ROLE OF PHYTOESTROGENS AS NUTRACEUTICALS IN HUMAN HEALTH

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Summary

Phytoestrogens are the phytochemicals quite similar in function to gonadal estrogen hormone and are potential alternatives to the synthetic selective estrogen receptor modulators currently used in hormone replacement therapy. They can be classified as flavonoids, isoflavonoids, coumestans, stilbenes, lignans and terpenoids. Soybean is rich in isoflavones like genistein, daidzein and their methyl ether derivatives, biochanin A and formononetin. Consumption of these in high quantities is associated with reduced risk of osteoporosis and related health problems. The main dietary source of phytoestrogenic stilbenes is *trans*-resveratrol from red wine and peanuts. Coumestrol and 4′-methoxy-coumestrol are two potent members of coumestans mainly found in sprouted legumes. Secoisolariciresinol and matairesinol are two lignan dimers which are not estrogenic by themselves, but readily convert to the mammalian lignans, enterodiol and enterolactone, respectively and have estrogenic, antiviral, antifungal and antioxidant activities. Terpenoids (ferutinine, tschimgine, and tschimganidine) found in the Umbelliferae family have estrogenic activities. In females, life is affected by a variety of estrogen-related conditions such as osteoporosis, cognitive and cardiovascular decline, increased risk of breast cancer and other symptoms that decrease the overall quality of life. Phytoestrogens are effective in maintaining bone mineral density, prevent bone loss, and help in the prevention and/ or treatment of such health related problems. Plant-derived food may supply a variety of phytoestrogens capable of producing a range of pharmacological effects and protection from various diseases.

Key words: Phytoestrogens, flavonoids, isoflavonoids, stilbenes, coumestans, lignans, terpenoids, osteoporosis, cancer and cardiovascular diseases.

Introduction

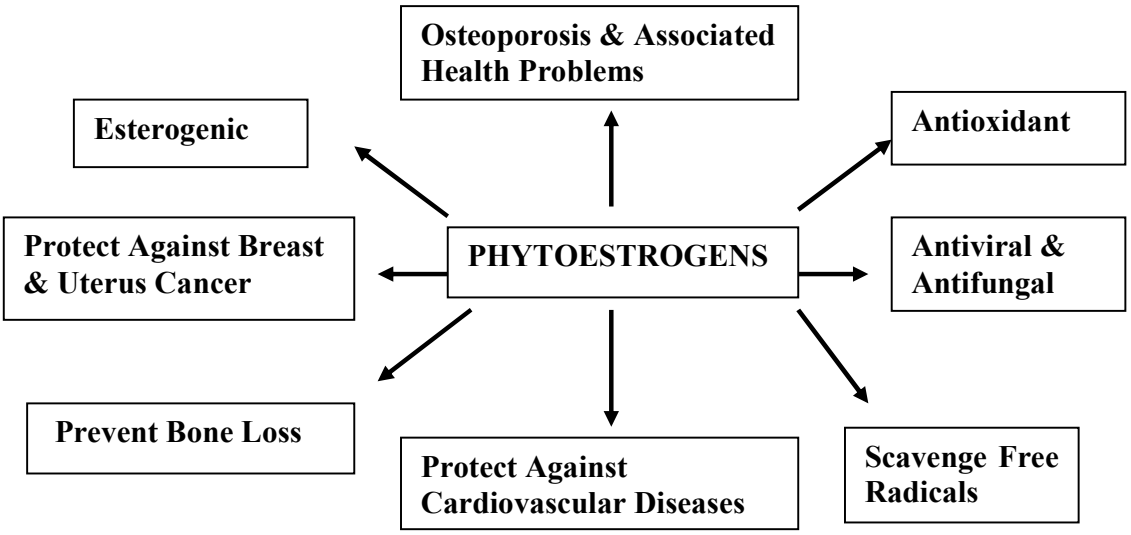
The nutraceuticals comprises bioactive phytochemicals that protect or promote health and occur at the intersection of food and pharmaceutical industries. Such substances may range from isolated nutrients, dietary supplements and specific diets to genetically engineered designer foods, herbal products, processed foods and beverages. ‘Nutrigenomics' is the next frontier in nutraceutical therapy progressing in the battle against ageing, diseases and sufferings by the availability of genomic information. The interface between the nutritional environment and cellular/genetic processes is being referred as nutrigenomics. It provides a molecular genetic understanding of phytonutrients that affect health by altering the expression and structure of an individual’s genetic make-up. This in turn may alter initiation, development or progression of specific diseases. Nutraceuticals have tremendous impact on the health care system and may provide medical health benefits including the prevention and/ or treatment of diseases and physiological disorders [1-4].

Plants with estrogen-like biological activity are being used in traditional systems of medicine and folklore, for example, the pomegranate is associated with fertility, the Thai vine, *Pueraria mirifica*, as rejuvenator and aphrodisiac and hops to lower libido by the German clergy in the Middle Ages. Till now, several hundred plants have been found to exhibit estrogenic activity due to the presence of phytochemicals called phytoestrogens (PE). They are recommended for the prevention of disturbed hormone related diseases [5, 6].

Estrogen (Greek *Oistros,* 'mad desire' and *gennan,* 'to produce') is the generic term for chemically similar family of substances that function endogenously as hormones affecting female reproductive function and/or anatomy. They are steroidal in nature and play an important role in maintaining bone density by regulating the formation and resorption of bone. Since lower circulating estradiol levels are found during menopause, calcium is lost from the bone into blood plasma, leading to osteoporosis. Hormone replacement therapy (HRT) stimulates bone formation and may prevent bone loss, osteoarthritis and incidence of osteoporosis in postmenopausal women. However, if taken alone, HRT can increase the risk of developing ovarian, uterine and breast cancer [7-11].

Phytoestrogens (PE) are non-steroidal phytochemicals quite similar in structure and function to gonadal estrogen hormone. They offer an alternative therapy for HRT with beneficial effects on cardiovascular system and may even alleviate menopausal symptoms. They are potential alternatives to the synthetic selective estrogen receptor modulators (SERMs), which are currently applied in HRT. As such, PE may act as natural SERMs that elicit distinct therapeutical effects by selectively recruiting co-regulatory factors to estrogen receptor-β (ER- β), which then specifically affect transcription. The relative binding affinity of estrogen for each isotype receptor is stated to be 1000-fold higher than that of phytoestrogens, but the latter could evoke biological responses, because of their higher concentrations in plasma as compared to the endogenous hormone estradiol [10-11]. Apart from their estrogenic properties, other features (Figure 1) could also be involved in their observed diverse action mechanisms, including binding to other nuclear receptors, antioxidant effects due to their polyphenolic nature, anti-carcinogenic, modulation of steroid metabolism or of detoxification enzymes, interference with calcium-transport and favorable effects on lipid and lipoprotein profiles [8-12].

Figure 1: Biological properties of Phytoestrogens



On the basis of chemical structure phytoestrogens can be classified as flavonoids, isoflavonoids, coumestans, stilbenes, lignans and terpenoids. They occur (Tables 1-3) in either plants or their seeds, soybean is rich in isoflavones, whereas the soy sprout is a potent source of coumestrol, the major coumestan [5, 13, 14].

Table 1: Isoflavonoid content of some commonly used foods

Sources	Isoflavones (μg/g)	Sources	Isoflavones (μg/g)
Soy	610-2440	Kidney bean	0.1-4.1
Soy sprouts	250-530	Black gram	6.4-12.6
Soy protein	465-1993	Green gram	7.0
Soy milk	13-211	Red gram	2-5.6
Soy cheese	33-593	Beans	0.3-1.3
Tofu	79-635	Lentil	0.23-0.4
Miso	227-892	Barley	0.21
Soy sauce	12.7-23.0	Peas	0.4
Groundnut	3.5-8.4	Coconut	0.19
Tea	2.34	Currents	2.25

Table 2: Resveratrol content of some commonly used foods

Sources	Resveratrol (μg/g)	Sources	Resveratrol (μg/g)
Wine	0.32-15.35	Green grapes	0.016-0.318
Peanut butter	0.015-0.982	Black grapes	0.945-1.874
Peanuts	0.003-0.073	Raisins	0.0005-0.003
Green peanuts	0.183-0.716	Grape juice-black	0.087
Polygonum cuspidatum	296-377	Grape juice-green	0.0015

Table 3: Lignan content of some commonly used foods

Sources	Lignans (μg /g)	Sources	Lignans (μg /g)
Soybean	9.6	Banana	2.8
Flaxseed	347.5-1140.3	Orange	2.1
Lentils	19.6	Apple	2.5
Cowpea	1.9	Mango	1.7
Green gram	1.7	Carrot	29.3
Walnut	1.7	Cabbage	18.6
Cashew	2.6	Cauliflower	16.2
Peanut	1.8	Onion	10.3
Wheat	0.8-2.8	Garlic	10.5
Rice	0.2-6.0	Potato	4.1
Barley	1.3	Cucumber	5.9
Strawberry	7.7	Tomato	3.3

Flavonoids: The isoflavonoids are a subclass of flavonoids, where one phenolic ring has migrated from C-3 to C-2. Isoflavones have similar structure to estrogen and have the capacity to exert both estrogenic and anti- estrogenic effects, they may block the effects of estrogen in some tissues e.g. the breast and womb lining but act like an estrogen in providing possible protection against bone loss and heart diseases. The precursors of these substances are widespread in the plant kingdom, but mainly found in Leguminosae[15] and are especially abundant in soybean and its products, legumes, berries, whole-grains and cereals (Table 1). Among these, genistein (5,7,4′-trihydroxy-isoflavone), daidzein (7,4′-dihydroxy-isoflavone) and their 4-methyl ether derivatives, biochanin A and formononetin, respectively, are the best-known examples (Figure 2). The main isoflavones, genistein and daidzein, commonly exist as inactive glucosides. They are also derived from precursors, biochanin A and formononetin, which are converted to genistein and daidzein respectively, after breakdown by intestinal glucosidases. Daidzein is further partially metabolized to O- desmethyl-angiolensin (O-DMA) and equol (Figure 3). Because of their non-steroidal skeleton and different special structure, phytoestrogens when bound to the estrogen receptors (ER) were expected to act totally differently. They share structural features with estrogen, in the sense that the presence of particular hydroxyl groups that can be positioned in a stereo chemical alignment virtually identical to one of the estrogen. They can exist as glucosides or as aglycones, the glucosides being readily hydrolyzed in the gut to their aglycones (Figure 3). The aglycones are easily transported across intestinal epithelial cells [16-20]. Once ingested, the absorption of these compounds requires initial hydrolysis of the sugar moiety or demethylation, respectively, by gut/bacteria-released intestinal enzymes in the digestive tract. The metabolization of isoflavones to equol and O-desmethyl-angolensin (O-DMA) for daidzein and to 2-(4-hydroxyphenyl) propanoic acid and tri-hydroxy-benzene (THB) for genistein by gut bacteria (Figure 3) are subjects of large inter individual variation, depending on gastrointestinal micro flora and diet [21-25]. A closely related compound to the isoflavonoids is 8-prenyl-naringenin, an isoflavanone, found in hops (*Hummulus lupulus*), an ingredient used in beer. Populations in China, Japan, Taiwan and Korea are estimated to consume high quantities of isoflavones (Table 1) and women of these countries complain fewer incidences of osteoporosis and related health problems, especially hot flushes, cardiovascular diseases, lower incidence of hormone dependent breast and uterine cancer. Isoflavones have also been reported to inhibit angiogenesis, cell cycle progression, aromatase enzyme inhibition, stimulation of sex hormone binding globulin (SHBG) synthesis and digitalis-like activity [26-33].

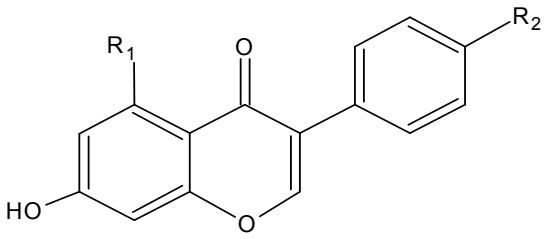


Figure 2.1: R_1 = OH, R_2 = OH, Genistein
Figure 2.2: R_1 = H, R_2 = OH, Daidzein
Figure 2.3: R_1 = OH, R_2 = OMe, Biochanin A
Figure 2.4: R_1 = H, R_2 = OMe, Formononetin

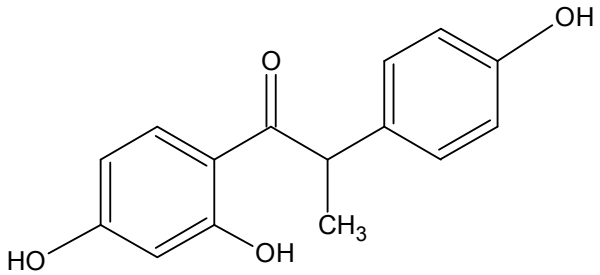


Figure 2.5: O-Desmethyl-angiolensin (O-DMA)

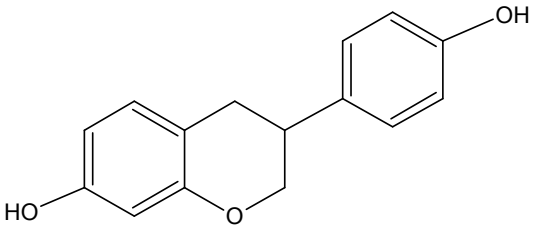
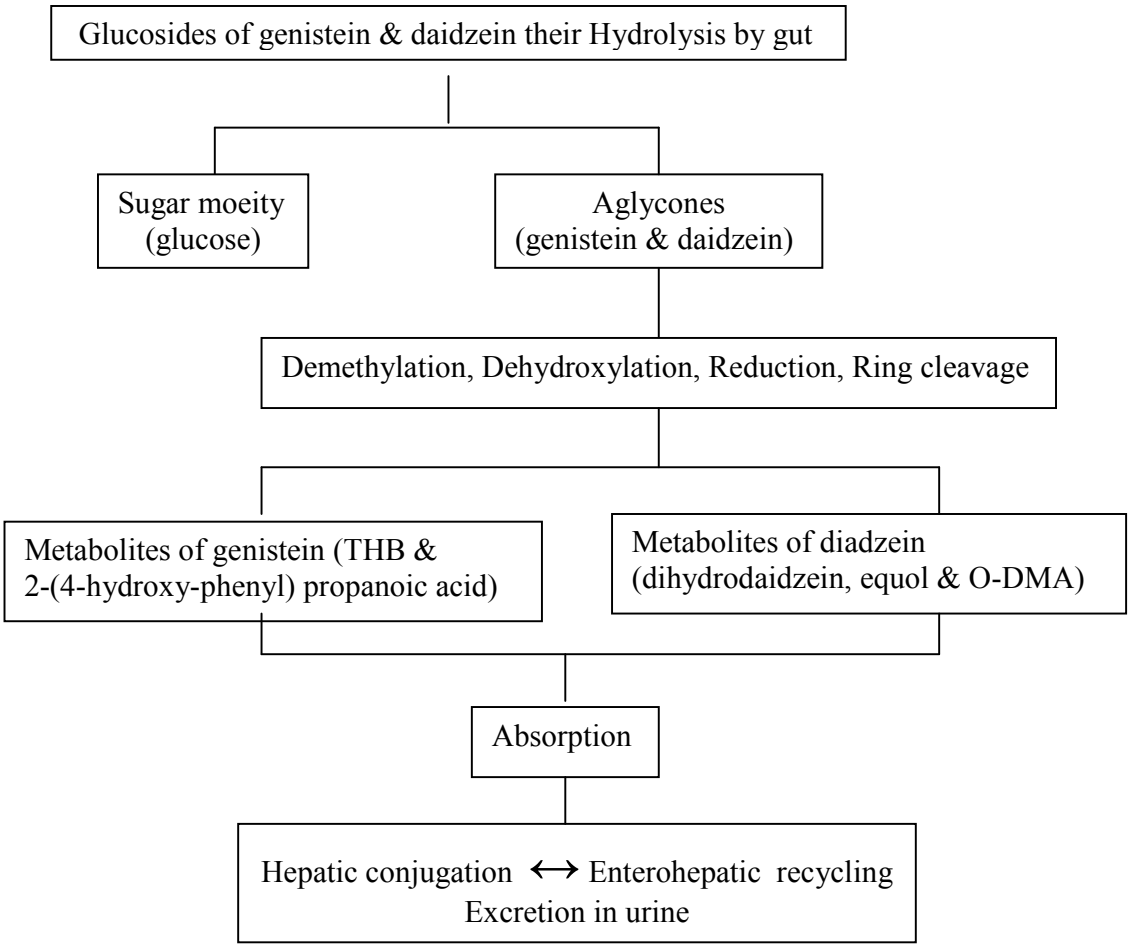


Figure 2.6: Equol

Figure 3: Metabolic conversion of isoflavones glucosides



Stilbenes: The main dietary source of phytoestrogenic stilbenes (Figure 4) is resveratrol from red wine and peanuts (Table 2). Although there are two isomers of resveratrol, *cis* and *trans*, but only the *trans* form has been reported to be estrogenic. It is found only in the skin of red grapes, in green grapes and white wine very low levels of *trans*-resveratrol are found. The content of resveratrol in wine depends on cultivars, geographic location, season and presence of Botrital fungus. The level of *trans*-resveratrol in red wines, fermented with grape skins, can be as high as 14.5 mg/lit. Boiled peanuts were fount to contain more resveratrol than peanut butter and roasted peanuts. As the peanut matures, the resveratrol content in the nut declines, while smaller immature peanuts have higher levels of resveratrol [34-37].

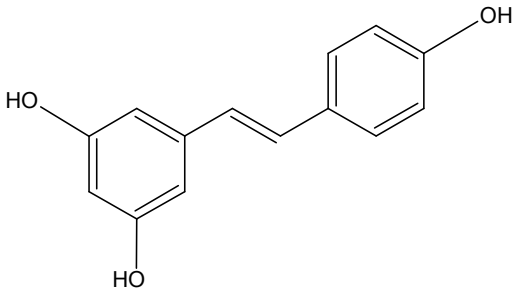


Figure 4.1: *Trans*-resveratrol

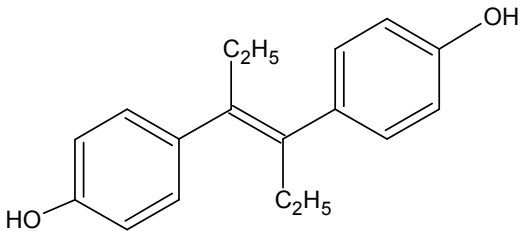


Figure 4.2: Diethyl-stilbestrol

Coumestans: Although there are a large number of coumestans (Figure 5), only a small number have shown estrogenic activity, predominantly coumestrol and 4′-methoxy-coumestrol are two potent members of this group. The main dietary sources of coumestrol are sprouted legumes such as soy, and alfalfa; however low levels have been reported in brussel sprouts and spinach. Clover and soybean sprouts are reported to have its highest concentration [38-40].

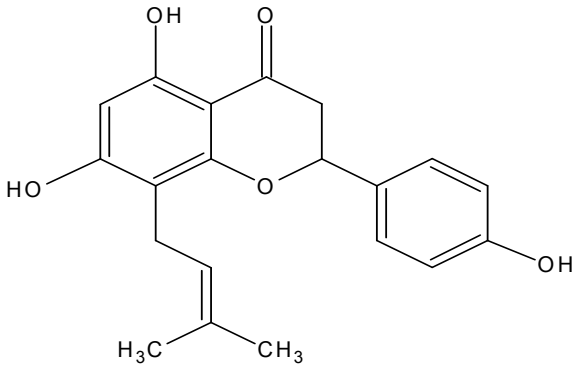


Figure 5.1: 8-Prenylnaringenin

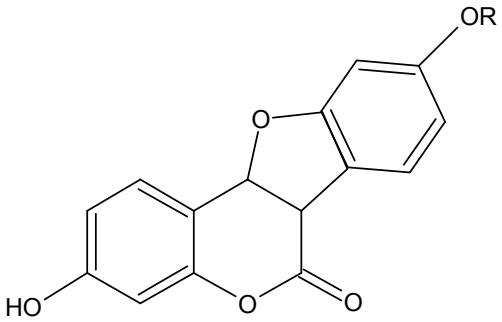


Figure 5.2: R = H, Coumestrol
Figure 5.3: R = Me, 4′-methoxy-coumestrol

Lignans: The term lignan is used for a diverse class of phenylpropanoid dimers and oligomers. Secoisolariciresinol and matairesinol are two lignan dimers which are not estrogenic by themselves, but readily convert to the mammalian lignans, enterodiol and enterolactone (Figure 6), respectively, which are estrogenic [41-42]. These are of great interest because of their estrogenic, antiestrogenic, anticarcinogenic, antiviral, antifungal and antioxidant activities. The phytolignans are found in high amounts in flaxseed, asparagus, whole grains, vegetables, and tea (Table 3). Fruits also have their low levels with the exception of strawberries and cranberries. In humans, after consumption of plants rich in isoflavones and lignans, enzymatic metabolic conversions occur in the gut, by micro flora and the mammalian lignans are readily absorbed [43, 44].

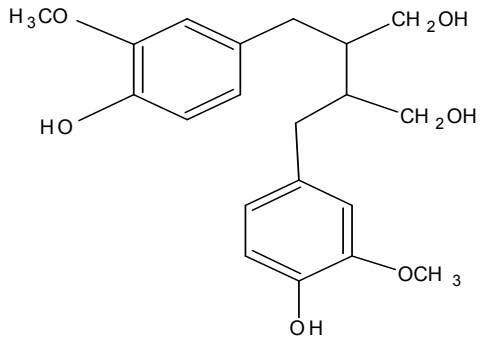


Figure 6.1: Secoisolariciresinol

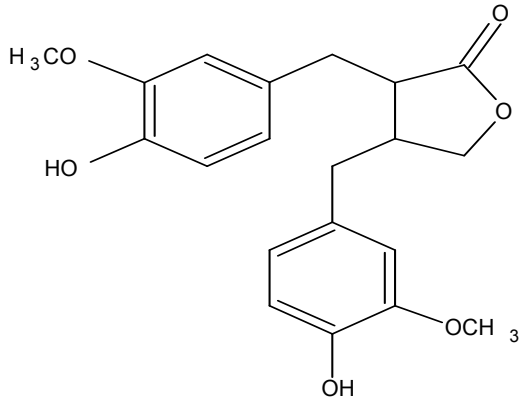


Figure 6.2: Matairesinol

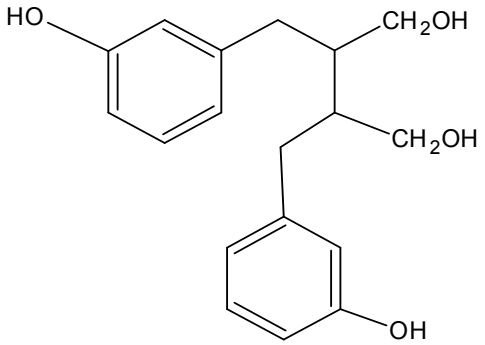


Figure 6.3: Enterodiol

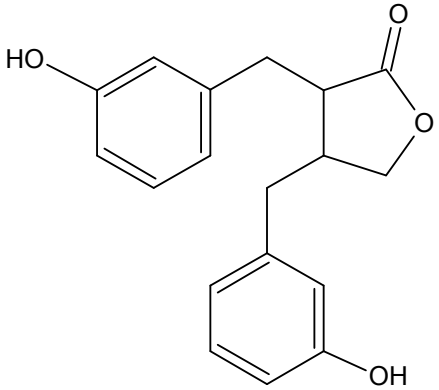


Figure 6.4: Enterolactone

Terpenoids: Ikeda et al. [45] surveyed estrogenic and antiestrogenic activities of terpenoid phytochemicals found in the Umbelliferae family and revealed that three compounds (tschimgine, tschimganidine and ferutinine) have agonistic and/or antagonistic activities for ER-α and ER-β. Ferutinine and tschimganidine are sesquiterpenoids and tschimgine is a monoterpenoid (Figure 7). The structures and biosynthesis of these terpenoids are distinct from the well-known phytoestrogens such as isoflavones [46]. Ferutinine isolated from *Ferula jaeschkeana* was reported to increase uterine weight and prevent pregnancy when administered orally in rats. It may modulate estrogen signaling similar to phytoestrogens specifically, estrogen receptor subtype selective PE and may be useful as natural SERMs. It is an agonist for ER-α and an agonist/antagonist for ER-β, tschimgine is an agonist for both ER-α and ER-β and tschimganidine is an agonist for ER-α only. It was assumed that they affect the endocrine system similar to other man-made endocrine disrupters to exert their effects through estrogen receptors, specifically ER-α and ER-β [47].

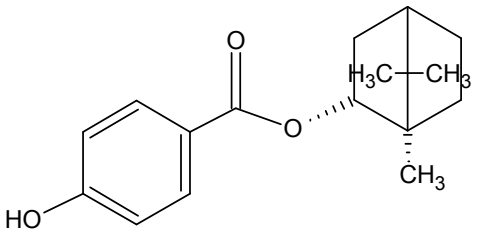


Figure 7.1: Tschimgine

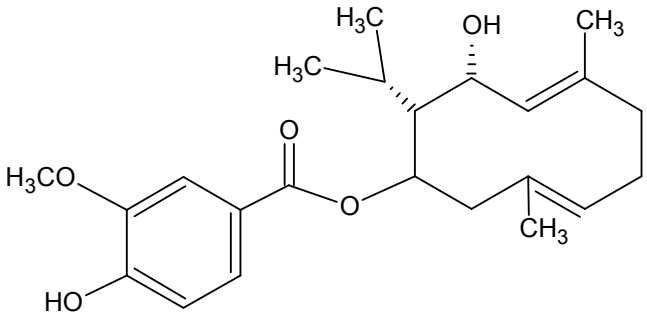


Figure7.2: Tschimganidine

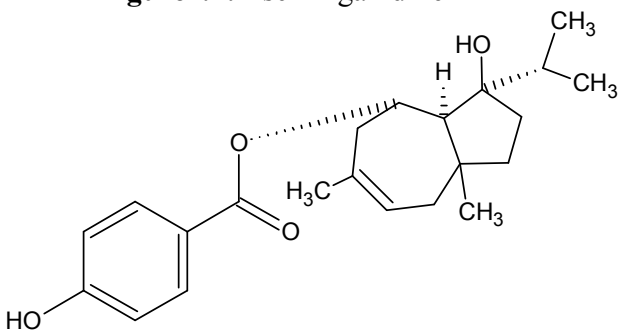


Figure 7.3: Ferutinine

Role of Phytoesterogens in Human Health:

Osteoporosis: It is painful, disfiguring and debilitating condition resulting in the loss of bone mass and vertebral fractures that shorten height and may also lead to rounding of the spine known as Dowager's hump. Osteoporosis is related to multiple factors including aging, hormone deficiency and diet. Because of this insidious process, it is not uncommon for older people to loose up to 7-8 cm in height due to skeletal damage and compression, which can lead to nerve problems and increased pain. Most of the studies suggest that phytoestrogens are somewhat effective in maintaining bone mineral density (BMD) in postmenopausal women [48-53]. Ipriflavone (7- isopropoxy-isoflavone), a synthetic flavonoid, inhibits osteoclast recruitment and function, and its use at a dose of 600 mg/day prevents bone loss in osteoporotic postmenopausal women. Evidence from several human studies demonstrates that certain dietary phytoestrogens can produce estrogenic effects in the postmenopausal women, including estrogen-like effects on vaginal cytology and reductions in hot flushes [27, 28, 53-54].

Cardiovascular health: In postmenopausal women, cardiovascular diseases (CVDs) are one of the leading causes of death in United States and Europe. Estrogen can affect the vascular system both directly, through the estrogen receptors located in vascular tissue, and indirectly through altering the lipoprotein profile. Isoflavonoids or soy products/soy protein and flaxseed have the ability to lower total and LDL cholesterols and raise HDL cholesterol resulting in reduced risk of CVDs [55-57]. There is evidence to support the hypothesis that phytoestrogen consumption contributes to the lower incidence of CVDs in Asian countries and in vegetarians and that they may also be cardio protective. A study of Rhesus male and female monkeys has shown that isoflavone-intact soy protein supplementation resulted in

hypocholesterolemic effect that appears to be significantly related to pretreatment plasma cholesterol. Dietary phytoestrogens may provide cardio protective benefits via direct effect on lipids, inhibition of platelet aggregation and antioxidant effects [6, 19, 39].

Cancer: A large number of epidemiological studies had shown that people who consume high amounts of isoflavonoids (phytoestrogens) in their diets have lower incidences of various types of cancers including breast, prostate and colon cancer. A high plasma concentration of the mammalian lignan, enterolactone, is correlated with a reduced risk of breast cancer. Similar correlations have also been found between dietary intakes of isoflavonoids and lignans and thyroid, ovarian, and breast cancers in pre and postmenopausal women [17, 18, 29-33]. The incidence of hormone dependent tumors is lower in Asia and Eastern Europe where consumption of phytoestrogens is higher than western countries and amongst vegetarians. Breast, ovarian, prostate, and colon cancer show a negative correlation with PE intake when compared with mortality rates due to cancer. The epidemiological, animal, and cell-line data suggest that phytoestrogens may play a protective role against the development of prostate and breast cancer [30-33, 58-60]. It has been reported that increased consumption of beans, lentils and peas, tomatoes, and dried fruits was associated with significantly decreased prostate cancer risk. Hirayama [61] showed the protective effects from prostate cancer with consumption of green leafy vegetables. In human prostate cancer cell lines, high concentrations of genistein and biochanin A inhibit the growth of both androgen-dependent and independent cells [6, 29-30, 60, 62, 63].

Estrogenic and antiestrogenic activity: Phytoestrogens are of biological interest because they exhibit both, estrogenic and antiestrogenic actions [5]. The estrogenic effect of phytoestrogens was first observed as reproductive disturbances in sheep. Isoflavones stimulate uterine hypertrophy in laboratory animals exhibiting estrogenic action [62]. When administered with estradiol, genistein functions as an antiestrogen, decreasing uterine estradiol uptake in animal models. Isoflavones exhibit anticarcinogenic activity *in vivo*. Genistein has been the phytoestrogen of greatest interest at present and, *in vitro*, has been shown to exert both proliferative (estrogenic) and antiproliferative (antiestrogenic) effects in human cell lines [6]. Sathyamoorthy and others [63] have shown similar stimulatory effect with daidzein, equol, and enterolactone at very low (10^{-6} M) concentrations. This anti-proliferative effects of genistein occurred in both ER-positive and ER-negative cell lines and thus appear not to be mediated by the estrogen receptors [13, 16, 19, 39, 64].

Diets rich in plant-derived products may supply a variety of phytoestrogens (Tables 1-3) capable of producing a range of pharmacological effects (Figure 1). In females, life is affected by a variety of estrogen-related conditions such as osteoporosis, cognitive and cardiovascular decline, increased risk of breast cancer and other symptoms that decrease the overall quality of life [30-33, 65]. Phytoestrogens appear to have physiological effects in humans, with the most supportive data being related to the effects of soy protein supplements on lipids and lipoproteins and on vascular function. Postmenopausal women who have the greatest breast cancer risk should be encouraged to increase their phytoestrogen intake. It may be that phytoestrogen ingestion needs to be life-long and combined with other low-risk dietary constituents. Non-estrogenic compounds present in phytoestrogen-rich plant sources used in clinical research may interact with them either by potentiating or interfering with

their activity and bioavailability. In addition, some phytoestrogens may act as estrogen agonists or antagonists depending on their structure and concentration [6, 28-30, 66].

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