



## RESEARCH ARTICLE

### ROLE OF PHYTOESTROGENS AS AN ALTERNATIVE TO HORMONE REPLACEMENT THERAPY IN POSTMENOPAUSAL WOMEN

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#### ABSTRACT

Menopause is characterized by rapid and progressive reduction in estradiol which brings about physiological and psychological changes in a woman's life. It is estimated that in 1998, there were over 477 million postmenopausal women in the world which may rise to 1.1 billion by the year 2025. Menopause is associated with vasomotor symptoms, loss of bone mineral density, urogenital atrophy, increased cardiovascular risk, sexual dysfunction which decreases the quality of life (QOL). Hormone replacement therapy (HRT) is the most common preferred treatment option for management of postmenopausal symptoms. The Women's Health Initiative (WHI) study demonstrates that the major risks of HRT are venous thrombo-embolism, breast cancer, cardiovascular diseases etc. Hence, alternative treatments are needed to overcome this problem with an intention to improve the women's QOL. In Unani system of medicine, phytoestrogens are emerging as an alternative to estrogen in the treatment of postmenopausal symptoms and due to the structural similarities to selective estrogen receptor modulator; it does not show negative side effects as compare to conventional therapies. The present paper is an effort to highlight the role of phytoestrogens present in Unani system of medicine which have multifaceted pharmacological actions and could be used as alternative to HRT.

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## INTRODUCTION

Unani system of medicine is a great healing art as well as science, whose theories, philosophies and practice of medicine are most appropriate to the human biological system which is mainly based on temperament. Unani physicians have divided the entire period of life into four stages based on the quantity of *Rutubate ghariziyah* or *ratubateustuqussiyah* present in the body which are known as *asnanarba'* (four ages). These are *sin-al-namu* (period of growth and development), *sin-al-waquf* (adult-hood), *sin-al-kahulah* (Aetusverelis), *sin-al-shaykhukhah* (old age). *Sine yaas* (Menopause) occurs in the age group of *sin-al-kahulah* (40-60 years). (Ahmed, 2009)

## MATERIALS AND METHODS

For Unani concept of menopause, available authentic text of Unani Medicine was searched.

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Literature was also searched on PubMed/Google scholar with the keywords; Herbs for menopause, phytoestrogens, Unani medicine, Hormone replacement therapy.

## Etiopathogenesis

In Unani system of medicine, post-menopausal syndrome is not defined the same as known today, due to lack of biochemical analysis of blood parameters, almost all disease states have been defined based on clinical observations. The most obvious manifestation of PMS is amenorrhoea. It occurs at 40-50 years of age which is the actual age of *sinneyaas*. Temperament of women changes to cold and dry at menopause due to reduction in *ratubateghariziya* and *hararateghariziya* which begins from middle age (process of aging) as a result basal metabolic rate decreases, which in turn leads to decline in the moisture of the body (Shah, 2007). Liver is considered to be one of the dynamic and vital organs of the body responsible for metabolic functions whose temperament is hot & moist (Ahmed, 2009). At menopause, temperament of women changes to cold and dry which leads to *zo'afejigar* resulting in *zo'afequwwatedafi'a* and

*quwwatemumayyeza*. Hence, liver is unable to separate *maaiyat* from blood leading to formation of *Ghaleez khoon* (viscous blood), which in turn causes *suddaeurooqirehm* and *burudaterehm* resulting in amenorrhoea. (Ibn Sina, 2010) (Razi Abz, 2001). *Buqrat* states that temperament of *khiltesauda* is same as temperament of women at menopause, which may cause *ehtebase tams* (amenorrhoea). Diseases caused by *khiltesauda* are similar to those found in postmenopausal women like hysteria, melancholia, insomnia etc. (Tabri RAA, 2010) Hence, it can be concluded that change in temperament during menopause causes *zo'afejigar*, which in turn leads to abnormal production of *khiltesauda*. It affects *quwa* (faculty) & *Af'al* (function) of the different organ leading to menopausal symptoms.

### Clinical features

*Ibn Sina* mentioned that menopausal women may suffer from following symptoms:

**Vasomotor symptoms:** Hot flushes, excessive sweating (Azam HKM, 2011) (Ibn Sina, 2010)

**Genitourinary disorders:** Dysuria, oliguria & dryness of vagina. (Ibn Sina, 2010)

**Gastrointestinal disorders:** Indigestion, anorexia, gastritis and ascites (Razi Abz, 2001)

**CNS disorders:** Epilepsy, Headache, Paralysis, Hysteria (Tabri, 2010)

**Cardiovascular disorders:** Palpitation, fatigue (Ibn Sina 2010, p.1096-97) (Azam, 2011)

**Respiratory system disorders:** Cough, Asthma (Tabri, 2010)

**Musculoskeletal system:** Back ache, neck pain (Ibn Sina, 2010)

### Management

**A) *Ilajbilghiza* (Dietotherapy):** During menopause hot & moist diet is recommended for correction of temperament.

**Fig (*Ficus carica* Linn.):** It is hot and moist in temperament (Itrat *et al.*, 2013) and act as laxative and expectorant. Calcium level in fig is very high. It contains essential fatty acids, omega-3, omega-6 and phytoesterol which has a significant anti-cholesterolemic effect and helps in proper functioning of the heart, brain and nervous system. Fiber present in fig reduces the risk of colo-rectal cancer. (Khare, 2007) Hence, daily intake of fig may be useful in prevention of postmenopausal osteoporosis, cardiovascular diseases & cancer.

**Wheat (*Triticum aestivum* Linn):** It is moderate hot in temperament helps in restoration of *hararateghareeziya*. Roasted wheat flour is *muqawwiejigar* (Itrat *et al.*, 2013) and wheat germ oil is rich in tocopherol (Vitamin E) and ergosterol (provitamin D). Vitamin E is anti-oxidant and helps in improvement of cognition. (Villiers and Pines, 2013) In vivo

study on adult rats has shown that wheat germ oil significantly decreased VLDL-cholesterol, triglycerides, and increased the HDL-cholesterol. (Khare, 2007) (Reddy and Rao, 2013) Hence, use of wheat in daily diet prevents cardiovascular diseases & improves cognition in post-menopausal women. (Villiers and Pines, 2013)

**Gram (*Cicer arietinum* Linn):** It's hot in temperament and contains Isoflavones, biochanin A and form one tin which exhibits hypolipidemic activity. Seed contains pangamic acid which has anti-stress and anti-hyperlipidemic properties. (Khare, 2007) Hence, useful in post-menopausal depression and prevents cardiovascular disorders.

**Coconut (*Cocos nucifera*):** It's temperament is hot and moist and it has a high nutritive value. (Itrat *et al.*, 2013) Fruit is used as stomachic, laxative, diuretic and sedative useful in dyspepsia and burning sensation. Endosperm oil is used in alopecia due to antiseptic property and root is used in genito-urinary disorders. (Khare, 2007)

**Honey:** It is hot in temperament (Itrat *et al.*, 2013) and contains flavonoids which exhibits a variety of biological effects including anti-bacterial, anti-inflammatory, vasodilator and antithrombotic. (Cook and Sammon, 1996) (Yaacob and Kadir, 2013) It has anti-oxidant and anti-inflammatory effects which inhibits pro-inflammatory cytokines responsible for bone loss and thus prevents postmenopausal osteoporosis.

### *Ilajbiltadbeer* (Regimenal therapy)

Moderate exercise & moderate massage with hot oil is recommended by Unani physician in postmenopausal women. International menopausal society recommended at least 150 minutes of moderate-intensity exercise per week, which reduces hot flushes, improves mood and quality of life. (Villiers and Pines, 2013) Study conducted by Oleivira *et al.* suggested that therapeutic massage is beneficial for improving subjective sleep quality, depression and anxiety in postmenopausal women.

### *Ilajbildawa* (Pharmacotherapy)

**Phytoestrogens:** These are non-steroidal diverse group of plant derived substances or metabolite that induces biological responses in vertebrates and can mimic or modulate the actions of endogenous estrogens usually binding to estrogen receptors. (Ashajyothi and Rao, 2009)

Based on their chemical structure, it can be classified as isoflavonoids, flavonoids, anthraquinones, triterpenes, lignans, and saponins and these comprise the major phytoestrogens. It structurally resembles estrogen and has property of SERM. In vivo study suggested that phytoestrogens can affect the regulation of ovarian cycles, promotion of growth, differentiation and physiological functions of female genital tract, pituitary, breast, several other organs and tissues. (Ashajyothi and Rao, 2009) According to British Menopausal Society 2013 phytoestrogens consumption provide relief from perimenopausal vasomotor symptoms such as hot flushes, night sweats (Patisaul and Jefferson, 2010) and has good effect on skeleton and cardiovascular system as well. (Panay and

Hamoda, 2013) Following are the list of Unanidrugs which possess different types of phytoestrogens and can be used in alleviating post-menopausal symptoms.



Fig.No.1: *Ispast/Red Clover (Trifoliumpratense Linn)*

**1. *Ispast/ Red Clover (Trifoliumpratense Linn)*:** Flowers and leaves possess isoflavones, formononetin and biochanin A which has estrogenic property and relief post-menopausal symptoms. *The British Herbal Pharmacopoeia* recognizes anti-inflammatory property of flower. It also possesses deobstruent, antispasmodic, expectorant, sedative & antineoplastic properties. A placebo controlled randomized clinical trial conducted by Tice *et al*, 2003 on post-menopausal women showed significant decrease in frequency of hot flashes. (Geller and Laura, 2005)



Fig. 2. *Satavar (Asparagus racemosus)*

**2. *Satavar (Asparagus racemosus)*:** *Asparagus racemosus* is mainly known for its phytoestrogenic properties. It has anti-stress, anti-diarrhoeal, anti-dyspepsia, adaptogenic, anti-ulcerogenic, antioxidant and cardio protective actions. The major active constituents of *Asparagus racemosus* are steroidal saponins (Shatavarins I–IV) which are present in roots. (Ashajyothi and Rao, 2009) (Khare, 2007).



Fig.3. *Anar/Pomegranate (Punicagranatum)*

**3. *Anar/Pomegranate (Punicagranatum)*:** A prospective, randomized, placebo-controlled, double-blind study demonstrated that *Punicagranatum* seed oil has significant role in insomnia in postmenopausal women. It is a rich source of sterolic phytoestrogens:  $\beta$ -sitosterol, campesterol, punicic acid, ellagic acid and stigmasterol. (Auerbach *et al.*, 2012) Rind of fruit has stomachic and digestive actions and it is used in diarrhoea, uterine disorders, palpitation & excessive thirst. Bark and root are febrifuge and is used in night sweats. Powder of flower buds is used in bronchitis. The proanthocyanidins of pomegranate showed hypolipidaemic activity by their ability to enhance resistance of vascular wall preventing penetration of cholesterol into atherogenic lipoproteins (Khare, 2007). Hence, it is useful in improvement of vasomotor symptoms, disorders of cardiovascular & respiratory system.



Fig.4. *Asaroon/Valerian (Valerian wallichii)*

**4. *Asaroon/Valerian (Valerian wallichii)*:** A randomized, triple-blind, controlled trial of valerian extract has shown improvement of sleep quality in postmenopausal women experiencing insomnia. (Taavorian and Ekbatani, 2011) Rhizome and root contains Cyclopentapyrans, which exhibits sedative, tranquilizing and bacteriocidal properties (Khare, 2007).



Fig.5.Maweez/Grapes (*Vitisvinifera*)

**5. Maweez/Grapes (*Vitisvinifera*):** It has polyphenols like resveratrol and pterostilbene which act as antioxidants & anti-cancer. It reduces mortality from coronary heart disease by increasing high density lipoproteins like cholesterol and inhibiting platelet aggregation. (Khare, 2007)



Fig.6. Katan/Flax seeds/Linseed (*Linumusatissimum* Linn.)

**6. Katan/Flax seeds/Linseed (*Linumusatissimum* Linn.):** Flax seed is the richest source of Lignans, which are reported to have both weak estrogenic and antiestrogenic activities. It interferes with sex hormone metabolism, increases SHBG from liver and thereby decreases the clearance of circulating estrogen. It act as SERM; it exhibit antioxidant property and play a role in limiting osteoclast formation and bone resorption, thus it reduces bone loss in postmenopausal women.

The seeds are an excellent source of dietary alpha-linolenic acid for modifying plasma and tissue lipids. Human studies demonstrated the use of flaxseed in atherosclerosis, hypercholesterolemia, chronic renal diseases and in prevention of cancer due to the presence of active principle: lignan precursor secoisolariciresinol di glycoside (Khare, 2007).



Fig.No.7. Barsem/Alfalfa (*Medicago sativa* Linn.)

**7. Barsem/Alfalfa (*Medicago sativa* Linn.):** Alfalfa contains the highest concentration of coumestrol, which is the most potent phytoestrogen. In vivo study has shown that seeds extracts on rabbits has prevented hypercholesterolemia, triglyceridemia & atherogenesis due to presence of saponins. Human trials have shown that alfalfa extract completely reduces hot flushes and night sweats. Hence it has traditionally been used for women with menopausal symptoms. (Khare, 2007)



Fig.No.8:Badiyan/saunf/Fennel (*Foeniculumvulgare* Mill)

**8. Badiyan/saunf/Fennel (*Foeniculumvulgare* Mill):**A double-blind randomized placebo-controlled trial has shown that *Foeniculumvulgare* vaginal cream has significant role on vaginal atrophy (Yaralizadeh and Abedi, 2015). In vivo study has shown that ethanolic extract of *Foeniculumvulgare* possesses osteoprotective effect in post-menopausal women (Mahmoudieta, 2012)

**9. Methi/Fenugreek (*Trigonellafoenum* Linn.)**

In vivo animal study has shown that the administration of *T. foenum-graecum* improves metabolic features, and corrects inflammatory alterations associated with menopause which is attributed to phytoestrogen compounds like *diosgenin* (AbedinzadeNasri et al., 2015).

Following are the List of Unani drugs with phytoestrogens namely isoflavonoids, flavonoids, anthraquinones, triterpenes, lignans and saponins. These comprise the major phytoestrogens.

Table 1. List of Unani medicine which possess *Isoflavones*

| S.N. | Unani name | Botanical name                     | Family                         | part used   | Action and uses   |
|------|------------|------------------------------------|--------------------------------|-------------|---|
| 1.   | Arhar      | <i>Cajanuscajan</i> Linn.          | <i>Papilionaceae; Fabaceae</i> | LeavesPulse | Anti-hypercholesterolaemic  |
| 2.   | Nakhud     | <i>Cicerarietinum</i> Linn.        | <i>Papilionaceae; Fabaceae</i> | Leavespulse | Antistress, antihyperlipidemic                                      |
| 3.   | Seesham    | <i>Dalbergiasissoo</i> Roxb ex DC. | <i>Papilionaceae; Fabaceae</i> | Barkwood    | Anti-hypercholesterolaemic  |
| 4.   | Barsen     | <i>Medicagosativa</i> Linn.        | <i>Papilionaceae; Fabaceae</i> | SeedFlower  | Stimulant,astringent, Anticholerin                                  |
| 5.   | Irsa       | <i>Iris ensata</i> Thunb           | <i>Iridaceae</i>               | Leavesroot  | Anticholesterolemic   |
| 6.   | Ispast     | <i>Trifolium pretense</i>          | <i>Papilionaceae</i>           | Flower      | Diabetes and hypertension.<br>Liver diseases<br>Sedative,Bronchitis |

Table 2. List of Unani medicine which possess *Lignans*

| S.N. | Unani Name       | Botanical name                   | Family                                    | Part used      | Actionand uses  |
|------|------------------|----------------------------------|---|----------------|---|
| 1.   | Qurtum           | <i>Carthamustinctorius</i> Linn. | <i>Asteraceae</i>                         | OilFlower      | Arteriosclerosis Coronary heart disease<br>Kidney disorders |
| 2.   | Kunjad, Til      | <i>Sesamum indicum</i> Linn      | <i>Pedaliaceae</i>                        | SeedsOil       | Diuretic, laxative,Useful in amenorrhoea                    |
| 3.   | KishmishKaabu li | <i>Viscummonoicum</i> Roxb.      | <i>Viscaceae;</i><br><i>Laoranthaceae</i> | Leave<br>Fruit | Cardiotonic activity,Immunomodulator,<br>Antineoplastic     |
| 4.   | Afsanteen        | <i>Artemisia vulgaris</i> Linn.  | <i>Compositae;Asteraceae</i>              |                | Antispasmodic, Nervine tonic                                |

Table 3. List of Unani medicine which possess *Anthraquinones*

| S. N. | Unani name          | Botanical name  | Family                                     | Part used              | Action and uses   |
|-------|---------------------|---|--|------------------------|---|
| 1.    | Sanaa-makki         | <i>Cassia angustifolia</i> Vahl                             | <i>Caesalpinaceae</i>                      | LeavesDried fruits     | Laxative  |
| 2.    | Kasondi             | <i>Cassia occidentalis</i> Linn                             | <i>Calsalpinaceae</i>                      | Leaves, Roots          | Diuretic, Tonic,Expectorant   |
| 3.    | UsaareRewand        | <i>Rheum officinale</i> Baillon                             | <i>Polygonaceae</i>                        | Rhubarb                | Anti-inflammatory, Liver diseases                                   |
| 4.    | Gul-baglaa          | <i>Rhinacanthusnasutus</i> Kurz                             | <i>Acanthaceae</i>                         | Leaf, seed, root       | Skin diseases   |
| 5.    | Manjeeth            | <i>Rubiaccordifolia</i> Linn                                | <i>Rubiaceae</i>                           | Roots, Dried stems     | Blood purifier,<br>Urogenitaldisorders, Rheumatism                  |
| 6.    | HammazBarri         | <i>Rumexacetosa</i> Linn                                    | <i>Polygonaceae</i>                        | Flower, Root, Leaf     | Laxative, Hepatoprotective  |
| 7.    | Beejband<br>Haleela | <i>Rumexmaritimus</i> Linn<br><i>Terminaliachebula</i> Retz | <i>Polygonaceae</i><br><i>Combretaceae</i> | Leaves, Seeds<br>Fruit | Aphrodisiac, Laxative<br>Hepato-renaldisorders,<br>Bronchial asthma |
| 9.    | Siras               | <i>Albizialebeck</i> (Linn)                                 | <i>Mimosaceae</i>                          | Barks, Seeds, Root     | Bronchitis<br>Asthma  |
| 10    | Chaksu              | <i>Cassia absus</i> Linn                                    | <i>Caesalpinaceae</i>                      | Seed, Roots            | Blood-purifier, Stimulant   |

Table 4. List of Unani medicine which possess *Saponins*

| S.N. | Unani name     | Botanical name                                   | Family                  | Part used        | Action and uses                                 |
|------|----------------|--|-------------------------|------------------|---|
| 1.   | Kateera        | <i>Cochlospermungossypium</i> DC.                | <i>Cochlospermaceae</i> | Gum              | Sedative  |
| 2.   | Ushbahindi     | <i>Decalepishamiltonii</i> Wight & Arn.          | <i>Asclepiadaceae</i>   | Root             | Diabetics Blood purifier                        |
| 3.   | Khubkalan      | <i>DescurainiaSophia</i><br>(Linn.)Webb ex Prant | <i>Brassicaceae</i>     | Leaves<br>Flower | Expectorant,<br>Anti-inflammatory,Hypoglycaemic |
| 4.   | Chobchini.     | <i>Smilax glabra</i> Roxb.                       | <i>Liliaceae</i>        | Roots            | Blood purifier                                  |
| 5.   | Khaar-e-Khasak | <i>Tribulusterrestris</i> Linn                   | <i>Zygophyllaceae</i>   | Fruits           | HypoglycaemicTonic& aphrodisiac                 |
| 6.   | SaatarFaarsi   | <i>Zatariamultiflora</i> Boiss.                  | <i>Labiatae</i>         | OilHerb          | Hepatoprotective, Diuretic                      |

(Khare, 2007)



Fig.9. Methi/Fenugreek (*Trigonellafoenum* Linn.)



Fig.10. Kunjad/ Til/Sesame (*Sesamum indicum* Linn.)

**Kunjad/Til/Sesame (*Sesamum indicum* Linn.):** Seeds are an important source of protein, thiamine and niacin. It exhibits diuretic, laxative and emollient actions. Leaves are used in affections of kidney and bladder. It has phenolic antioxidant namely sesamol. Non-saponifiable fraction of theseed oil gave sterols, lignans, sesamin and nitrolactone, sesamol. (Khare, 2007)



Fig.11. Anisoon/ *Pimpinellaanisum*

**Anisoon/*Pimpinellaanisum*:** A double blind randomized controlled trial was conducted on 72 women and 330 mg of *Anisoon* was given orally three times a day for four weeks has shown significant improvement in frequency and intensity of hot flushes in postmenopausal women due to estrogenic property exhibited by trans-anethol. (Nhidakariman, 2012)

#### Research Studies conducted at NIUM

1. A placebo-controlled randomized single blind study was conducted to evaluate the efficacy of *Asgand* (*Withaniasomnifera* dunn) as an alternative to HRT in the management of postmenopausal syndrome. The study demonstrated significant improvement in hot flushes, night sweats, anxiety, insomnia and serum estrogen levels. This study confirms the efficacy of the *Asgand* as potent anti-oxidant, sedative, anxiolytic and adoptogenic. A Placebo-controlled randomized single blind trial was conducted at NIUM to evaluate the efficacy of *Kharekhasak* (*Tribulusterrestris* Linn) in Menopausal transition. The study demonstrated significant improvement in somatic, psychological and urogenital symptoms. This study confirms the efficacy of the *Kharekhasak* in alleviating menopausal transition related symptoms compared to placebo and can be considered as an alternative to HRT for postmenopausal symptoms.

#### Conclusion

Long-term hormonal deficiencies in post-menopausal women affect various organs of the body. Women spend two and a half decades of their lives in menopause which increases morbidity and mortality. Hormone replacement therapy (HRT) is the most common preferred treatment option for management of postmenopausal symptoms but it is associated with venous thrombo-embolism, breast cancer, cardiovascular diseases and liver diseases. Unani system of medicine is enriched with herbs

containing phytoestrogens which act as a SERM with no such risk. In conventional medicine, animal and human data regarding the use of isolated phytoestrogens ability to alleviate menopausal symptoms, their potential reduction in breast cancer risk and potential increase in bone mineral density are positive. However, many questions remain unsolved regarding long term safety, beneficial harmful doses, interaction with other drug and dietary products. These compelling data should serve as stepping stones for further research evaluating phytoestrogens present in Unani system of medicine as alternatives or adjuncts to conventional HRT.

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