Preventive effects of phytoestrogens against postmenopausal osteoporosis as compared to the available therapeutic choices: An overview

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Abstract
Estrogen deficiency is a major risk factor for osteoporosis in postmenopausal women. Although hormone replacement therapy (HRT) has been rampantly used to recompense for the bone loss, but the procedure is coupled with severe adverse effects. Hence, there is a boost in the production of newer synthetic products to ward off the effects of menopause-related osteoporosis. As of today, there are several prescription products available for the treatment of postmenopause osteoporosis; most of these are estrogenic agents and combination products. Nevertheless, in view of the lack of effect and/or toxicity of these products, majority of the postmenopausal women are now fascinated by highly publicized natural products. This is an offshoot of the generalized consensus that these products are more effective and free from any adverse effects. Recently, certain plant-derived natural products, mostly phytoestrogens (isoflavones, lignans, coumestanes, stilbenes, flavonoids) and many more novel estrogen-like compounds in plants have been immensely used to prevent menopause-related depletion in bone mineral density (BMD). Although, a number of papers are published on menopause-related general symptoms, sexual dysfunction, cardiovascular diseases, Alzheimer’s disease, diabetes, colon, and breast cancers, there is paucity of literature on the accompanying osteoporosis and its treatment. In view of the controversies on synthetic hormones and drugs and drift of a major population of patients toward natural drugs, it was found worthwhile to investigate if these drugs are suitable to be used in the treatment of postmenopausal osteoporosis. Preparation of this paper is an attempt to review the (a) epidemiology of postmenopausal osteoporosis, (b) treatment modalities of postmenopausal osteoporosis by hormones and synthetic drugs and the associated drawbacks and adverse effects, and (c) prevention and treatment of postmenopausal osteoporosis by phytoestrogens, their drawbacks and toxicity. It is apparent that both the categories of treatment are useful and both have adverse effects, but the plant products are nonscientific and hence are not advised to be used till more studies are undertaken to ensure that the benefits clearly outweigh the risk, in addition to recognition by Food and Drug Administration.

Key words: Menopause, osteoporosis, phytoestrogens

INTRODUCTION
Hormonal changes in a woman’s body are conspicuous by the beginning of fertility at puberty with the onset of first menstrual bleeding and ending at menopause. The average age for the onset of the menopause is 45-51 and it is defined as having taken place when the woman completes 12 menstrual cycles without any menstrual bleeding. Following menopause, the ovaries stop producing estrogen, a hormone that helps prevent bone loss. The estrogen deficiency is known to cause significant alterations in bone metabolism. Some people may develop osteopenia, a condition characterized by low bone density. Osteopenia can eventually lead to osteoporosis, a more severe condition with lower bone density. Threat of osteoporosis is one of the most important health issues for menopausal women. Menopause, coupled with hypogonadism in women, strongly predisposes them to osteoporosis.1

The condition
Anyway it was found that women are more prone to osteoporosis due to lower “peak” bone mass and the higher risk of fractures. Consequently, the prevalence of lumbar spine and/or hip fractures has been related to osteoporosis beyond the age of 50 years. However, it is reported to be much lower than those reported for Caucasian women (30%). The incidence of osteoporotic fractures is estimated to be 1.5 million per year. Most of the American women under the age of 50 have normal BMD. However, between 35-50% of women over 50 have at least one vertebral fracture. By the age of 80 years, 27% are osteopenic and 70% are osteoporotic at the hip, lumbar spine or forearm with advancement in age. Extensive differences in the epidemiological pattern of osteoporosis among geographic and ethnic groups have been reported, but there is lack of information about the incidence of postmenopausal osteoporosis and related protective and risk factors in developing countries. Nevertheless, most available data in the literature are from western countries.

More than half of postmenopausal women in western countries lived in rural areas. The incidence of obesity, hypertension, hypothyroidism, diabetes, and osteoporosis was found to be more in these women due to a particular style of life they live. It is estimated that 10 million Americans >50 years old have osteoporosis and approximately 34 million are at risk of the disease. The incidence of fragility fractures is estimated to be 1.5 million per year. Most of the American women under the age of 50 have normal BMD. However, between 35-50% of women over 50 have at least one vertebral fracture. By the age of 80 years, 27% are osteopenic and 70% are osteoporotic at the hip, lumbar spine or forearm, and 20% in women who have reached 70 years of age. The incidence of osteoporosis in Northern European countries is very high. The incidence of hip fractures is common among women who have reached their 65th year of age. Majority of the incidents are associated with climate, which limits physical activity and exposure to sunlight. Nevertheless, despite the increased incidence of osteoporosis, strict preventive measures are not being adopted. Among the postmenopausal Mexican women, the prevalence of lumbar spine and/or hip has been related to osteoporosis beyond the age of 50 years. However, it is reported to be much lower than those reported for Caucasian women (30%). Furthermore, it was found that women are prone to osteoporosis two to three times more than men, due to lower “peak” bone mass and the accelerated loss that occurs after the menopause.
In a study on vertebral osteoporosis on German residents, Raspe et al.[17] have shown that the prevalence of back-, neck- and joint-pain is consistently higher in females than in males in all age groups. The prevalence in postmenopausal females (55-64) showed a peak. The total number of osteoporotic fractures in the Czech Republic is close to that in the developed western countries. The fractures of vertebrae and of the proximal femur are common.[18]

The incidence of osteoporosis is reported in 1/3 of the Turkish postmenopausal women. The different etiological factors were habitual tea, coffee, tobacco, and milk product consumption. Advanced age (> 65) and being illiterate were negative factors, while high education levels, being overweight, and being treated with HRT had a positive effect on BMD.[19] A study on the influence of educational level on BMD in Turkish postmenopausal women revealed that there is a significant correlation between educational level and BMD. Losses in BMD for women of lower educational level tend to be relatively high, and losses in spine and femur BMD showed a decrease with increasing educational level.[20] In a study on Caucasian premenopausal women, Gulbahar et al.[21] reported that the women with joint hyper mobility have lower BMD when compared to the controls and hyper mobility increases the risk for low bone mass.

Osteoporosis with postmenopause in Jordanian women is extremely high, and is even found in younger age categories. The age, years of menopause, low-density lipoprotein and follicle-stimulating hormone have strong independent associations with BMD at all lumbar and femoral neck regions. It is also reported that these women experience many potential risk factors including associated medical illnesses, and other hormonal alterations experienced during menopausal period. Therefore, increased health awareness and intensive screening programs are mandatory for early detection of low bone mass.[21] There were smaller postmenopausal decreases in femoral and radial BMD in Lebanese women compared with US/European women.[22] The prevalence of osteoporosis in Israel among postmenopause women (aged 45-74) is estimated to be 13.7%, which is similar to that for the United States. The association of osteoporosis with risk factors is age dependent.[23] The Jewish Menopausal women were more knowledgeable and showed great interest in physical activities.[24]

The exact age of menopause in African women is not known, but it is reported to occur earlier than European or American women. Although, multiple parity in a short period of time is the main reason, but social, economic, and nutritional factors may also influence the biological pattern.[25] The Egyptian women are shown to get menopause at 46 years approximately, which is low compared to many countries. Generally, they have a lower BMD compared to western women. Most of them suffer from osteoporosis after menopause, which is regarded by them as “just a physiological change”. There exists a need for an awareness campaign in order to educate them about this important stage of their lives.[26] The approximate age at menopause in women from Kenya is shown to be 48 years. However, a review of the current and past records show that the average age of menopause in women of Kenya, has remained relatively constant at 50 years, but almost all women are menopausal before they reach 55. Clinical symptoms include osteoporosis and increased incidence of bone fractures, in addition to other general symptoms of menopause.[27]

The age of menopause in Saudi women is 48 years approximately. This is similar to other Arab countries, but lower than western countries. This may be due to cultural differences, in addition to the role of genetics. Although, the incidence of osteoporosis is common among postmenopausal Saudi women, it is often associated with either, early or late onset of menopause.[28] Sadat-Ali et al.[29] found that osteoporosis and osteopenia are common (60%) among postmenopausal Saudi Arabian women. The causative factors are pregnancy, multiparity, and prolonged lactation. In a study on the prevalence of vertebral fractures in postmenopausal women in Saudi Arabia, Sadat-Ali et al.[30] showed that the mean age of the women getting the fractures was around 65. The reported incidence varies between 50-60% in Al-Khobar, an Eastern region of the Kingdom of Saudi Arabia. The results indicated that postmenopausal Saudi women in Alkhobar suffer from osteoporosis and osteopenia higher than those from other parts of the country.[31]

In Iran, regular consumption of cheese, milk, chicken, egg, fruit, consumption of tea, HRT and calcium supplements were found to be significant protective factors, while steroid therapy and consumption of red meat were the prominent risk factors for postmenopausal osteoporosis.[32] The average age for Indian women to get menopause is between 40-41 years, which is much earlier than the women in Egypt, Saudi Arabia and western countries. Most of the Indian women are from low-income groups and hence consume diets that have inadequate calories, proteins and micronutrients. Furthermore, the nourishment lacks calcium supplementation. Hospital-based data suggest that these women have osteoporotic hip fractures at a much earlier age than western women.[33] Regular consumption of soya, almonds, fish, fruits and milk tea appeared to be significant protective factors in India. Furthermore, pure vegetarianism in India was reported as one of the risk factors for osteoporosis.
There are some studies on comparison of postmenopausal osteoporosis between different countries. The available literature has depicted limited and scattered information on Asian and western populations, Jewish and Arab women and Iranian and Indian women. In a study on comparison of osteoporosis between Asian and western populations, Huang[36] found that the awareness and use of HRT among Asians were significantly low. A comparison between the Jewish and Arab menopausal women showed less concern for physical activity and calcium intake among the Arab women, while the Jewish menopausal women were more knowledgeable and show great interest in physical activities. However, expanding knowledge about osteoporosis may prove beneficial for increasing participation in preventive behavior in both Israeli-Jewish and Arab women groups. [24] There were no significant differences in association of risk factors and osteoporosis between Iranian and Indian subjects. A protective role of certain nutritional dietary components and also exercises are reported in both populations. These attributes can be exploited in preventive educational strategies on osteoporosis in both the countries. Consumption of red meat and steroid therapy in Iran and pure vegetarianism in India were observed to be risk factors in these two countries. The different protective factors were regular consumption of cheese, milk, chicken, egg, fruit, consumption of tea, in addition to calcium consumption and HRT in Iran, while in India the protective factors were regular consumption of Soya, almonds, fish, fruits and milk tea.[32]

**TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS BY HORMONES AND SYNTHETIC DRUGS**

With the advent of menopause, the levels of reproductive hormones fluctuate causing the symptoms of menopause including osteoporosis. These symptoms are regulated by HRT in the form of medication. Most of the hormones prescribed for HRT include estrogen, progesterin, progesterone, testosterone in different combination products such as prempro, acteulla, femhrt, comi patch, ortho-prefest, prephase, estratest, estropitate, estrin, medroxyprogesterone acetate.[37] (The generic names and formulation of these drugs[37] are detailed in Table 1.) Treatment with estrogens blocks the osteoclastic resorption and conserves the bone mass. Anabolic hormones, including progesterone, stimulate osteoblastic building of bone. The combination of estrogen and progesterone is known to lower the risk of uterine malignancy, besides curing the osteoporosis. In addition to estrogen therapy and progesterone replacement, the victims of fracture may benefit from androgen replacement to increase their bone mass. Furthermore, replacing androgens using nandrolone decanoate in women may cure the natural loss of their adrenal hormones.[38] There is an increase in the potential role for androgen supplementation in postmenopausal health. Androgen replacement is reported to provide additional relief of menopausal symptoms with a positive impact on bone density.[39] The HRT has been rampant ly used to recompense for the bone loss, but the procedure is coupled with severe adverse effects. Hence, there is a boost in the production of newer synthetic products to ward off the effects of menopause-related osteoporosis.

As of today, there are several prescription products available for the treatment of postmenopausal osteoporosis. The different prescription products [Table 2] that are given wide publicity include antiresorptive agents (bisphosphonates, ibandronate, calcitriol and selective estrogen receptor modulators -- SERMs (raloxifene, tamoxifen), bone anabolic agents (teriparatide, calcium salts, sodium fluoride) and some other agents (RANKL inhibitors, strontium ralenate; nutrition (calcium, vitamin D).[40-44] Bisphosphonates and strontium ralenate are good choices for first- or second-line treatment and estrogen/progesterin is no longer a first-line approach for the treatment of osteoporosis in postmenopausal women.[45] SERMs are defined as a group of compounds that behave both like estrogen agonists in some tissues and antagonists in other tissues,[46] while parathyroid hormone is used for the second-line treatment of osteoporosis in the elderly.[47]

**ADVERSE EFFECTS AND DRAWBACKS OF HORMONES AND SYNTHETIC DRUGS**

Although HRT and synthetic hormones are shown to recompense for the depletion of the hormone and to impede the bone loss, the treatment is controversial and has been associated with a number of complications and adverse effects.[48-53] The major toxicity of hormones is their carcinogenic potential. This et al.[54] reported that estrogens promote the growth of malignant cells. No authors listed[55] interpreted that the risk of breast cancer is increased in women using HRT; the incidence is directly proportional to the duration of use. The benefits derived from the synthetic hormones are time bound; the discontinuation of treatment often relapse the deterioration.[56] Moreover, the therapy is not advised
in case menopausal women who are unable to produce sufficient natural hormones. Estrogen-progesterin therapy in treatment of osteoporosis in postmenopausal women caused increased risk of breast cancer, stroke, venous thromboembolism, and coronary disease. Parathyroid hormone is discouraged because of its deleterious effects on bone. SERMs are reported to be incapable to prevent fractures associated with menopause. Bisphosphonate therapy is shown to cause osteonecrosis and a vascular necrosis of the jaw. Tissue SERM, Raloxifene, decreases serum total and low-density-lipoprotein cholesterol concentrations. Although it is known to reduce breast cancer risk, it increases thromboembolic events and hot flashes. Tibolone is a synthetic steroid whose metabolites have estrogenic, androgenic, and progestagenic properties. It is used in the management of osteoporosis in some countries; however, it was discontinued early due to an excess risk of stroke. Because of the reported carcinogenic potentials of hormones and the adverse effects of synthetic drugs, majority of the postmenopausal women were reluctant to be exposed to exogenous hormones and toxic drugs and are shifting to natural products (importantly, phytoestrogens) for relief.

Table 1: List of HRT medications and their formulations

| Drugs and their formulations used as HRT | Formulation | Trade name |
|----------------------------------------|-------------|------------|
| Conjugated equine estrogen and medroxyprogesterone acetate | In addition to what is indicated in the drug, it contains estrogen from urine of pregnant mares. It is also formulated with a 5 mg dose of progesterone | Prempro |
| Estradiol and norethindrone acetate | In addition to what is contained in the drug, it also contains synthetic, plant-based sterol | Activella |
| Ethinyl estradiol and norethindrone acetate | The composition is similar to activella, but with modified estradiol and different progesterin dosage. It also contains synthetic, plant-based sterol | Femhrt |
| Estradiol and norethindrone acetate | In addition to what is indicated in the drug, patch option with progesterin is given for women with an intact uterus | Combi patch |
| Estradiol and norgestimate | The ingredients are included as shown in the drug. Cyclic progesterin is added on a 6-day cycle. 3 days on, then 3 days off | Ortho-Prevest |
| Conjugated equine estrogen and medroxyprogesterone acetate | The ingredients are included as shown in the drug. Cyclic progesterin is added on a 28-day cycle: 14 days on and 14 days off | Premphase |
| Esterified estrogen and methyltestosterone | In addition to what is indicated in the drug. Adding testosterone may help women with severely diminished libido | Estratest |

Table 2: Synthetic or extracted products used to compensate HRT

| Generic name | Formulation | Trade name(s) |
|--------------|-------------|--------------|
| Ibandronate  | Ibandronate | Boniva       |
| Calcitonin   | Calcitonin  | Capsitonin   |
| Raloxifene   | A self-emulsifying raloxifene HCl liquid formulation | Evista |
| Tamoxifen    | Tamoxifen dihydrogen citrate, SOLTAMOX | Nolvadex, istubal, and valodex |
| Teriparatide | Teriparatide acetate, human recombinant PTH[1-34]] | Forteo |
| Calcium salts| Calcium     | Calcium salt |
| Sodium fluoride | Sodium fluoride | Sodium fluoride |
| Strontium ralenate | Strontium ralenate | Protaxos |
| Vitamin D    | Vitamin D   | Drisdol      |

The advantages and disadvantages of HRT and synthetic drugs are presented in Table 3.
TREATMENT OF POSTMENOPAUSAL
OSTEOPOROSIS BY PHYTOESTROGENS

Phytoestrogens are plant-derived polyphenol compounds that show a structural similarity to steroid hormone (17-beta-estradiol). Although phytoestrogens are not as potential as the endogenous estrogens, they are widely self-prescribed against the treatment of menopause and postmenopausal osteoporosis and are considered safe and beneficial throughout the world.\(^{62,63}\) Most of the flavonoids (isoflavones) are classified as phytoestrogens, based on their ability to mimic estrogen.\(^{64}\) The classical phytoestrogens constitute a group of compounds (isoflavones, lignans, coumestanes, stilbenes, flavonoids quercetin and kaempherol) of plant origin [Table 4].

Isoflavones are natural endocrine active phytoestrogens found in Leguminosae and are generally considered to prevent osteoporosis by promoting bone health. Exposure to these products is through soy foods and soy protein, in addition to processed foods or through supplements.\(^{65}\) They may be useful as dietary alternative or supplement to postmenopausal HRT, because of their beneficial effects on atherosclerosis and cancer risk.\(^{66}\) Soy isoflavones are structurally and functionally related to 17-beta-estradiol and are known to act on both osteoblasts and osteoclasts through genomic and nongenomic pathways and have beneficial effects on BMD, bone turnover markers, and bone mechanical strength in postmenopausal women.\(^{65,67}\) The effect of isoflavones on bone formation is by binding on estrogen receptors on the target cell surface; hence it is believed that isoflavones may help in the treatment of patients by estrogen replacement therapy for osteoporosis.\(^{68}\)

Genistein and daidzein are the other isoflavones of soy that have been shown to conserve bone in ovariectomized rodent models and probably have similar conservatory effects in higher mammalian species.\(^{69}\) Hooshmand et al.\(^{70}\) reported genistin-rich isoflavones to prevent loss of BMD in the rat model of ovaridectomy. Isoflavone-containing soy intake was found to physiologic fluctuations in bone turnover, thereby preventing osteoporosis, in addition to protection against breast cancer and cardiovascular diseases.\(^{71}\) [Table 4]

There are yet some other plants (black cohosh, licorice, red raspberry, red clover, and kudzu) that contain phenolic compounds and are suggested to have estrogenic potential for relieving menopausal symptoms.\(^{72}\) In a study to assess the estrogen bioactivity of some herbs, Oerter Klein et al.\(^{73}\) found that soy, clover, licorice, hops, and fo-ti to have high

### Table 3: Advantages and disadvantages of hormone replacement therapy and synthetic drugs

| Advantages | Disadvantages |
|------------|--------------|
| HRT includes medications containing female hormones replace the ones the body no longer makes after menopause | Estrogen without progestin increase the risk of uterine cancer |
| Estrogens blocks osteoclastic resorption and conserves bone mass | Cause thromboembolism and coronary disease |
| Combination of estrogen and progesterone lower the risk of uterine malignancy and cure osteoporosis | Cause breast cancer |
| In addition to estrogen therapy and progesterone replacement, the victims of fracture may benefit from androgen replacement to increase the bone mass | Cause stroke |
| Replacing androgens using nandrolo decanoate in women may cure the natural loss of their adrenal hormones | Cause blood clots |
| HRT is effective in preventing symptoms of menopause, including hot flashes, osteoporosis, vaginal atrophy | Cause mammography abnormalities |
| Decrease heart disease | The discontinuation of treatment often relapse the deterioration |
| Decrease colorectal cancer | HRT cannot be used in women whose system cannot produce sufficient endogenous hormones |
| Benefits are time bound | Parathyroid hormone cause deleterious effects on bone |
| | SERMs are incapable to prevent fractures associated with menopause |
| | Bisphosphonates cause osteonecrosis and vascular necrosis of the jaw |
| | SERM and raloxifene decreases serum total and low-density lipoprotein cholesterol concentrations |
| | Tribolone cause excess risk of stroke |
| | HRT is not recommended by FDA |
Estrogen activity, while chaste tree berry, black cohosh and dong quai did not have measurable estrogen activity. They further found that removal of the glycone group from soy increases its estrogen bioactivity significantly. Many more novel estrogen-like compounds in the plant kingdom are being discovered, thus expanding the spectrum of phytoestrogens in nature.\textsuperscript{[74,75]} Danggui Buxue Tang, a Chinese medicinal decoction containing Radix astragali and Radix angelicae sinensis, was found to stimulate osteoblast proliferation, estrogen promoter activation, in addition to increasing the anti-platelet aggregation activity.\textsuperscript{[76]} Red clover (Trifolium pratense), a phytoestrogen is shown to

### Table 4: List of plants and herbs used to compensate HRT

| Plants having estrogenic property | Phytoconstituent/ decoction | Family         |
|----------------------------------|-----------------------------|----------------|
| Glycine max, soy bean, soya bean | Isoflavones (genistein, daidzein) | Fabaceae       |
| Kadsura interior                 | Plant phenol (lignans)      | Schisandraceae |
| Sophora japonica                 | Coumestanes                 | Fabaceae       |
| Vitis vinifera                   | Stilbenes                   | Vitaceae       |
| Schrad                           | Quercetin (flavonoids)      | Cucurbitaceae  |
| Asparagus racemosus              | Kaempferol                   | Asparagaceae   |
| Cimifuga racemosa (black cohosh) | Cimifugoside                | Ranunculaceae  |
| Glycyrrhiza glabra (licorice)    | Glycyrrhizin                | Papilionaceae  |
| Rubus idaeus (red raspberry)     | Pectin, citric acid and malic acid | Rosaceae      |
| Trifolium pratense (red clover)  | Phenolic glycosides         | Fabaceae       |
| Pueraria lobata (kudzu)          | Flavonoids, isoflavonoids, daidzein | Fabaceae    |
| Radix astragali (astragalus root) | Polysaccharides             | Fabaceae       |
| Angelicae sinensis (dong quai)   | Ligustilide, n-butylidine phthalide, palmitic acid, bet-sitosterol | Apiaceae    |
| Humulus lupulus (hops)           | Sesquiterpene               | Cannabaceae   |
| Polygonum multiflorum (fo-ti root) | Anthraquinones             | Liliaceae     |
| Vitis vinifera                   | Flavonoids, glycosides, terpenoids | Verbenaceae  |
| Camellia sinensiswi (green tea) | Polyphenols                  | Theaceae       |

### Table 5: Advantages and disadvantages of plants and herbs used against HRT

| Advantages                                                                 | Disadvantages                                                                 |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Isoflavones are reported to prevent osteoporosis by promoting bone health and prevent breast cancer and cardiovascular diseases | Phytoestrogens are considered as endocrine disruptors, indicating that they have potential to cause adverse health effects |
| Soy isoflavones are known to act on osteoblasts and osteoclasts and have beneficial effects on mineral density | Supplemental phytoestrogens are shown to cause grade 1 endometrioid adenocarcinoma of the endometrium |
| Genistein and daidzein conserve bone in ovariectomized rodent models | Ingestion of phytoestrogens affects breast growth and lactation, uterine diseases, and fibroids |
| Plants like black cohosh, licorice, red raspberry, red clover, and kudzu are suggested to have estrogen potential for relieving menopausal symptoms | Chaparral is shown to be associated with acute nonviral toxic hepatitis |
| Species of radix were found to stimulate osteoblast proliferation, in addition to increasing the anti-platelet aggregating activity | There is lack of analytical standards of phytoestrogens |
| Camellia sinensis is shown to improve the markers of osteoporosis, such as bone resorption, osteoclast activity, collagen degradation, bone loss, and bone density | There is limited scientific evidence describing different constituents, active ingredients |
|                                                                          | The beneficial effects of isoflavones on bone are life-stage specific and dependent on the number of estrogen receptors and endogenous hormone background |
|                                                                          | The results on experimental research of these products are conflicting with differences in study design, estrogen status |
|                                                                          | There is growing evidence of the impact of estrogen contaminants in the herbal products and food supplements |
|                                                                          | Use of isoflavine genistein is reported to induce proteinase inhibitor 9 which blocks the cytotoxicity of breast cancer cells by immune cells |
|                                                                          | The efficacy and long-term safety of these products are not regulated by the Food and Drug Administration |
improve deteriorating bone health during menopause. It was also found to improve arterial compliance, a risk factor for atherosclerosis.[77] Whelan et al.[78] showed natural health products to prevent and treat osteoporosis in postmenopausal women. Das et al.[79] found that the supplementation of the phytoestrogen (Camellia sinensis) showed a significant improvement in the markers of osteoporosis, such as bone resorption and osteoclastic activity, collagen degradation, bone loss, and bone density [Table 4].

**ADVERSE EFFECTS AND DRAWBACKS OF PHYTOESTROGENS**

Laboratory studies in animals showed that the treatment with phytoestrogens (soy isoflavones) has serious adverse effects.[80] The extensive use of supplemental phytoestrogens is shown to cause grade 1 endometrioid adenocarcinoma of the endometrium.[81] McLachlan et al.[82] found that ingestion of phytoestrogens affects breast growth and lactation and has a role in uterine diseases such as fibroids and endometriosis. Chaparral, an estrogen-containing product, is shown to be associated with acute nonviral toxic hepatitis.[83] In addition to the adverse effects of phytoestrogens, they are associated with some serious drawbacks: (1) There is lack of analytical standards of phytoestrogens with no adequate methods for measurement of their levels in foods and the individual variability of metabolism of precursors introduced with the diet. Thus, there is utter confusion about the effectiveness of these products.[84] (2) There is limited scientific evidence describing different constituents, active ingredients, the dose, in addition to the presence of some unexpected agents.[84,85] (3) The beneficial effects of isoflavones on bone are life-stage specific and dependent on the number of estrogen receptors and endogenous hormone background.[86] (4) The results on experimental research of these products are haphazard. They are conflicting with differences in study design, estrogen status of the body, and metabolism.[67] (5) There is growing evidence of the impact of estrogenic contaminants in the herbal products and food supplements and the ingestion of which might induce feminizing potentials in the male population too.[82] (6) Use of isoflavine genistein is reported to induce proteinase inhibitor 9, which is known to block the cytotoxicity of breast cancer cells by immune cells.[86] Finally, (7) the efficacy and long-term safety of these products are not regulated by the Food and Drug Administration.[64] The advantages and disadvantages of plants and herbs used to compensate HRT are presented in Table 5.

**CONCLUSION**

Deficiency of estrogen is known to cause significant alterations in bone metabolism. HRT therapy is considered as the major option to recompense the estrogen deficits. However, several reports associate it with serious adverse effects, in addition to an unfavorable and expensive procedure. Hence, several new drugs and hormonal preparations are being produced and marketed in order to substitute the HRT therapy. Nevertheless, in view of their deficient impact on the target and known toxicity including malignancy, most women are now enthralled by the extremely publicized natural products, including, phytoestrogens. These products are shown to be health protective in menopausal complaints associated with osteoporosis. Nonetheless, ingestion of phytoestrogens is shown to affect breast growth and lactation and has a role in uterine diseases such as fibroids and endometriosis. Furthermore, extensive use of supplemental phytoestrogens is reported to cause nonviral toxic hepatitis, grade 1 endometrioid adenocarcinoma of the endometrium. The effect of phytoestrogen is shown to be dependent on the number of estrogen receptors and endogenous hormone background. There is lack of scientific evidence on active constituents and definite dose; hence, the effectiveness of these products is uncertain. Moreover, their efficacy and long-term safety are not synchronized by the Food and Drug Administration. Taken together, it is apparent that both the synthetic hormones and drugs and phytoestrogens can be used against postmenopausal osteoporosis and both have adverse effects. Nevertheless, the synthetic hormones and drugs are scientific and regulated by the Food and Drug Administration, while the plant products are nonscientific and are not advised to be used till more studies are undertaken to ensure that the amount of benefit clearly outweighs the amount of risk, in addition to recognition by Food and Drug Administration.

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