which are also thought to have the highest estrogenic activity. They are found in legumes such as soy, chickpeas, clover, lentils and beans. The isoflavones are bound to glucose, and when ingested by humans, they are enzymatically cleaved in the gut to the active forms. The metabolism of the phytoestrogens varies from person to person, and there also seems to be a sex difference, with women appearing to metabolise them more efficiently. The lignans (enterolactone or enterodiol) are found in flaxseed, lentils, whole grains, beans fruits and vegetables. Other classes which are more rarely ingested, are the coumestans (found in sprouting plants), flavones, flavanones, chalcones, terpenoids, and saponins

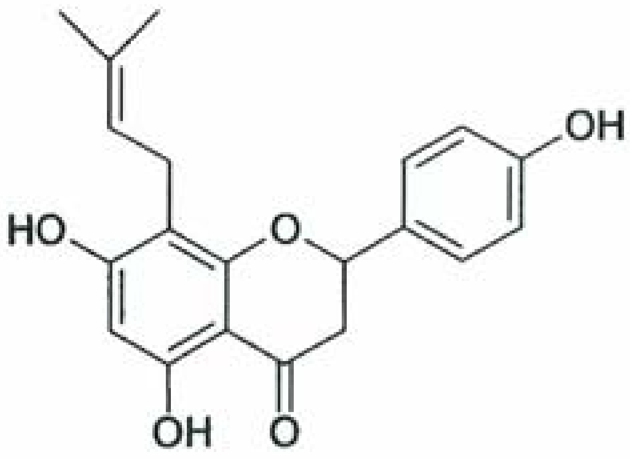


Genistein

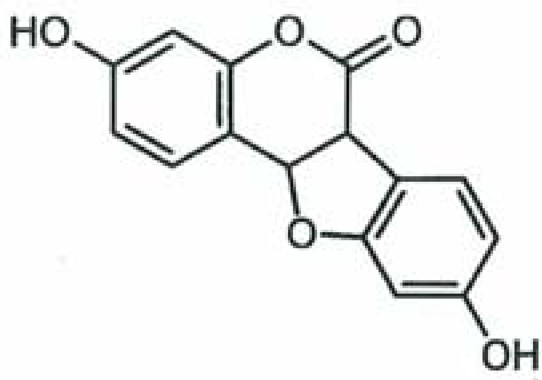


Daidzein

Molecular structures of the phytoestrogens genistein and daidzein, important phytoestrogens present in soy.



8-prenylnaringenin



Coumestrol

Molecular structures from 8 prenylnaringenin a phytoestrogen present in hop and from coumestrol a compound present in alfalva.

As shown by Kuiper et al. [9] in Receptor Binding Assays (RBA; see table below) the estrogenic potency of phytoestrogens is significant, especially for the ERß, and they may trigger many of the biological responses that are evoked by the physiological estrogens

Compound	RBA[a]		RBA[b]	
	ERα	ERß	ERα	ERß
17 ß-estradiol	100	100	100	100
Coumestrol	20	140	34	100
Genistein	4	87	0.7	13
Daidzein	0.1	0.5	0.2	1
Naringenin	0.001	0.11	ND	0.2

RBA[a]: determined from solid phase competition experiments; RBA[b]: determined from solubilised receptor experiments; ND: not determined.

Safety

With respect to adverse effects of phytoestrogens in general no specific data are available and this needs further investigation. Thus far mainly beneficial effects were noted on basis of epidemiological studies. It was observed that the rates of colon, prostate, and breast cancers were much lower in Japan and other Southeast Asian societies than in the United States [10, 11]. The same was found for cardiovascular diseases [12] and with respect to menopausal symptoms it was found that Asian women had approximately 10% the incidence of hot flashes that American women had (these results, however, should be corrected for cultural definitions and beliefs [13, 14]). Since Japanese migrating to the US developed an increased incidence of 'western' diseases within 1 or 2 generations, it was concluded that the genetic background could not be the only factor and attention was turned to the diet [15]. One of the most significant differences observed was the high quantity of soy in the Asian diet. The daily soy intake in an Asian population is 20 to 50 times higher than in an American population [16]. Soy contains high levels of phytoestrogens, particularly isoflavones (genistein, daidzein). Since no particular adverse effects are observed in the Asian population it can be concluded that up to these levels (20 to 50 mg/d of soy) the use is safe.

Breast development in male, however, is seen as an unwanted effect and medically defined as gynecomastia. Male breast development can be caused by the intake of estrogenic drugs, from industrial exposure or from exposure to estrogen containing ointments. It is, however, difficult to distinguish true enlargement of breast tissue from lipomastia, in particular in overweight men. In this regard it is important to realise that the bulk of breast tissue in normal women and in most men is adipose tissue.

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