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PREVENTION AGAINST CVD, OSTEOPOROSIS AND CARCINOMA IN POSTMENOPAUSAL WOMEN THROUGH PHYTOESTROGEN: A REVIEW STUDY

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ABSTRACT

Ageing affects differently to man and woman. The risks of cardiovascular disease and osteoporosis in women are doubled after menopause. Estrogen which is acting as prevention against these diseases throughout reproductive period is deficient during postmenopausal time and which makes women more vulnerable towards these diseases. Longer life expectancy of women has resulted in rise in their health needs. Tremendous amount of researches have been done on phytoestrogens which are plant derived compounds and are proving to be an effective alternative to Hormone replacement therapy. These plant derived compounds can reduce the risk of these conditions along with reducing financial burden and major side effects of hormone replacement therapy. Many sources of phytoestrogens in herbs are still unexplored. Protective effect of Soy which is rich in phytoestrogen is already studied. Herbs with phytoestrogenic effects can be studied in women with risk factors of developing these grave conditions. Clinical data for relieving menopausal symptoms through such herbs are sufficiently available. Further research is needed to study the same herbs for maintaining hormone homeostasis and preventing these challenging conditions.

KEYWORDS: Phytoestrogens, CVD, Osteoporosis, Carcinoma.

INTRODUCTION

Men and women reach old age with different prospects for older age, significantly because of sex hormone induced differences in the cholesterol lipoprotein profile and other

cardiovascular factors. Menopausal health is globally gaining significance as longevity in women has increased by 20-30 years while the age of menopause has been declining from 50-52 years to 45-50 years. Menopause, the permanent loss of menstruation after amenorrhea lasting more than 1 year due to the loss of estrogen production by the ovaries, is a major aging process of women and most women encounter this hormonal change between 40 and 55 yr of age.[1] Therefore, many women spend almost 1/3 of their lives in postmenopause. As women age, they are more likely to experience disease and disability.[2] Multiple health issues arise in postmenopausal period like cardiovascular diseases, osteoporosis which have gained attention of all health providers. Carcinoma of breast and endometrium as a long term consequence of hormone replacement therapy is demanding an effective alternative with no risk of carcinoma.

MATERIALS AND METHODS

Postmenopausal related conditions like osteoporosis, cardiovascular disease and carcinoma which are major health concern were studied in relation with hormonal changes. The efficacy of treatments along with risks and side effects were highlighted. The role of phytoestrogens in preventing these conditions and the researches evaluating the results are presented here.

Cardiovascular Disease and Menopause

The fact that estrogen deficiency is the major cause of health consequences in aging women is now accepted world wide.

CVD is the leading cause of death in women around the world. Hypertension affects more men than women until 55 years of age, but after age 55, the percentage of women is higher. Estrogen deficiency has been linked to the rapid increase in CVD in women who have undergone natural or surgical menopause.[3]

Menopause is a risk factor for CVD because estrogen withdrawal has a detrimental effect on cardiovascular function and metabolism. Other factors which increase risks are changes in body fat distribution from a gynaecoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased blood pressure, increased sympathetic tone, endothelial dysfunction and vascular inflammation which are attributed to estrogen deficiency.[4,5,6]

Osteoporosis and Menopause

Postmenopausal osteoporosis is associated with significant morbidity, mortality, reduction in quality of life and increasing health care costs. Estrogen deficiency leads to increased bone resorption and thus increases cortical porosity. It also augments erosion depth of bone by prolonging resorption phase of the remodelling cycle thorough increased osteoclast life span. Fractures with minimal trauma with poor healing and more financial burden are major concern. Prevention through achieving peak bone mass during adolescent and decreasing bone loss in postmenopausal period can optimize postmenopausal health.

Breast & Endometrial Carcinoma

The incidence of breast cancer in India is on the rise and is rapidly becoming the number one cancer in females pushing the cervical cancer to the second spot. The seriousness of the situation is apparent after going through recent data from Indian Council of Medical Research (ICMR). One fourth (or even approaching one thirds) of all female cancer cases are breast cancers. Breast cancer is the leading cause of cancer death, and is a major health concern for menopausal women, Any therapies that reduce or increase the risk will have a major impact on woman's health.

Endometrial carcinoma is a cancer that most primarily occurs in postmenopausal women and is increasingly virulent with advancing age. The role of estrogen in the development of endometrial cancers has clearly been established. Any factor that increases exposure to unopposed estrogen increases the risk of endometrial cancer.[7]

Hormone Replacement Therapy

Hormone replacement therapy was considered as an effective treatment in the female individuals at risk of developing osteoporosis and coronary heart disease. The HERS (Heart Estrogen/Progestin Replacement Study) data showed that long term HRT increases the risk of cardio vascular diseases. Hence hormone therapy is not a viable intervention for primary prevention of Coronary Heart Disease. It does not reduce or slow the progression of established coronary heart disease. It is also recommended as a conclusion of trials done by Women Health Initiative under HERS I and HERS II (The Heart and Estrogen Progestin Replacement study) that post-menopausal women with existing atherosclerosis should not be given hormone therapy.[8,9]

In addition to this, latest research data indicates an excess risk from HRT regarding the incidence of breast and endometrial cancer as well as increased incidence of stroke, coronary artery disease and other thrombotic diseases. The risk of cardiovascular event rather increased in women treated with HRT for many years after menopause.

Alternatives to HRT

The search for alternative to HRT with minimum risks and desired actions lead to development of new agents called as SERMs. Selective estrogen receptor modulators (SERMs) are a class of drugs that act on the estrogen receptor (ER). A characteristic that distinguishes these substances from pure ER agonists and antagonists (that is, full agonists and silent antagonists) is that their action is different in various tissues, thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues.[10]

The SERM – estrogen receptor complex is a unique structure which in the presence of several co-regulatory proteins, exhibits estrogenic and anti estrogenic activities in different target organs. They act as anti estrogenic in breast and uterine tissue, but estrogenic in bone, brain and lipid metabolism.[11]

Research studies conducted on management of CVD, breast cancer in post-menopausal women with alternatives like SERMs (Selective Estrogen Receptor Modulators) such as *Raloxifen* and *Tamoxifen* showed increases incidences of venous thromboembolism, DVT, and pulmonary embolism.

Hot flushes are increased with raloxifene and tamoxifen whereas raloxifene alone is associated with leg cramps. It is observed and concluded through various studies that Tamoxifen should not be used in patients with DVT, VTE and other thromboembolic diseases.[12,13] Increased occurrence of vaginal discharge and irregular menses has also been reported among women who use tamoxifen. Retinopathy has also been observed among women who use high-dose tamoxifen.[14]

Phytoestrogen – Natural alternative

Phytoestrogens are a diverse group of plant-derived compounds that structurally or functionally mimic mammalian estrogens and show potential benefits for human health. The research interest of phytoestrogen effect on animals was studied in 1940s but its beneficial

effect on humans especially in women is gaining attention of all medical sciences since last two decades. They 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 endometrium but act like an estrogen in providing possible protection against bone loss and heart diseases. Due to this agonist and antagonist effect of single molecule on different tissues, phytoestrogen minimizes risks of cardiovascular disease and osteoporosis while preventing breast carcinoma and endometrial carcinoma.

Classification of phytoestrogens

Most of the plants containing phytoestrogens are non steroidal. They belong to the family of compound called phenolics. They are divided into 3 groups.

(1) Isoflavones (2) Coumestans (3) Lignans

Isoflavones are further classified into.

(i) Diadzein (ii) Genistein (iii) Glycetin

Ayurveda, the oldest system of medicine, has provided many herbs which can be used in prevention of geriatric problems in women. About 300 herbs containing phytoestrogens and possessing estrogenic property have been studied; following is the list of some identified herbs containing phytoestrogens.[15,16]

Common phytoestrogenic food/herbs containing: Coumestrol

• Brassica spp. (Brussels Sprouts, Cabbage) • Pisum sativum (Pea) • Vigna radiata (Mungbean).

Common phytoestrogenic food/herbs containing: Biochanin A

• Baptisia tinctoria (Wild Indigo) • Vigna radiata (Mungbean)

Common phytoestrogenic food/herbs containing: Daidzein

• Phaseolus coccineus (Scarlet Runner Bean) • Pueraria spp. (Kudzu; Pueraria) • Vigna radiate.

Common phytoestrogenic food/herbs containing: Formononetin

• Pueraria spp. (Kudzu; Pueraria) • Vigna radiata (Mungbean).

Common phytoestrogenic food/herbs containing: Genistein

• Baptisia tinctoria (Wild Indigo) • **Glycyrrhiza glabra (Licorice root)** • Pueraria spp. (Kudzu; Pueraria) • Vigna radiata (Mungbean)

Common phytoestrogenic food/herbs containing: Beta-Sitosterol

• Allium cepa (Onion) • **Allium sativum (Garlic)** • Aloe vera (Aloe) • Anethum graveolens (Dill)

• Angelica archangelica (Angelica) • Angelica sinensis (Dong Quai) • Artemisia annua (Sweet Annie)

• Artemisia dracunculus (Tarragon) • Artemisia vulgaris (Mugwort) • Asarum canadense (Wild Ginger)

• Asclepias syriaca (Milkweed) • Calendula officinalis (Marigold)

• **Capsicum** annuum **(Chili Pepper)**

• Centella asiatica (Gotu Kola) • Commiphora myrrha (Myrrh) • Cucurbita pepo (Pumpkin) • Daucus carota (Wild Carrot) • **Echinacea spp. (Echinacea)** • Elettaria cardamomum (Cardamom) • **Eleutherococcus senticosus (Siberian Ginseng)**) • Foeniculum vulgare (Fennel) • **Glycyrrhiza glabra (Licorice root)** • Gossypium spp. (Cotton) • Hordeum vulgare (Barley) • Inula helenium (Elecampane) • Liquidambar orientalis (Oriental Styrax) • Mentha spicata (Spearmint) • Ocimum basilicum (Basil) • • Pisum sativum (Pea) • Plantago psyllium **(Psyllium seed)** • Punica granatum (Pomegranate) • Rosmarinus officinalis (Rosemary) • Smilax spp. (Sarsaparilla) • Solanum dulcamara (Bitter Nightshade) • Taraxacum officinale (Dandelion) • Theobroma cacao (Cacao) • Tribulus terrestris (Puncture-vine) • Trigonella foenum-graecum (Fenugreek) • Urginea maritima (Squill) • **Valeriana officinalis (Valerian)** • Viburnum opulus (Crampbark) • Vinca minor (Periwinkle) • Vitis vinifera (Wine Grape)• Withania somnifera (Ashwagandha) • Zea mays (Corn silk).

• **Zingiber officinale (Ginger) Common phytoestrogenic food/herbs containing: Diosgenin**

• Asparagus officinalis (Asparagus) • Balanites aegyptiaca (Desert Date) • Daucus carota (Wild Carrot) • Dioscorea bulbifera (Potato Yam) • Dioscorea villosa (Mexican Wild Yam) • Jateorhiza palmata (Calumba Root) • Momordica charantia (Bitter Melon) • Smilax spp. (Sarasaparilla) • Solanum dulcamara (Bittersweet) • Solanum nigrum (Black Nightshade) • Tribulus terrestris (Puncture-vine) • Trigonella foenum-graecum (Fenugreek)

RESULTS AND DISCUSSION

PHYTOESTROGENS AND CARDIOVASCULAR DISEASE

The beneficial effects of phytoestrogens on the cardiovascular systems is by inhibiting new intima formation, decrease in LDL, increase in HDL and thus providing protection from coronary artery disease. The cardiovascular benefits with isoflavones are by the following mechanism of action whereby cholesterol is reduced, inhibition of cholesterol synthesis reduction in lipoprotein levels and up regulation of LDL receptors in liver. In addition to this there is increased bile acid synthesis, by enhanced removal of cholesterol from LDL, responsible for making cholesterol dissolve in bile. Isoflavones, genestein and daidzein inhibit platelet aggregation by preventing thrombozane A2 form binding with its receptor.[17]

PHYTOESTROGEN IN PREVENTION OF OSTEOPOROSIS

Many researches conducted on soy and other sources of phytoestrogens which are structurally and functionally related to 17-beta-estradiol are known to have beneficial effect on Bone mineral density, bone turnover markers in postmenopausal women. This is through their action on both osteoblasts and osteoclasts through genomic and non genomic pathways, also by binding estrogen receptors on target cell surface. Isoflavones are hence believed to be helpful in therapy for osteoporosis.[18,19,20]

Other group of isoflavones like genistein and daidzein have shown to conserve bone in rodent models and in higher mammalian species.[21] In a further study -containing soy intake was found to physiologic fluctuations in bone turnover, thereby preventing osteoporosis, in addition to protection against breast cancer and cardiovascular diseases.[22,23]

PHYTOESTROGEN AND BREAST CANCER

Genistein inhibits the enzyme tyrosine kinase that is involved in the regulation of cell growth.[25] It also augments transforming growth factor B which inhibits the cell cycle and cell growth. It influences transcription factors that are involved in programmed cell death. Isoflavones also have antioxidant activity, anti proliferative effects and anti angiogenic effects.[25,26]

Phytoestrogens may exert a protective effect on breast cancer, which may be partly explained by reduction in endogenous sex steroid levels and reduction in luteal phase. The highest level of mammary cell proliferation occurs during the luteal phase of menstrual cycle, therefore prolongation of the follicular phase of the cycle would reduce the number of total cycles a

woman would have in her lifetime and thereby reduce the risk of getting breast cancer. Further, epidemiological studies suggest that soy containing diet in adult women is protective with regard to breast cancer and it may be beneficial if consumed in early life before puberty or during adolescence.[25]

All the epidemiologic studies and research on phytoestrogens, particularly studies relevant to genistein, daidzein, resveratrol and quercetin, suggests that these compounds do not act by a single mechanism to achieve their effects. Instead, these plant substances exert their effects by way of various mechanisms, including effects on estrogen-metabolizing enzymes, cell cycle, cell differentiation, proliferation, apoptosis, the inflammatory response and various cell signalling pathway to decrease risk of breast cancer.[26]

PHYTOESTROGENS AND ENDOMETRIAL CANCER

In a case control study it was found that high consumption of soy products and other legumes was associated with decreased risk of endometrial cancer.[27] In Hawaii's multiethnic population, greater consumption of tofu alone or in combination with other soy products was associated with a 50% reduction in endometrial cancer risk.

In one epidemiologic study, quercetin consumption in non – Asian population reduced endometrial cancer risk.[28]

In addition to lowering endogenous estrogen levels and binding competitively to estrogen receptors, phytoestrogens may also affect endometrial cancer risk through the inhibition of aromatase, the enzyme responsible for the conversion of androstenedione to estrone and thus affecting endometrial thickness and endometrial hyperplasia.

MECHANISM OF ACTION OF PHYTOESTROGEN

Adaptogenic activity of phytoestrogens is considered to be its main action. They can be beneficial in both hyperestrogenic and hypoestrogenic state in the body. Thus they have mixed estrogenic and anti estrogenic actions, depending on target tissue. This variation in activity may be due to the fact that phytoestrogens have a greater affinity for the estrogen receptor (beta) β compared with estrogen receptor (alpha) α. When phytoestrogens are metabolized, they bind on the same cellular sites as do estrogens.[29, 30, 31]

In addition to interaction with ERs, phytoestrogens may also modulate the concentration of endogenous estrogens by binding or inactivating some enzymes and may affect the

bioavailability of sex hormones by depressing or stimulating the synthesis of sex hormone-binding globulin (SHBG).[32]

CONCLUSION

Role of estrogen deficiency in cardiovascular disease and osteoporosis and use of HRT to prevent and manage these conditions which increases the risk of endometrial cancer and breast cancer is very well established. Search for a cost effective alternative led to tremendous researches and epidemiologic studies on phytoestrogens. In Ayurveda more than 300 herbs are identified to be containing phytoestrogens, but studies on their role in maintaining postmenopausal health and minimizing risk of these grave conditions is limited. Studies on Shatavari containing saponins classified under phytoestrogens has shown encouraging results in minimizing bone loss.[33,34] Further evaluation of these herbs is needed on cardiovascular functions, osteoporosis with minimizing the risk of developing breast carcinoma and endometrial carcinoma.

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