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REVIEW ARTICLE

HEALTH BENEFITS OF PHYTOESTROGENS

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Abstract

Phytoestrogens are phenolic non-steroidal plant derived compounds possessing estrogen like activity. They are called estrogen like molecules because of their structure similarity to estradiol, the basis for their hormonal activity so they can bind to estrogen receptors and have a beneficial role in humans against deficiency of estrogen. Estrogen level begin to decline with a woman's age and resulting in the end of menstrual cycle which results in menopausal symptoms, including hot flashes, urogenital atrophy, incontinence, insomnia, heart problems and osteoporosis. These may compete with endogenous mammalian estrogens, bind to the ER and prevent estrogen-stimulated growth in mammals. These come into focus of interest due to their positive effects in prevention of hormone dependent cancer, cardiovascular diseases by improving plasma lipid concentrations, osteoporosis and cognitive decline. Phytoestrogens are used as an alternative to the ERT which is associated with the risk of breast cancer. The present article is focused on different phytoestrogens, their sources and recent knowledge on their biological impact.

INTRODUCTION

Phytochemicals are compounds found in plants that contain biologically active components which affect our body and these have been linked to lower incidences of cancers, relieving menopausal symptoms, heart disease and risk of osteoporosis. Phytoestrogens fall under the category of phytochemicals. The word phytoestrogen from "phyto" meaning plant, and "estrogen" due to their ability to affect estrogenic activity in the body. It describes a property that has been identified in some foods, plants and herbs. These have gained much interest in recent years because of their potential protective effect against hormone-dependent cancers and age related diseases and conditions. These have been shown to have estrogen agonist or antagonist effect in animals and humans depending on the dose of the phytoestrogen. Their structural similarity to estrogens is the basis for their hormonal activity so they can bind to estrogen receptors, causing estrogen-like effects. As estrogenic, these stimulate growth of estrogen-dependent MCF-7 human breast cancer cells. These have been shown to enhance cell proliferation at low concentration. As antiestrogenic, at high concentration have been shown its inhibitory effect on MCF-7 cell growth. These may compete with endogenous mammalian estrogens, bind to the ER and prevent estrogen-stimulated growth in mammals[37]. At lower concentration, they tend to stimulate the proliferation of breast cancer cell lines; whereas, at high concentration, they exert strong cytotoxic effect[36]. The major classes of of phytoestrogens are isoflavones, coumestanes and lignans. The most studied phytoestrogens are genistein and daidzein belonging to the isoflavones class. These have a beneficial role in humans against estrogen deficiency.

Estrogens are steroid hormones responsible for many physiological activities which are important in homeostatic regulation of many cellular and biochemical events. These are important for sexual and reproductive development, mainly in women. It is involved in development of mammary glands and the uterus, in maintaining pregnancy and bone density, in reducing the risk of cardiovascular disease and helps in relieving menopausal symptoms. Estrogen

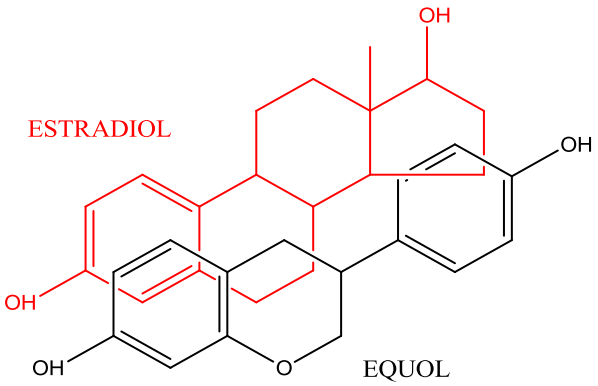
level begin to decline with a woman's age and resulting in the end of menstrual cycle which results in menopausal symptoms, including hot flashes, urogenital atrophy, incontinence, insomnia , heart problems and osteoporosis.
Both deficiencies and excess of estrogen are associated with many health issues. Administration of estrogen (ERT) to post menopausal women is beneficial in reducing the risk associated with estrogen deficiency. But estrogen can stimulate the development of estrogen-dependent tumors (breast and uterus cancer). Phytoestrogen are used as an alternative to the ERT because of the chemical structure similarity with estradiol. These are derived from plants that structuraly or functionally mimic mammalian estrogens and play important role in prevention of menopausal symptoms, cancers, heart disease and osteoporosis.[14]
Phytoestrogens are found in grains, vegetables and fruits but these are mainly present in higher concentration in legumes. Isoflavones are most common phytoestrogens found in legumes such as soybeans whereas lignans are found mainly in flax seed, coumestans are found in clover, and stilbenes are found in cocoa and grape-containing products, particularly red wine[1,2]

METABOLISM OF PHYTOESTROGEN[8,9,10,11]

Phytoestrogens undergo significant metabolism in the gastrointestinal tract with the help of bacteria. They are hydrolysed before entering the the blood stream, isoflavones glucosides are hydrolysed by enzymes in saliva and small intestinal mucosa and also by beta glucosidase in intestinal bacterium to their aglycones (daidzein to daidzein). The glycosidases cleave the sugar moieties, releasing the biologically active isoflavones (genistein and daidzein). The aglycones and metabolites are absorbed at intestinal tract and then transported to the liver via the portal vein. The aglycones are metabolized to sulphate, glucuronide and sulphoglucuronide conjugates and are excreted to the bile, making isoflavones more water soluble, thus improving their excretion. These hydrophilic metabolites and aglycones can be further metabolised to equol, dihydrodaidzein, dyhdrogenistein and O-desmethylangolensin. And lignans secoisolariciresinol and matairesinol are converted to mammalian lignans enterolactone and enterodiol by human gut bacteria through dehydroxilation and demethylation[47]

MECHANISM OF ACTION

Phytoestrogens are a large family of plant derived estrogens possessing significant estrogen agonist/antagonist activity. These may have the same effect as estrogen or block estrogen's effects. These can act like estrogen at low doses and estrogen blocker at high doses. Phytoestrogens favour interaction with ER[5]. These are able to bind to estrogen receptors because of structure similarity with 17-beta estradiol. And the interaction of phytoestrogen with ERs leads to the activation of estrogen response elements located on the inner side of the nuclear membrane. In this way transcription processes are affected. The affinity of genistein to ER β is comparable to the affinity of estradiol, it is 20-30 times higher than to ER α. The affinity of other isoflavones is 100-500 times lower than that of estradiol. These can act as agonist to ERs, but their activity is lower than that of estradiol. The effects of isoflavones depends on the level of endogenous estradiol, isoflavones and estradiol and they compete for their binding on ERs. In state of high levels of endogenous estrogens, isoflavones may obstruct full estrogen activity by occupying a part of the ERs. And in state of low levels of endogenous estrogens, the estrogen activity of isoflavones may become manifest[7].



ESTROGEN RECEPTORS

Estrogens exert their effects via their respective receptors i.e. estrogen receptor α and β which are members of the nuclear receptor superfamily. These have been identified in human cells and have distinct tissue expression patterns. The organs related to reproductive functions such as the mammary gland, the ovaries and the uterus are characterized by high estrogen receptor content and cardiovascular system, the brain, the immune system, bone and the liver characterized by lower estrogen receptor content. ER alpha and ER beta are co-expressed in many tissues. ER alpha is primarily expressed in uterus, liver, heart, kidney on the other hand ER beta is primarily expressed in the ovary, prostate, lung, gastrointestinal tract, bladder, central nervous system and hematopoietic system[3]. ER binds with steroidal as well as numerous non steroidal compounds. For binding effectiveness, an aromatic ring and a hydroxyl group is important. The steric and hydrophobic properties of a compound as well as the hydrogen bonding between the phenolic hydroxyl group and the ER binding site, are important features that enable chemicals to bind to an ER[1]. Isoflavones have a relatively greater binding affinity for ER beta than for ER alpha, but are 10^2 to 10^5 times less active than steroidal estrogens.

CLASSIFICATION

They have been categorized based on their chemical structures, which resemble to 17β-estradiol into isoflavones, coumestans and lignans.

Lignans

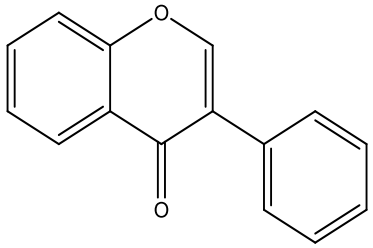
These are diphenolic compounds and one of the three major classes of phytoestrogens. These helps in maintaining good cognitive function in postmenopausal women and reduce breast cancer. The behavior of the lignans depends on the biological level of estradiol. At normal estradiol level, the lignan act as estrogen antagonists and at low estradiol levels, they act as weak estrogens. It plays major role in cancer prevention and diabetes prevention. These are found in a variety of of plants materials including flax seed, pumpkin seed, sesame seed, soybean and some berries. These also found in most fiber rich plants including grains (wheat, barley and oat) and vegetables such as garlic and carrots. Secoisolariciresinol diglucoside is the major lignan in flax seed, which act as an antioxidant. Flax contains other lignans as well-namely matairesinol, pinoresinol, lariciresinol and isolariciresinol. Lignans are very complex class of plant compounds which have a role in the plant's natural defense mechanism. They are phenyl propane dimers linked by ß-ß bonds with a 1, 4-diarylbutane structure.

Coumestans

These are class of chemicals from plants that behave like estrogen in the body. They are thought to have a greater estrogenic activity than the isoflavones. Coumestans are the least studied of all phytoestrogens, but research has shown some cancer-preventing effects. These are present in alfalfa, cabbage and lesser extent in soybeans. Clover and soybean sprouts are reported to have the highest concentration 28 and 7 mg/100g dry wt. And the mature soybeans only have 0.12mg/100g dry wt[18]. The chemical structure of coumestan is resembling to that of our own estrogen represents the structure of the most well-known coumestan (coumestrol).

Isoflavones

These are a group of plant derived phenolic compounds and belong to the subclasses of the flavonoid family. These are structurally similar to estrogen and mimic its effect in the body. Isoflavones are major phenolic compounds predominantly found in soyabeans. The primary isoflavones found in soy are genistein and daidzein. They are found in red clover, germs of alfalfa and linseed also. The isoflavone content varies considerably in soybean depending on different factors like cultivation, geographical and environmental conditions and can vary between different soybean varities like soybean oil contains no isoflavones and soy sauce has little or no isoflavones. Soybeans contain approximately 2 grams of isoflavones products per kilogram fresh weight[4,5]. Dry soybeans contain 1.2-4.2 mg/g isoflavones. Their concentration depends on many factors climate, soil in which they are grown, stage of their maturity or level of processing. The main isoflavones which are found in soybeans are genistein and daidzein, glycitein is also present although in much smaller amounts. The chemical structure of isoflavones is very similar to that of human estrogen. Because of this similarity in structure, they can interfere with the action of human estrogen and are capable of binding to ERs. These possess higher affinity to ERβ than to ERα. The affinity of isoflavones is about 100-500 lower than that of 17-β estradiol. The affinity of genistein to ERβ is about 20-30 times higher than to ERα that is comparable to the affinity of 17-β estradiol. They are present mainly as glycosides, glycoside acetyl and malonyl form of genistein, daidzein and glycitein.



ISOFLAVONES

HUMAN HEALTH AND PHYTOESTROGEN

Phytoestrogens as potent antioxidants are thought to reduce the risk of mammary cancer, prevent cardiovascular disease, stop the progression of atherosclerosis, and have some positive effect on hot flashes, vaginal symptoms, cognitive function and dementia in postmenopausal women[2].

Phytoestrogens and cancer[12,16,18,36]

Asian immigrants to western countries suffer more frequently from cancer due to change in dietary habits(lower intake of soybeans)[37]. Environmental factors contribute to the development of tumors.[38] The postmeopausal women who consume high amounts of isoflavonoids in their diet found to be have reduction of breast cancer and proliferation ability of mammary gland cells. These reduce the bioavailabilty of sexual hormones in hormone dependent tissues with its ability to increase serum SHBG concentration[39]. These inhibit enzymes involved in the process of proliferation and by inhibiting aromatase P450, reduce estradiol availability[40]. Estrogenic effects have been observed, at low concentration these stimulate the growth of estrogen-dependent MCF-7 human breast cancer cells, and its antiestrogenic effect has been shown to inhibit MCF-7 cell growth at high concentration. These may compete effectively with mammalian estrogens, bind to ER and prevent estrogen-stimulated growth in mammals. These have the ability to inhibit cell proliferation and block the cell cycle at G2 phase in normal mammary cells may help to prevent the risk of breast cancer. These may affect communication pathways between cells and prevent the formation of blood vessels to tumors or alter processes involved in the processing of DNA for cell multiplication. These may inhibit aromatase enzyme that synthesizes estrogens by converting androstenedione and testosterone into estrone and estradiol which plays major role in the development of breast cancer. Protein tyrosine kinases involved in tumor cell signal transduction and proliferation. Isoflavones especially genistein inhibit cellular PTKs and inhibit the growth of different human cancer cells. Isoflavones inhibits DNA topoisomerases that are involved in DNA replication and catalyze topologic changes in DNA[50]. Genistien have been observed to stabilize the topoisomerase II-DNA complex by mediating double strand break and prevent from being resealed.

Cardiovascular disease

In menopause the risk of coronary heart disease increases due to the loss of estrogen[42]. Postmenopausal women experience decreased plasma concentration of high density lipoprotein cholesterol and increased plasma concentrations of low density lipoprotein choltestrol[49]. Animal studies have indicated that phytoestrogens reduce risk of heart disease by improving plasma lipid concentration (total cholesterol levels). These have the ability to lower total cholesterol, LDL cholesterol and raise HDL. These exerts cardioprotective effects by inhibiting the coagulation process[43], inhibiting tyrosine kinase[46] and platelet aggregation[44].

Osteoporosis[18]

Animal studies suggest that isoflavones may prevent cardiovascular disease by multiple mechanisms[51]. Estrogen deficiency may also lead to risk of osteoporosis in postmenopausal women. It may lead to immediate disability and risk of hip fracture increases. Estrogenic effect of phytoestrogens has been observed to increase bone density and prevent bone resorption. Most of the studies suggest that a diet rich in phytoestrogens are effective in maintaining bone mineral density in postmeopausal women. Estrogens play an important role in maintaining bone density. During menopause lower circulating levels are found, calcium is lost from the bone into blood stream and it leads to osteoporosis. Isoflavones stimulate osteoblast cell proliferation and protect the cells from oxidative damage and increased apoptosis of osteoclast cells or inhibit osteoclastic bone resorption and prevent overall bone loss in overiectomized rats or mice[52,53].

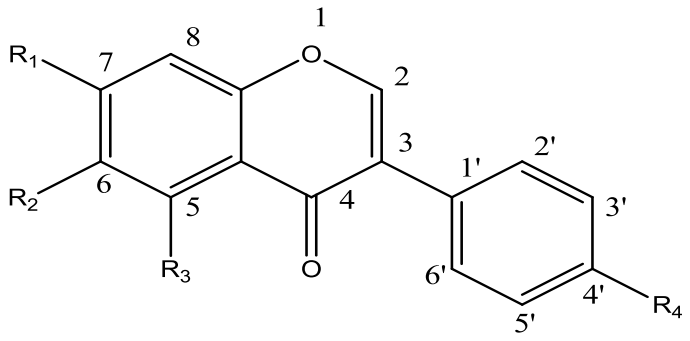
Cognitive abilities

During menopause many womens feel that their cognitive abilities decline. Diet high in soy increased person's long term and short term memory and mental flexibility[18]. A series of studies on brain structure, learning memory and anxiety in rats led to alter the volume of sexually dimorphic brain regions, increase anxiety and improve learning, logical thinking and planning ability in postmenopausal women[41,54].

Estrogen replacement therapy

ERT is recommended for postmenopausal women to prevent menopausal symptoms, osteoporosis and CVD, but it may cause cancer of breast[43]. So phytoestrogens are used as an alternative to ERT. Phytoestrogen supplements are commercially marketed for use by postmenopausal women as natural and safe alternatives to hormone replacement therapy.

STRUCTURE OF ISOFLAVONES



ISOFLAVONOIDS

ISOFLAVONES	R_1	R_2	R_3	R_4
Daidzein	**OH**	**H**	**H**	**OH**
Genistein	**OH**	**H**	**OH**	**OH**
Biochenin A	**OH**	**H**	**OH**	**OCH_3**
Formononetin	**OH**	**H**	**H**	**OCH_3**
Glycitein	**OH**	**OCH_3**	**H**	**OH**
Prunetin	**OCH_3**	**H**	**OH**	**OH**

Diaryl ring is important for estrogenic activity**.** In isoflavons, benzyl ring is present at 3 position, which increases its estrogenic activity than flavones. Two aromatic rings are separated by two carbons (carbonyl and vinylic carbon), increases the affinity to ER than separated by one carbon

The hydroxyl group and its position is important for estrogenic activity. If OH present are more than four, then it decreases the binding activity. If hydroxyl group is methylated then activity is diminished. And Isoprenylation of methylated isoflavones may increase the estrogenic activity. Hydroxyl groups at 6, 7 or 4^1 confers more potent estrogenic activity than hydroxyls at positions 3,5 or 2^1. Two adjacent OH on A or C ring , decreases the binding activity. E.g. 7,8 dihydroxyisoflavone. A OH at position 5 forms an intra-molecular hydrogen bond with the carbonyl C-4 (ring C) and it increases the acidity of 7-OH hydrogen and its ability to become a proton donor, thereby increasing ER binding affinity.

CONCLUSION

A balanced diet containing high amount of phytoestrogens such as fruits, grains and vegetables is able to exert beneficial effects. These effects are seen as beneficial to our health, in vitro studies support the role of phytoestrogens in lowering the risk of cancers such as breast cancer, prostate cancer and cardiovascular diseases. These have shown effects on osteoporosis and conditions associated with the menopause. Results froms the study have shown that genistein a isoflavone have played major role in controlling cell growth which is important in cancer prevention. But more research is required to establish the clear role of phytoestrogens.

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