Published online in http://ijam.co.in ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 14 (4), 2023; 912-925

Phytoestrogen: A protective shield for post-menopausal symptoms and breast cancer risk

Research Article

Prajakta Dhairyashil Sawant[1], Swagata Dilip Tavhare[2*]

1. PG scholar, 2. Associate Professor, Department of Dravyaguna,
Dr D. Y. Patil College of Ayurved and Research Centre, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pimpri, Pune India.

Abstract

Menopause is a physiological unavoidable condition in women's life which leads to vasomotor, psychological, urogenital and chronic diseases collectively termed as post-menopausal symptoms (PMS). Hormone replacement therapy (HRT) is conventional line of treatment for treating PMS in which estrogens replacement is major choice for better therapeutic efficacy against symptoms like hot flushes, osteoporosis, hormonal balances, insomnia, obesity etc. However, estrogen is reported risk factor for breast cancer. The review discusses Ayurveda based strategies for management of PMS with phytoestrogen herbs, diet, lifestyle modification, de-addiction measures, yoga, aroma therapies etc. supported by evidence-based documentation.Herbs namely *Dhanyaka* (*Coriander sativum*), *Manjishtha* (*Rubia cordifolia* L), *Chandana* (*Santalum album* L), *Ashwagandha* (*Withania somnifera* L. Dunal), *Jatamansi* (*Nardostachys jatamansi* DC), *Shatavari* (*Asparagus racemosus* L), Kumari (*Aloe vera* L), *Yashtimadhu* (*Glycyrrhiza glabra* L), *Haridra* (*Curcuma longa* L), *Triphala* (Combination of fruits of *Haritaki*, *Bibhitak*, *Amalaki* in the proportion 1:2:4), *Gokshura* (*Tribulus terrestris* L), *Arjuna* (*Terminalia arjuna* L.), *Guduchi* (*Tinospora cordifolia* L.), *Ela* (*Elettaria cardamomum* L), *Narikela* (*Coccus nucifera* L), *Masha* (*Phaseolus vulgaris* L), *Mudga* (*Vigna radiata* L). *Shunthi* (*Zingiber officinale* Roxb), *Methika* (*Trigonella foenum-graecum* L), *Tila* (*Sesamum indicum* L) are the natural sources of phytoestrogens. Phytoestrogen don't exert side effects like synthetic estrogen molecules. These herbs are useful for management of various symptoms of PMS. Having anti-cancer potential against breast carcinoma these are useful for prevention of risk of breast cancer.

Keywords: Ayurveda, Ashwagandha, Breast cancer, Estrogen, HRT, Menopause, Post-menopausal syndrome.

Introduction

Menopause is one of the crucial and unavoidable physiological phases in women's life. Post-menopausal population across globe is increasing and comprises 26% of all women and girls below age 50. (1) There is 21% raise seen in early age menopause. The changing hormonal milieu of estrogen and progesterone associated with menopause, makes women more susceptible for symptoms of hot flushes, vaginal dryness, disrupted sleep, insomnia, urogenital infections, osteoporosis, increased cardiovascular mortality, early onset of coronary heart disease, anxiety, depression, diabetes, depression and cognitive difficulties etc. which are in-toto termed as post-menopausal symptoms (PMS). (2)

Lifestyle changes, alcohol consumption, smoking, low body mass index are considered as risk factors for early menopause. In contemporary lifestyle due to consumption of hormonal pills, food habits, stress etc. early menopause is observed. For PMS management, hormone replacement therapy (HRT) is one of the effective treatments. (3) Some types of HRT are reported as a risk cause for development of breast cancer, cardiovascular diseases etc.

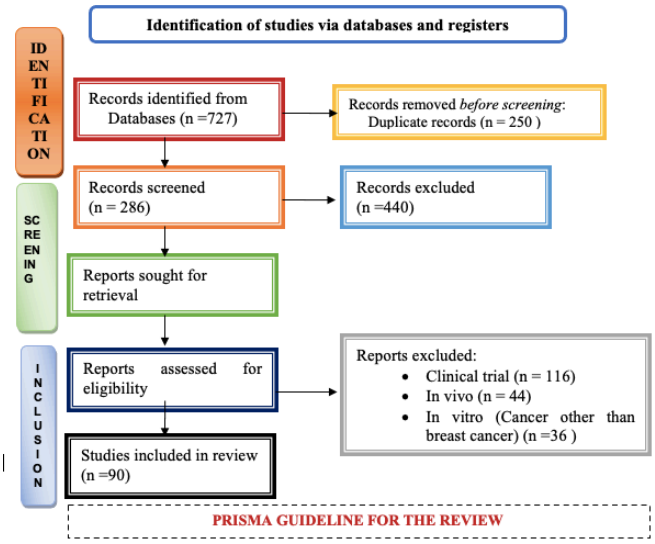
Ayurveda treatment principles have huge potential for managing PMS. However, research evidence-based documentation is yet insufficient. (4) This article proposes strategies for management of PMS; which are easy, cost-effective, diet and lifestyle based, considering abundant availability of herbs across globe; supported by evidence-based documentation.

Materials and Methods

The review on physiology and pathological aspect of menopause was overlooked from texts and research articles. Herbs mentioned for their action in post-menopausal syndrome were reviewed from classical texts and lexicons of Ayurveda supported by research evidences. Researches documents were reviewed from databases like Scopus, Web of Science, PubMed, Google Scholar using keywords namely phytoestrogens, herbal management, breast cancer, hormonal replacement therapy, anti-cancer, etc. with the MeSH terms like 'AND', 'OR', or free text terms. Conference abstracts, editorials, meta-analyses, narrative reviews and publication written in languages

*** Corresponding Author:**
Swagata Dilip Tavhare
Associate Professor, Department of Dravyaguna, Dr. D. Y. Patil College of Ayurved & Research Centre, D.Y. Patil Vidyapeeth (Deemed to be university), Maharashtra, Pimpri, Pune. India.
Email Id: drswagata32@gmail.com

other than English were excluded. Articles of duration 1st January 2001 till 1st January 2021 were included. The data collected was analysed for the authenticity in relevance to present topic. Limitations found during search were unavailability of some full text articles, information about role of phytoestrogen in breast cancer and hormone replacement therapy. The terminologies used in Ayurvedic science were translated into conventional science terms by using NAMASTE portal developed by CCRAS. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement has been followed to report the outcomes of this review.



Results

Post-menopausal symptoms are primarily attributed to decrease level of estrogen as ovary is no longer able to respond to pituitary hormone. These are categorized under four core categories; vasomotor, psychological, sexual-urogenital and chronic diseases as described in Figure 1. As the symptoms affects various systems namely central nervous, gastro-intestinal etc. a comprehensive approach is needed to tackle the symptom cluster. Use of phytoestrogen herbs, lifestyle modification like diet, exercise and proper daily routine, de-addiction etc., non-pharmacological therapies like yoga, aromatherapy are essential for management of PMS, considering symptoms association, chronicity, *prakriti* (constitution), occupation etc. (Figure 2)

Ayurveda have defined therapeutic action of herbs which will be helpful to relieve PMS as described in table 1.

Terminology translation

Balya	Improves strength and immunity
Bastishodhana	Cleanses and detoxifies bladder
Bruhmana	Nourishes body
Dahashamana	Relieves burning sensation
Guru	Heavy to digest
Kanduhara	Useful in skin itching
Klama-shrama hara	Relieves tiredness, fatigue
Kushtahara	Useful in skin diseases
Laghu	Light to digest
Medohara	Reduces unhealthy lipids, fat and cholesterol
Mutrala	Diuretic
Picchila	Sticky, slimy
Pushtiprada	Improves body nourishment
Rakta-prasadana	Detoxifies blood, useful in bleeding disorders
Rasayana	Rejuvenator
Ruksha	Dry
Shothahara	Reduces inflammation
Shramahara	Relieves tiredness, fatigue
Snigdha	Unctuous, oily
Varnya	Improves skin complexion
Vishaghna	Detoxicant
Vrushya	Aphrodisiac

Table 1: Therapeutic action for management of PMS

SN	Name of herb	PMS symptom	Therapeutic action for PMS management	Reference
1	***Dhanyaka***	Urine incontinence, burning micturition	*Mutrala, Dahashamana*	(6)
2	***Manjishtha***	Hot flushes	*Rakta-pitta prasadana, dahashamana*	6)
		Edema	*Shothahara, vishaghna*	
		Skin discoloration	*Varnya, vishaghna,*	
3	***Chandana***	Hot flushes	*Raktaprasadana, Daha-shamana*	(8)(9)
		Fatigue	*Klama-shramahara*	(8)
		Irritability	*Alhadana*	(6)
4	***Ashwagandha***	Fatigue, sexual vigor	*Balya, pushtiprada*	(6)
		Immunity concerns	*Rasayana*	
5	***Jatamansi***	Insomnia	*Nidrajanana, medhya, balya*	(7)
		Stress, psychological disturbance	*Bhutaghna, manasa-doshahara*	(6) (9)
6	***Shatavari***	Fatigue, weakness	*Balya*	(6)
		Immunity concerns	*Rasayana*	
		Sexual urges	*Shukrala*	
		Lack of concentration	*Medhya*	

7	***Kumari***	Skin diseases	*Twak-rogahara, rakta-pittahara, vishahara*	(6)
		Urogenital infections, vaginal dryness and itching	*Kandughna*, *Vishahara*, *Pitta-raktashamana*	
8	***Yashtimadhu***	Skin diseases	*Varnya*, *kandughna, snehopaga*	(6), (7)
		Hair-fall	*Keshya*	(6)
9	***Haridra***	Skin diseases	*Kanduhara*	(9)
		Skin diseases	*Kushtahara*	(6)
10	***Triphala***	Skin diseases	*Kushtahara*	(6)
11	***Gokshura***	Lessen sexual urge	*Vrushya*	(9)
		Urine incontinence	*Bastishodhana*	(6),(8)
		Hypertension	*Mutrala, kledahara*	(6)
12	***Guduchi***	Ageing	*Vayasthapana*	(6)
		Fatigue, weight loss	*Bruhmana*, *balya*	(7)
		Hot flushes	*Dahashamana*	(9)
		Osteoporosis	*Bhagnahara*	(6)
13	***Arjuna***	Hypertension, Cardiovascular risk	*Hrudya, Raktadoshahara, Medohara, Shramahara*	(6)
		Osteoporosis	*Bhagnasandhanakrut*	
14	***Ela***	Urine incontinence	*Mutrakruccha,*	(6),(8)
		Anxiety, depression, hypertension	*Vatahara*	(6),(8)
15	***Narikela***	Urine incontinence	*Mutrala*	(6)
16	***Masha***	Fatigue, weight loss	*Balya, bruhana, snigdha*	(6)
17	***Mudga***	Fatigue, weight loss	*Pushti-balaprada*	(8)
18	***Shunthi***	Musculo-skeletal pain	*Shothahata, Shoolahara*	(6)
		Hot flushes, night sweating	*Snigdha, Vatahara*	(6)
19	***Methika***	Musculo-skeletal pain	*Vatapranashini*	(9)
20	***Tila***	Fatigue, weight loss	*Balya,snigdha, vataghna*	(9)
		Hair-fall	*Keshya*	

Herbs mentioned in table 1 are reported through research evidences to possess action useful for the management of various symptoms of PMS as depicted in table 2 and figure 3.

Table 2: Research evidences for herbs useful for treatment of PMS

SN	Name of herb	Researches on action useful for management of PMS symptoms	R
1	***Dhanyaka* (*Coriander sativum* L) Family: Apiaceae**		
i	Anxiety	Essential oil content and flavonoid exerts Anxiolytic effect via the gamma-aminobutyric acid $(GABA)_A$ receptor complex.	(10)
ii	Insomnia	Linnalol shows sedative action, anti-depressant and cognitive effects.	(10)
ii	Loss of memory or psychological ailments	Linnalol helps in prevention of neurodegenerative diseases, by exerting multifarious effects like memory-improvement, lowering of cholesterol and anticholinesterase action, increasing endogenous enzyme levels of SOD, glutathione, catalase and total protein levels.	(10)
2	***Manjishtha* (*Rubia cordifolia* L) Family: Rubiaceae**		
i	Memory impairment	Increases levels of dopamine thus help in neuro-protection.	(11)
3	*Chandana* (*Santalum album* L) Fam: Santalaceae		
i	Hypertension	Lowers the systolic blood pressure. Increases the level of acetyl cholinesterase.	(1,213)
4	***Ashwagandha* (*Withania somnifera* L Dunal) Family: Solanaceae**		
i	Hot flushes	Decrease the genetic expression of interlukin-8 (IL-8) against estrogen which increases during hot flushes.	(14)
5	***Jatamansi (Nardostachys jatamansi* DC) Family: Valerianaceae**		
I	Anxiety	Significant increase in levels of brain monoamine and GABA neurotransmitter	(15)
Ii	Loss of concentration, Memory impairment	Enhances memory by facilitation of cholinergic transmission. Being rich antioxidant, helpful in restoration of memory.	(16)

6	***Shatavari (Asparagus racemosus* L) Family: Liliaceae**		
I	Fatigue, weakness	Improves myosin contractility and restores muscles strength. shatavari-derived phytoestrogens, including rutin, kaempferol, genistein, daidzein and quercetin, bind to E2R with greater affinity than a selective estrogen receptor modulator.	(17)
ii	Osteoporosis	Phytoestrogen acts through estrogen -2 and protect bone mass and architecture by stimulating osteoclast apoptosis and inhibiting apoptosis in osteoblasts and osteocytes and by production of pro-osteoclastic cytokines e.g., interleukin 1, interleukin 6 and tumor necrosis factor alpha (TNFα) by osteoblasts.	(17)
iii	Hot flushes	Phytoestrogen helps to control moderate to severe hot flushes by managing decline in estrogen and correcting instability in the hypothalamic thermoregulatory set-point.	(17)
iv	Stress	Estrogenic component of *Shatavari* manages stress mediated hormonal imbalances caused due to cortisol release.	(18)
7	***Kumari (Aloe vera* L) Family: Liliaceae**		
I	Urogenital infections, atrophic vaginitis	Aloe possess potent antimicrobial activity by rupturing bacterial cell walls, antioxidant effect by free radical- and superoxide radical-scavenging action and anti-inflammatory action by inhibition of the cyclooxygenase pathway. It is good moisturizing and anti-aging agent and possess weak estrogenic like activity on topical applications.	(19)
8	***Yashtimadhu (Glycyrrhiza glabra* L) Family: Fabaceae**		
I	Hot flushes, palpitation, night sweats	Licorice exerts significant estrogenic activities.	(20)
ii	Atrophic vaginitis	Licorice possess positive effect on the growth of superficial cells of the vaginal mucus Significant decreases in vaginal pH. Possess anti-allergic, anti-bacterial and anti-inflammatory action.	(2,122)
9	***Haridra (Curcuma longa* L) Family: Zingiberaceae**		
i	Urogenital infection, burning, itching	Anti-fungal, anti-bacterial, anti-inflammatory activity.	(23)
ii	Vulvo-vaginal infections	Inhibition of release of hydrogen ion from fungal cells which break down its membrane; leading to intracellular fluid leakage and cell death.	(24)
iii	Skin dryness, loss of texture	Daily topical application of curcumin improves epithelial cell survival and recovery in irradiated skin, reduces the expression of cyclooxygenase-2 and nuclear factor-kappaB.	(25)
iv	Skin problems like pruritis, inflammatory symptoms	Topical application of curcumin reduces inflammation by inhibition of the potassium channels and reducing inflammatory markers namely IL-17A, IL-17F, IL-22.	(26)
10	***Triphala* (Combination of fruits of *Haritaki*, *Bibhitak*, *Amalaki* in the proportion 1:2:4)**		
i	Obesity	Decreases adipogenesis in 3T3-L1 cells by reducing lipid accumulation and inhibiting the expression of adipogenic genes. Downregulates mRNA expression of GLUT4 and FAS which are responsible for lipid accumulation in adipocytes. Rich antioxidant.	(27, 28)
ii	Gut disturbances	Decreases myeloperoxidase and xanthine oxidase levels in intestinal epithelium. Replenishes depleted protein, glutathione and phospholipid levels from the brush borders of intestinal villi. Phytochemicals like quercetin and gallic acid promotes the growth of lactobacillus and other gut micro-biome species.	(28)
iii	Constipation	Increase in bowel movements Being antibacterial, helps to increased reduced motility because of bacterial infections	(29)
11	***Gokshura (Tribulus terrestris* L) Family: Zygophyllaceae**		
i	Loss of sexual desire	Steroidal saponins present in *Tribulus terrestris* converts androstenedione to estrogen which enters the circulation and exerts estrogenic effect on central nervous system.	(30)
ii	Urine incontinence, burning etc.	Seed and fruits of T. terrestris are rich in nitrates and potassium salts which exert significant diuretic action.	(3,132)
12	***Guduchi (Tinospora cordifolia* L) Family: Menispermaceae**		
i	Cognitive impairments	Ameliorates age-associated up-regulation in the protein targets responsible for neuro-inflammation further aggravated by estrogen deficiency responsible for cognitive impairments. Reduction in age-associated elevation of serum pro-inflammatory markers (IL-1β, Il-6, MCP-1, and TNF-α).	(33)

ii	Osteoporosis	Stimulates proliferation, differentiation and growth of osteoblasts, increases the differentiation of cells into osteoblastic lineage and mineralization of bone like matrix.	(34)
iii	Immuno-compromised status	Enhances immunoglobulin levels like IGA, IgG, IgM in post-menopausal women Excellent booster of immune-competence	
13	***Arjuna (Terminalia arjuna* L) Family: Combretaceae**		
i	Osteoporosis	Helps in bone formation and anti-osteoporotic activity.	(35)
ii	Hypertension	Antioxidant, cardio-protective activity.	(36)
14	***Ela (Elettaria cardamomum* L) Family: Zingiberaceae**		
i	Depression	Attenuates depression-like symptoms in reserpine-injected rats by improving the behavioral changes.	(37)
ii	Anxiety	*Elettaria cardamomum* L in the dose of 400 mg/kg, significantly improves anxiety-like behavior in a rat model of post- traumatic stress disorders	(38)
iii	Hypertension	*Elettaria cardamomum* L powder in the dose of 3 g in two divided dose for 12 week; significantly decreases systolic, diastolic and mean blood pressure and significantly increases fibrinolytic activity. *Significant raise in* total antioxidant status	(39)
15	***Narikela (Cocos nucifera L)* Family: Arecaceae**		
i	Osteoporosis	Young coconut juice proven to be beneficial in mitigating bone loss in women during early menopause which delays the start and reduces the total duration of anti-osteoporotic drug therapy. It helps to prevent post-menopausal gain in body weight.	(40)
ii	Depression	*Coconut water shows* antidepressant effect by causing decline in 5-hydroxytryptamine, noradrenaline and dopamine, metabolites 5-hydroxyindoleacetic acid, 3, 4-dihydroxyphenylacetic acid, homovanillic acid and increase in 5-hydroxyindoleacetic acid/5-hydroxytryptamine ratio.	(41)
iii	Urine incontinence, burning micturition etc.	*Coconut water contains b*eneficial nutrients like flavonoids, phenolic acids, and amino acids, which causes diuresis. Exhibit acute and prolonged diuretic effects by suppressing the AQP and RAAS pathways in saline-loaded rats	(42)
16	***Masha (Phaseolus vulgaris L.)* Family: Leguminosae**		
i	Hypertension	*Phaseolus vulgaris is reported to possess significant anti-hypertensive action in-vivo through* rennin-angiotensin system.	(43)
		Methanol extract of Phaseolus vulgaris in the dose of 1 g/kg in rats for 10 weeks showed increase in bone and ash density, significantly increases bone calcium and mechanical strength and improves bone microarchitecture.	(44)
17	***Mudga (Vigna radiata L.)* Family: Leguminosae**		
i	Cardiovascular disease risk, diabetes	Green gram seed in the dose of 2 g/kg is reported to lowers blood glucose, plasma C-peptide, glucagon, total cholesterol, triglyceride, and BUN levels and markedly improves glucose tolerance and increased insulin immune-reactive levels.	(45)
18	***Shunthi (Zingiber officinale* Roscoe) Family: Zingiberaceae**		
i	Hot flushes, night sweating and musculoskeletal pain	*Zingiber officinale* 1g powder significantly reduced the intensity of menopausal symptoms like hot flushes, night sweating and musculoskeletal pain with a significant increase ($p < 0.001$) in serum estrogen levels and significant reduction in serum level of FSH as reported through clinical trial.	(46)
19	***Methika* (*Trigonella foenum-graecum L) Family: Fabaceae***		
i	Vasomotor and musculoskeletal symptoms	Fenugreek seeds with 3:1 (w/w) ratio of protodioscin to trigonelline given in the dose of 250 mg BD for 4 days helpful in alleviating the postmenopausal discomforts due to vasomotor and musculoskeletal symptoms like leg pain and improvement in quality of life within two weeks.	(47)
20	**Tila (*Seasamum indicum* L) Family: Pedaliaceae**		
i	Osteoporosis	Sesamin promotes osteoblastic differentiation in rats bone marrow stromal cells by regulating the Wnt/β-catenin pathway, and improved bone structure.	(48)

The herbs having effect in treatment of PMS also reported to possess anti-cancer potential against breast cancer cells as depicted in table 3 and figure 3.

Table 3: In-vitro anticancer action of herbs on mammary cells

SN	Name of herb	Anti-cancer activity on breast cancer cells	
1	*Coriander sativum* L	Inhibition of DNA damage and prevention of MCF-7 (breast cancer cell line) cell migration.	(49)
2	*Rubia cordifolia* L	Cyclic hexa-peptides exhibit significant antitumor activity by arresting of protein synthesis.	(50)
3	*Santalum album* L	Induces cell cycle arrest and apoptosis in cancer cell line.	(51)

4	*Withania somnifera* L Dunal	Activation of ERK (Extracellular signal-regulated kinase) /RSK-DR5 (Ribosomal S6 Kinase- Death receptor 5 in MCF-7 cell line. Inhibit vimentin cytoskeleton, Inhibition of cell invasion in MDA-MB 1 cell line.	52, 53)
5	*Nardostachys jatamansi* DC	Exhibit cell cycle arrest, apoptosis in MBA-MB-231 cell line.	(54)
6	*Asparagus racemosus* L	Anti-proliferative activity on T47D cancer cell lines	(55)
7	*Aloe vera* L	Inhibits cell proliferation, induces apoptosis in MCF-7 cell line and increase the therapeutic efficacy of conventional drug like cisplatin.	(56)
8	*Glycyrrhiza glabra* L	Inhibit breast cancer cell growth.	(57)
9	*Curcuma longa* L	Inhibition of androgen and estrogen signaling pathways, activation of tumor suppressor gene(p53), apoptosis induction, epigenetic alterations and inhibition of cell cycle promotion (CDK2).	(58, 59)
10	*Triphala*	Modulates multiple cell signaling pathways including, ERK, MAPK, NF-κB, Akt, c-Myc, VEGFR, mTOR, tubulin, p53, cyclin D1, anti-apoptotic and pro-apoptotic proteins.	(60)
11	*Tribulus terrestris* L	Apoptosis of breast cancer cell lines by down- regulating expression of Bcl-2 (B cell CLL/lymphoma-2) and up-regulation of FADD (fas associate with death domain), AIF (apoptosis-inducing factor), and caspase 8 (cysteine-aspartate protease 8) genes. Decrease metastasis of breast cancer cells by lowering CCR7 (CC chemokine receptor 7), CXCR4 (CXC chemokine receptor 4) levels.	(61)
12	*Tinospora cordifolia* L	Inducing ROS (Reactive Oxygen Species) and mitochondrial-mediated apoptosis by restoring p53 activity in MDA-MB-231 cells.	(62)
13	*Terminalia arjuna* L	Inhibiting the proliferation of MCF-7 by blocking cell cycle progression in the G0/G1 phase and inducing apoptosis.	(63)
14	Elettaria cardamomum L	Induces G2/M arrest and apoptosis via activation of the JNK– FOXO3a pathway MCF-7 and MDA-MB-231	(64)
15	*Cocos nucifera L*	Freeze-dried coconut water vinegar is reported to reduce cell viability, induction of apoptosis in 4T1 cells line. In vivo experimentation observed delayed 4T1 breast cancer progression in mice by inducing apoptosis and delaying the metastasis. Promotes immune cell cytotoxicity and production of anticancer cytokines.	(65)
16	*Phaseolus vulgaris L.*	Causes changes in the phosphorylation states of mammalian target of rapamycin (mTOR) substrates (4E-binding protein 1 and p70S6 kinase) A seed component, hemagglutinin causes cell cycle arrest in G2/M phase, externalisation of phosphatidylserine and depolarisation of mitochondrial membrane.	(6,667)
17	*Vigna radiata L.*	Apoptosis and higher inhibitory effect against the MCF-7 cell line by programmed cell death.	(68)
18	*Zingiber officinale Roscoe*	Apoptosis, accompanied by loss of cell viability, chromatin condensation, DNA fragmentation, activation of caspase 3, and cleavage of poly (ADP-ribose) polymerase attributed to upregulation of Bax and downregulation of Bcl-2 proteins. Downregulates expression of pro-survival genes, such as NF-κB, Bcl-X, Mcl-1, and Survivin, and cell cycle-regulating proteins, including cyclin D1 and cyclin-dependent kinase-4 (CDK-4).	(69)
19	Trigonella foenum-graecum L	Apoptosis in breast cell mediated by Fas receptor-independently of either FADD, Caspase 8 or 3, and p53	(70)
20	Sesamum indicum L	Sesamin dose-dependently (1,10 and 50 μM) causes apoptosis, reduces cell viability, increases LDH release. Significant increase of sub-G1 phase arrest in the cell cycle after sesamin treatment. Increase in the expression of apoptotic markers of Bax, caspase-3, and cell cycle control proteins, p53 and checkpoint kinase 2	(71)

Discussion

In Ayurveda classics; menopause is termed as "*rajonivrutti*" i.e., cessation of menstrual cycles. The onset of menopause is a sign of ageing i.e. depletion of optimum functioning of *dhatus* in women. (72) The transition is observed due to shift from *pitta* predominant phase towards *vata* dominancy which brings various hormonal fluctuations. Aggravated *vata* shows increases in *ruksha* (dryness), *laghu* (lightness), *sheeta* (coldness) properties in body which leads to depletion of *asthi-dhatu* causing degenerative changes like osteopenia, osteoporosis etc. The aggravated *vata* further vitiates *pitta* leading to symptoms like hot flushes, disturbed sleep, episodes of anxiety, depression etc. The further vitiation involves association of *kapha* causing joint pain, insomnia etc.

Herbal management

Menopause is a natural phase in women's life as every women has to suffer from PMS transition which affects her physical and psychological attributes**.** PMS related symptoms are primarily attributed to the decreased level of circulating estrogen. Hormone replacement therapy (HRT) predominantly containing estrogen is advised primarily for reduction of PMS and prevention of its complications. Conventional HRT

drugs, especially diethyl-stilbestrol, is reported to possess serious side effects like stroke, gallbladder disease and certain types of cancer. Because of this, there is increasing interest in the use of plant-derived estrogens, also known as phytoestrogens. Herbs like *Shatavari*, *Yashtimadhu* possess estrogenic action while *Guduchi* acts as estrogen receptor modulator. (73)(74) (75). Dietary substances having estrogenic action are black sesame,(76) garden cress seed,(77) cardamom, (78) coconut water,(79) dry ginger,(80) green gram,(81) common bean,(82) fenugreek,(83). (Figure 4) The herbs also possess anti-cancer action on breast cancer cell lines. (Table 3)

During menopausal state, ovaries, do not respond properly to the pituitary hormones. Due to disturbance in feedback inhibition, there is elevation in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) level increases and cease of ovarian estrogen, progesterone, and inhibin. Fenugreek and common beans are reported to reduce FSH in post-menopausal rats. (47)

Pre-clinical evidences and mechanism of herbs for management of PMS

Post-menopausal psychological symptoms mainly include irritability, anxiety, depression, mood swings etc. Linalool a major essential oil derived from coriander seed has marked effect on CNS as it behaves as a competitive antagonist of glutamate; excitatory neurotransmitter in CNS and brain. (84) *Rubia cordifolia* possess neuro-protective action and increases the level of dopamine as reported through in-vivo studies. (11) Dopamine helps in regulating behaviour and mood. Estrogen and dopamine possess positive association. Decline in estrogen levels results in decrease of dopaminergic functions which impact negatively on cognitive process like working, memory etc. (85) Administration of *Chandana* fortified water helps in reducing symptoms like anger outbreaks, anxiety, stress etc. Santalol an essential oil of sandalwood helps in relieving stress and also lowers the systolic blood pressure. (12) It possess sedative action proven against standard diazepam and pentazocine; reported through animal studies. (86). *Santalum album* in aqueous extract form is reported for increasing the level of acetyl cholinesterase which is essential in the brain for memory storage. (13) *Chandana* can be proposed to administer as processed water form, local application to reduce symptoms such as anxiety, poor memory, etc.

Estrogen replacement therapy is a risk factor for breast cancer. According to study conducted at the university of Tokushima during hot flushes macrophages senses a decline in estrogen and in response secretes Interlukin-8 (IL-8). Another study reported from university of Buffalo; concludes *Ashwagandha* decrease the genetic expression of IL-8 against estrogen. (14) The Withanolide compound present in *Withania somnifera* roots reduces the development and proliferation of tumor due to anti-inflammatory and cytotoxic effect like cell cycle arrest and increase apoptosis.(87) Withania by these two mechanisms serve an alternate solution for HRT. Osteoporosis is commonly seen during menopause due to decrease production of estrogen which leads to calcium deficiency. Estrogen like withanolide of *Withania* helps to prevents osteoporosis. (88)

Jatamansi shows neuro-protective action and improves memory by facilitating the cholinergic transmission in the brain. (16) Thus, it is helpful for balancing cognitive impairments.

Lack of estrogen during menopause accelerates muscle weakness, reduces bone mineral density and increases risk for fractures. (55) (89) Estrogen are important for maintaining bone mineral density and play important role in bone regulation. (90) Phytoestrogen present in *Shatavari* helps to maintain the estrogen levels and provide muscle strength. It improves muscle function, potentially by improving in myosin contractility and restoring muscles strength. (17)

Urogenital symptoms like vaginal dryness, itching, atrophy, etc. are prevalent in menopausal condition. Treatment includes local measures like moisturizers and lubricants. Systemic treatments like hormone supplements and lifestyle changes are advisable. (91) Vagina, vestibule, vulva, labia majora/ minora have high concentration of estrogen receptors and are sensitive biological indicator of serum levels of these hormones in women. Decline in the levels of estrogen after menopause causes estrogen receptor depletion which further decreases vaginal lactobacilli and increases pH causing vulvo-vaginal dysfunction and genitourinary symptoms. As the estrogen receptors in the vagina do not disappear completely; the remnant ones get sensitized to exogenous estrogen treatments which enhances estrogen receptor amount and leads to epithelial proliferation, vascularization and vaginal secretion. Long term application of estrogen cream reported to increase the chances of endometrial thickness and breast cancer. Aloe vera contains phytoestrogen (beta sitosterols) which mimic estrogen like action. It shows antimicrobial activity by rupturing bacterial cell walls. It shows antioxidant property by scavenging free radicals and superoxide radicals. Anti-inflammatory activity of aloe is seen due to inhibition of the cyclooxygenase pathway and reduction of prostaglandin E2 production. Hence, aloe vera vaginal cream can be used as an alternative for estrogen vaginal cream to treat vaginal atrophy and genitourinary inflammations and infections. (19)

Administration of *Haridra* detoxifies blood impurities, thus helpful in urogenital infections, hot flashes, etc. It helps to nourish blood as it is a rich source of curcuminoids; a natural anti-oxidant. On external application on wounds, it accelerates healing. Thinning of vaginal cell membrane leads to increase risk of bacterial and fungal infections. *Haridra* acts as a potent anti-fungal drug. Curcumin based vaginal creams are effective in treating vulvo-vaginal candidiasis. Curcumin inhibits the release of hydrogen ion from fungal cells which break down its membrane; causing intracellular fluid leakage and leads to death of fungal cells. (23)

Skin changes like loss in elasticity, dryness, discoloration etc. are seen during menopause as estrogen receptors also resides on cellular components of skin. (92) *Haridra* being rich antioxidant source can be administered in skin disease ailments like dimished elasticity and retain water content. Ayurveda states it as *Varnya* as it helps in maintaining the natural skin complexion.

According to American Society of Clinical Oncology, women who experience early menarche and late-onset menopause have increased risk of breast cancer. Turmeric helps to reduce the risk of breast cancer as it is a potent anti-cancer drug. *In vitro* and *in vivo* studies states anticancer mechanism of curcumin as inhibition of androgen and estrogen signalling pathways, (60) activation of tumor suppressor gene(p53), apoptosis induction, epigenetic alterations and inhibition of cell cycle promotion (CDK2). (61) Curcumin: It has potential anticancer effect on ER+ve as well as ER independent breast cancer cells.(93)

Flatulence and constipation are commonly observed symptom after menopause. This leads to gastrointestinal troubles like bloating, constipation, diarrhea etc. which are further aggravated by stress induced release of cortisol. (94) *Triphala* (a combination of *Haritaki* {*Terminalia chebula*}, *Bibhitaki* {*Terminalia bellirica*} and *Amalaki* {*Phyllanthus emblica*} exerts entero-protective effect due to its high antioxidant content. In vivo studies report, *Triphala* decreases myeloperoxidase and xanthine oxidase levels in intestinal epithelium. It also replenishes depleted protein, glutathione and phospholipid levels from the brush borders of intestinal villi. It contains phytochemicals like quercetin and gallic acid which promote the growth of lactobacillus and other gut microbiome species. (27) Thus, administration of *Triphala* helps to check gut disturbances.

Symptoms like burning micturition, urinary incontinence, loss of libido etc. are observed after menopause because of stress, decrease bladder function and malfunction of urinary sphincter muscle. Studies have reported that combinations of estrogen and alpha-adrenergic agonists are beneficial for treating urinary incontinence as they increase the tone of striated and smooth muscles. (95) *In vivo* study on *Tribulus terestris* seed powder in female Wistar rats proved its activity as uterine tonic by increasing levels of progesterone. The protodioscin present in *gokshura* is effective in alleviation of post-menopausal symptoms. Nitrates are recognized as effective diuretics. (32) Hence *gokshura* acts effectively for treating symptoms like burning micturition, urine incontinence etc. Estrogen has a direct or indirect effect on regulation of calcium absorption. It also modulates the calcium regulatory hormones such as parathyroid hormone; calcitonin and activated vitamin D. Osteoblasts possess estrogen receptors. Estrogen modulates and attenuates bone resorption. (96)

Alcoholic extract *of Tinospora cordifolia* affects the proliferation, differentiation and mineralization of bone like matrix on osteoblast as reported through *in vitro* models. Thus, it has potential role as anti-osteoporotic agent. It also stimulates the growth of osteoblasts, increases the differentiation of cells into osteoblastic lineage and mineralization of bone like matrix. (34)

Estrogen deficiency leads to central fat deposition. In-vivo studies on mice have demonstrated that the loss of ovarian function promotes a diet independent increase in adipose tissue mass. Obesity is a risk factor for diseases like hypertension, diabetes, cardiovascular diseases, osteoporosis etc. (97) Thus, during menopausal stage, a control over weight gain is needful. *Arjuna;* a reported phytoestrogen possesses properties as *medohara* (lipido-lytic) thus useful for treating obesity. Alcoholic extract of *Terminalia arjuna* exerts anti-obesity action in high fat diet induced obesity in rats. It further showed reduction in liver adipose tissue weight due to low absorption of lipid and non-deposition of visceral fat. (98)

A study conducted on bilateral ovariectomized induced post-menopausal osteoporosis in rats revealed that aqueous and methanol extract of *Terminalia arjuna* show elevation of bone formation and anti-osteoporotic activity. (35) During menopause there is decreased production of estrogen and *Arjuna* can be used as supplementation to provide strength to bones and fatigue. Bark of *T. arjuna* contains high level of flavonoids, like arjunolone, flavones, luteolin, quercetin and kaempferol evaluated with other medicinal plants particularly having favourable effects on cardiovascular diseases.(99)

Clinical evidences on herbs for management of PMS

For treatment of mild to moderate symptoms of menopausal syndrome drugs namely *Ashokarishta* (25 ml twice daily with equal quantity of water, after food, orally), *Ashwagandha churna* (3 g twice daily with milk, half an hour before food, orally) and *Pravala-pishti* (1 capsule of 250 mg twice daily with milk, half an hour before food, orally) for 3 months have been documented for fruitful results in somatic complaints including GIT disturbances, white discharge and hot flushes, etc. and psychological symptoms like mood swings, sleep disturbances, headache, irritability, depression, mood swings, etc. (100)

A clinical trial reports administration of *Yahstimadhu siddha basti* for eight days followed by *Triphala rasayana* helps in management of post -menopausal osteoporosis. (101)

A case report states patient treated by *Vayasthapana Gana Churna Ksheerapaka Basti* for 8 days and *Vayasthapana Gana Churna* in the dose of five gram with milk orally before food for two months resulted in significant improvement in the physical, psychological and vasomotor symptoms. (102)

Local application of licorice cream increases the maturation vaginal index (ratio of three vaginal epithelial cell types' changes) and decrease the vaginal pH thus helpful to alleviates signs and symptoms of vaginal atrophy in postmenopausal

phase reported through double blind randomized controlled trial. Reduction in vaginal dryness and itching is attributed to isoflavones and phytoestrogen content of licorice. (21)

Clinical studies show *Tribulus terestris* improves reproductive function, libido and ovulation by increasing concentration of estradiol. (103) Clinical trial on women suffering from sexual dysfunction treated with *Tribulus terestris* syrup increases sexual desire, improves lubrication and reduced pain during intercourse. (104)

A study reported on 30 female patients suffering from post-menopausal hypertension treated with *jatamansi* powder showed significant changes in fall of blood pressure. (105)

A randomised, double blind, placebo-controlled study revealed, *Ashwagandha* supplementation significantly reduces climacteric symptoms related to vasomotor, psychological and urogenital systems, in peri-menopause women. There is also increase in serum estradiol and reduction in levels of serum FSH and serum LH compared with the placebo. (106) Thus, *Ashwagandha* can be used as nutraceuticals supplementation during this phase.

Life-style modification

Life-style modification has dual menace for management PMS and its complication like obesity, hypertension, diabetes, psycho-somatic disturbances etc. Many research studies are available from the western countries on lifestyle modification and its impact on PMS; only few reported for Indian population. (107) Ayurveda has wisely described daily routine of an individual according to season and *prakruti* (epigenetics). Practicing daily or weekly *Snehana* (oleation), *swedana* (sudation), seasonal bio purification therapy like *snighdha virechana* (purgation with oils), *yapanbasti* (palliative enema), *rasayana* (rejuvenating therapies) during menopausal period would be beneficial for women. (108)

Inclusion of phytoestrogen diet

Food rich in phytoestrogen namely black seasam, garden cress seeds, coconut water, common beans, green gram, fenugreek leaves and seeds, dry ginger, cardamom etc to be included in routine diet in various recipes. (Figure 4)

De-addictions for healthy menopause

During menopausal stage, any kind of addiction may serve as trigger for developing cancer pathogenesis. Tobacco smoking is considered as a one of the risk factors for development of breast cancer as smoke contains mammary carcinogenic chemicals. (109) A generation cohort study reports the raised risk of invasive breast cancer in women who smoke more than five cigarettes per day and had 10+ packs per years in use. (110) Consumption of excess alcohol modifies hormone levels and associated signalling pathways. It creates a greater risk of ER-positive breast cancer tumor. (111)

Ayurveda strategies for improving Quality of life (QOL) in menopausal state

Quality of life is a wide-ranging phenomenon. During menopause it is affected by individual's physical health, psychological state. Duration of menopause and severity of PMS creates impact QOL of women. (112) Appropriate measures need to be made to improve QOL by administering less toxic medication, *rasayana* and regular bio-purification like *virechana*, *raktamokshana* (blood-letting) which helps to reduce aggravated *vata* and balance *tridosha*. Thus, helps to maintain QOL.

Yoga

Yoga practices generally involve physical poses or movement sequences, conscious regulation of breathing, and mindfulness techniques to increase present awareness or positivity. A systematic review and meta-analysis concluded evidences suggesting short-term effects of yoga on reliving psychological symptoms during menopause. (113) Thus, regular practise of Yoga is helpful to combat psychological symptoms.

Aroma therapy

Aromatherapy, also referred to as essential oil therapy, uses naturally extracted aromatic essences from plants to treat various physiological and psychological imbalances. The scented oils are believed to reduce anxiety and increase relaxation, which may be beneficial in easing stressful menopausal symptoms. (114) Aromatic herbs like *Chandana*, *Guggulu* (*Commiphora mukul* Wighti), *Karpura* (*Cinnamomum camphora* L), *Ushira* (*Vetivera zinoides* L), creates a pleasant aroma, pacifies aggravated *pitta*.

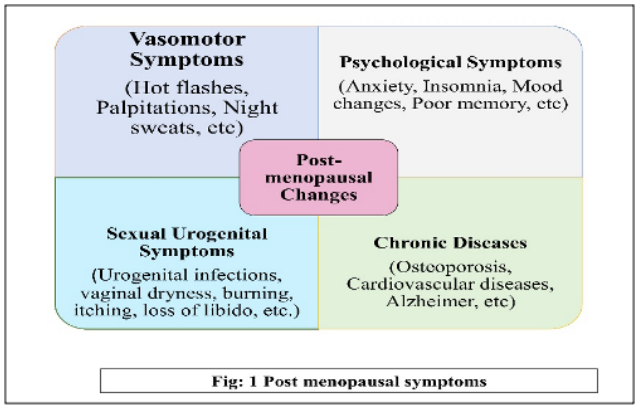


Fig: 1 Post menopausal symptoms

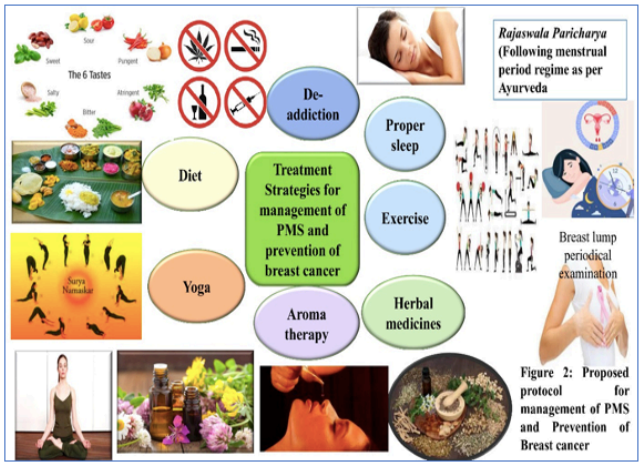


Figure 2: Proposed protocol for management of PMS and Prevention of Breast cancer

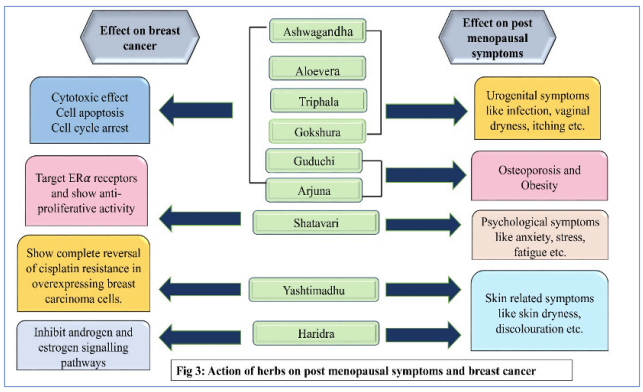


Fig 3: Action of herbs on post menopausal symptoms and breast cancer

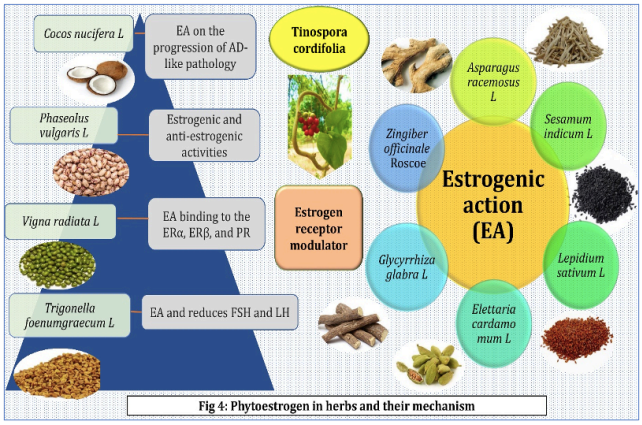


Fig 4: Phytoestrogen in herbs and their mechanism

Conclusion

Hormone replacement therapy is used for treatment of post-menopausal symptoms has positive association with higher risk of breast cancer. Phytoestrogen herbs can be a good replacement of synthetic estrogen to manage menopausal symptoms and additionally protect against risk of breast cancer. Apart from this, following protocols of healthy daily routine, seasonal bio purification measures, de-addiction, aroma therapy, yoga, will be useful for healthy menopause.

Acknowledgement: Authors acknowledges to management Dr. D. Y. Patil College of Ayurved & Research Centre, (Dr. D. Y. Patil Vidyapeeth), Pimpri, Pune for support and encouragement.

Conflict of interest: Nil

References

1. https://www.who.int/news-room/fact-sheets/detail/menopause
2. Shuster, L. T., Rhodes, D. J., Gostout, B. S., Grossardt, B. R., & Rocca, W. A. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010, *65*(2);161–166.
3. Flores, V. A., Pal, L., & Manson, J. E. Hormone Therapy in Menopause: Concepts, Controversies, and Approach to Treatment. Endocrine reviews. 2021; 42(6); 720–752.
4. Julia T. Arnold, Integrating ayurvedic medicine into cancer research program's part 1: Ayurveda background and applications, Journal of Ayurveda and Integrative Medicine. 2022;100676,
5. Santoro, N., Epperson, C. N., & Mathews, S. B Menopausal Symptoms and Their Management. *Endocrinology and metabolism clinics of North America*. 2015;*44*(3); 497–515.
6. Bhavamishra, Bhavaprakasha Nighantu, edited by G.S.Pandey, 1st edition, Chaukambaha Bharati Academy, Varanasi, 2006.
7. Raj Nighantu of Pandit Narahari, Dhanyavarga, Edited by Indradeo Tripathi, Chowkhamba Krishnadas Academy, Varanasi. 2003.
8. Kaiyadeva.Nighantu (Pathyaapthya vibhodika). Edited by Prof Priyavrat Sharma, Varanasi: Choukambha Orientalia; 2009.
9. Dhanvantari nighantu, edited by P.V.Sharma, 4th edition, Chaukamba Orientalia, Varanasi, 2005
10. Sahib, Najla et al. Coriander (Coriandrum sativum L.): A Potential Source of High-Value Components for Functional Foods and Nutraceuticals - A Review. Phytotherapy research. PTR. 2012; 27. 10.1002/p.4897.
11. Wen, M. et al.A comprehensive review of Rubia cordifolia L.: Traditional uses, phytochemistry, pharmacological activities, and clinical applications. Frontiers in pharmacology. 2022; 13, 965390.
12. Höferl, M. Hütter, C., & Buchbauer, G. A Pilot Study on the Physiological Effects of Three Essential Oils in Humans. Natural product communications. 2016; 11(10); 1561–1564.
13. Azamthulla, Mohammad et al. Effect of *Santalum album* linn on memory enhancing activity on mice. Journal of Chemical and Pharmaceutical Sciences. 2010; 3. 172-177.
14. Modi, M. B., Donga, S. B., & Dei, L. Clinical evaluation of *Ashokarishta*, Ashwagandha *Churna* and *Praval Pishti* in the management of menopausal syndrome. Ayu. 2012; 33(4), 511–516.
15. Razack, S. et al. Anxiolytic actions of *Nardostachys jatamansi* via GABA benzodiazepine channel complex mechanism and its biodistribution studies. Metabolic brain disease. 2018; 33(5); 1533–1549.
16. Joshi, H., & Parle, M. *Nardostachys jatamansi* improves learning and memory in mice. Journal of medicinal food. 2006; 9(1); 113–118.
17. O'Leary, M. F et al. *Shatavari* Supplementation in Postmenopausal Women Improves Handgrip Strength and Increases Vastus lateralis Myosin Regulatory Light Chain Phosphorylation but Does Not alter markers of bone Turnover. 2021; 13(12); 4282.
18. Pandey A. et al Impact of stress on female reproductive health disorders: Possible beneficial effects of shatavari (Asparagus racemosus), Biomedicine & Pharmacotherapy. 2018; Volume 103; 46-49p.
19. Tahereh Poordast et al. Aloe Vera; A new treatment for atrophic vaginitis, A randomized double-blinded controlled trial. Journal of Ethnopharmacology. 2021; 27; 113760.
20. Khan H.et al. Evaluation of estrogenic activity of licorice species in comparison with hops used in

botanicals for menopausal symptoms. PLoS One. 2013; 12; 8(7): e67947.
21. Sadeghi M, Namjouyan F, Cheraghian B, Abbaspoor Z. Impact of Glycyrrhiza glabra (licorice) vaginal cream on vaginal signs and symptoms of vaginal atrophy in postmenopausal women: A randomized double blind controlled trial. J Tradit Complement Med. 2019; 10(2):110-115.
22. Korhalkar Anagha et al. Pharmacological studies of Yashtimadhu (Glycyrrhiza glabra l.) in various animal models. Global J. Res. Med. Plants & Indigen. 2013; 2:152-164.
23. Ammon, H. P., & Wahl, M. A. Pharmacology of Curcuma longa. Planta medica; 1991;57(1); 1–7.
24. Abouali, N. et al. The effect of curcumin-based and clotrimazole vaginal cream in the treatment of vulvovaginal candidiasis. Journal of family medicine and primary care.2019; 8(12), 3920–3924.
25. Kim J. et al. Therapeutic effect of topical application of curcumin during treatment of radiation burns in a mini-pig model. J. Vet. Sci. 2016; 17; 435–444.
26. Kang D. et al. Curcumin shows excellent therapeutic effect on psoriasis in mouse model. *Biochimie.* 2016; 123; 73–80.
27. Banjare J et al. Regulates Adipogenesis through Modulation of Expression of Adipogenic Genes in 3T3-L1 Cell Line. Pharmacognosy Magazine. 2018;13(4); S834-S839.
28. Peterson, C. T., Denniston, K., & Chopra, D. Therapeutic Uses of Triphala in Ayurvedic Medicine. Journal of alternative and complementary medicine (New York, N.Y.).2017; *23*(8); 607–614.
29. Tarasiuk A, Mosińska P, Fichna J. Triphala: current applications and new perspectives on the treatment of functional gastrointestinal disorders. Chin Med. 2018;18; 13:39.
30. Lubna Fatima, Arshiya Sultana, Efficacy of Tribulus terrestris L. (fruits) in menopausal transition symptoms: A randomized placebo controlled study, Advances in Integrative Medicine. 2017; 4 (2); 56-65.
31. Chhatre, Saurabh et al. Phytopharmacological overview of Tribulus terrestris. Pharmacognosy reviews. 2014; 8; 45-51.
32. Keith NM, Whelan M, Bannick EG. The action and excretion of nitrates. *Arch Intern Med (Chic).* 1930; 46(5): 797–832.
33. Bhandari A, Sunkaria A, Kaur G. Dietary Supplementation with Tinospora cordifolia Improves Anxiety-Type Behavior and Cognitive Impairments in Middle-Aged Acyclic Female Rats. Front Aging Neurosci. 2022; 28; 14:944144.
34. Abiramasundari G, Sumalatha KR, & Sreepriya, M. Effects of Tinospora cordifolia (Menispermaceae) on the proliferation, osteogenic differentiation and mineralization of osteoblast model systems in vitro. Journal of ethnopharmacology. 2012; 141(1): 474–480.
35. Kakadia, N., & Kanaki, N. Anti-osteoporotic effect of Terminalia arjuna (Roxb.) Wight & Arn. In bilateral ovariectomized induced post-menopausal osteoporosis in experimental rats. Journal of complementary & integrative medicine, 10.1515/ jcim-2021-0068.
36. Chopra, R. N., & Ghosh, S. (1929). Terminalia Arjuna: Its Chemistry, Pharmacology and Therapeutic Action. The Indian medical gazette, 64 (2); 70–73.
37. Alaa A et al. Cardamom oil ameliorates behavioural and neuropathological disorders in a rat model of depression induced by reserpine, Journal of Ethnopharmacology. 2023; 308.
38. Yaser Masoumi-Ardakani et al. The effect of Elettaria cardamomum extract on anxiety-like behavior in a rat model of post-traumatic stress disorder, Biomedicine & Pharmacotherapy. 2017; 87,489-495,
39. Verma SK, Jain V, Katewa SS. Blood pressure lowering, fibrinolysis enhancing and antioxidant activities of cardamom (Elettaria cardamomum). Indian J Biochem Biophys. 2009; 46(6); 503-6.
40. Matsushita H, Minami A et al. Long-term supplementation with young coconut juice does not prevent bone loss but rather alleviates body weight gain in ovariectomized rats. Biomed Rep. 2017 May; 6(5); 585-591.
41. Rao, S.S., Najam, R. Young coconut water ameliorates depression via modulation of neurotransmitters: possible mechanism of action. Metab Brain Dis. 2016; 31, 1165–1170
42. Wei J, Zhao M, Meng K, Xia G, Pan Y, Li C, Zhang W. The Diuretic Effects of Coconut Water by Suppressing Aquaporin and Renin-Angiotensin-Aldosterone System in Saline-Loaded Rats. Front Nutr. 2022 Jun 23; 9:930506.
43. Jawaid T, Kamal M and Kumar S: Antihypertensive effect of the alcoholic extract of seeds of Phaseolus vulgaris Linn. (Fabaceae) on high salt diet induced hypertension in male rats. Int J Pharm Sci Res 2017; 8(7); 3092-97.
44. Shirke, Sarika S. PhD; Jadhav, Sanket R. MPharm; Jagtap, Aarti G. PhD. Osteoprotective effect of Phaseolus vulgaris L in ovariectomy-induced osteopenia in rats. Menopause. 2009; 16(3); p 589-596.
45. Yang Yao et al. Antidiabetic Activity of Mung Bean Extracts in Diabetic KK-Aʸ Mice. J. Agric. Food Chem. 2008, 56, 19; 8869–8873.
46. Taha N H., Dizaye K F. Impact of Zingiber officinale on Symptoms and Hormonal Changes During the Menopausal Period – A Clinical Trial in Duhok, Iraq. J Nat Sc Biol Med 2022;13:133-141
47. Jestin V. Thomas et al. Phytoestrogenic effect of fenugreek seed extract helps in ameliorating the leg pain and vasomotor symptoms in postmenopausal women: A randomized, double-blinded, placebo-controlled study, Pharma Nutrition, 2020; 14.
48. Ma ZP, Zhang ZF, Yang YF, Yang Y. Sesamin Promotes Osteoblastic Differentiation and Protects Rats from Osteoporosis. Med Sci Monit. 2019 Jul 17; 25; 5312-5320.
49. Tang, E. L., Rajarajeswaran, J., Fung, S. Y., & Kanthimathi, M. S. Antioxidant activity of

Coriandrum sativum and protection against DNA damage and cancer cell migration. BMC complementary and alternative medicine. 2013; 13: 347.

50. Patil, Rupali & Mohan, Mahalaxmi & Kasture, Veena & Kasture, Sanjay. Rubia cordifolia: a review. Oriental Pharmacy and Experimental Medicine. 2009; 9. 1-13. 10.3742.
51. Santha, S., & Dwivedi, C. Anticancer Effects of Sandalwood (Santalum album). Anticancer research, 2015; 35(6); 3137–3145.
52. Nagalingam A et al. Mechanistic elucidation of the antitumor properties of withaferin A in breast cancer. *Cancer Res*. 2014; 74:2617–29.
53. Thaiparambil JT et al. Withaferin A inhibits breast cancer invasion and metastasis at sub-cytotoxic doses by inducing vimentin disassembly and serine 56 phosphorylation. Int J Cancer 2011; 129:2744–55.
54. Chaudhary, S. et al. Evaluation of antioxidant and anticancer activity of extract and fractions of *Nardostachys jatamansi* DC in breast carcinoma. BMC complementary and alternative medicine. 2015; 15; 50.
55. Sharma R, & Jaitak V. *Asparagus racemosus* (Shatavari) targeting estrogen receptor α: - An in-vitro and in-silico mechanistic study. Natural product research. 2020; 34(11), 1571–1574.
56. Hussain, A.et al. Aloe vera inhibits proliferation of human breast and cervical cancer cells and acts synergistically with cisplatin. Asian Pacific journal of cancer prevention: APJCP, 2015; 16(7), 2939–2946.
57. Murray M. T. *Glycyrrhiza glabra* (Licorice). *Textbook of Natural Medicine*. 2020; 641–647.e3.
58. Mohajeri, M. et al. Curcumin: a phytochemical modulator of estrogens and androgens in tumors of the reproductive system. Pharmacological research. 2020; 156; 104765.
59. Zoi, V. et al. The Role of Curcumin in Cancer Treatment. Biomedicines. 2021. 9(9); 1086.
60. Sandhya, T., & Mishra, K. P. Cytotoxic response of breast cancer cell lines, MCF7 and T47D to triphala and its modification by antioxidants. Cancer letters. 2006; 238(2), 304–313.
61. Ghanbari, A. et al. Tribulus terrestris and female reproductive system health: A comprehensive review. Phytomedicine: international journal of phytotherapy and phytopharmacology. 2021; 84; 153462.
62. Rashmi, K. C. et al. A new pyrole based small molecule from Tinospora cordifolia induces apoptosis in MDA-MB-231 breast cancer cells via ROS mediated mitochondrial damage and restoration of p53 activity. Chemico-biological interactions. 2019, 299; 120–130.
63. Kuo PL et al. Casuarinin from the bark of Terminalia arjuna induces apoptosis and cell cycle arrest in human breast adenocarcinoma MCF-7 cells. Planta Med. 2005;71(3); 237-43.
64. Kong W, Li C, Qi Q, Shen J, Chang K. Cardamonin induces G2/M arrest and apoptosis via activation of the JNK-FOXO3a pathway in breast cancer cells. Cell Biol Int. 2020 Jan; 44(1):177-188.
65. Mohamad NE et al. *In vitro and in vivo* anti-tumour effects of coconut water vinegar on 4T1 breast cancer cells. Food Nutr Res. 2019; 10:63.
66. Thompson MD et al. Cell signaling pathways associated with a reduction in mammary cancer burden by dietary common bean (Phaseolus vulgaris L.). Carcinogenesis. 2012 Jan; 33(1):226-32.
67. Sze Kwan Lam, Tzi Bun Ng, Apoptosis of human breast cancer cells induced by hemagglutinin from Phaseolus vulgaris cv. Legumi secchi, Food Chemistry. 2011; 126; 2; 595-602.
68. K. Ashok and M. Babu. Improved micro propagation of Vigna radiata and anticancer activity of in vitro raised plant extract against human breast cancer cell line (MCF-7). Malaya Journal of Matematik, 2020; S(2), 4501-4508,
69. Elkady AI, Abuzinadah OA, Baeshen NA, Rahmy TR. Differential control of growth, apoptotic activity, and gene expression in human breast cancer cells by extracts derived from medicinal herbs Zingiber officinale. J Biomed Biotechnol. 2012: 614356.
70. Alshatwi AA et al. Fenugreek induced apoptosis in breast cancer MCF-7 cells mediated independently by fas receptor change. Asian Pac J Cancer Prev. 2013; 14(10); 5783-8.
71. Siao AC, Hou CW, Kao YH, Jeng KC. Effect of sesamin on apoptosis and cell cycle arrest in human breast cancer mcf-7 cells. Asian Pac J Cancer Prev. 2015;16(9); 3779-83. doi: 10.7314/apjcp.2015. 16.9.3779. PMID: 25987037.
72. Vaidya Yadavji Trikamji Acharya (ed), Sushruta Samhita of Sushruta with Nidandhasangraha Commentary Varanasi: Chaukhambha Surbharati Pralashan. Revised edition, 2012; p351
73. Ram Sharma & Vikas Jaitak. *Asparagus racemosus* (Shatavari) targeting estrogen receptor α: - An in-vitro and in-silico mechanistic study, Natural Product Research, 2020; 34: 11; 1571-1574.
74. Kang S. C et al. Evaluation of Oriental Medicinal Herbs for Estrogenic and Anti-proliferative Activities. *Phytother. Res.* 2006; 20 (11); 1017–1019.
75. Abiramasundari G, Mohan Gowda CM, Sreepriya M. Selective Estrogen Receptor Modulator and prostimulatory effects of phytoestrogen β-ecdysone in Tinospora cordifolia on osteoblast cells. J Ayurveda Integr Med. 2018; 9(3):161-168.
76. Wu, W. H et al. Sesame ingestion affects sex hormones, antioxidant status, and blood lipids in postmenopausal women. The Journal of nutrition. 2006;136(5), 1270–1275.
77. Doke, Snehal & Guha, Manisha. Garden cress (Lepidium sativum L.) Seed - An Important Medicinal Source: A Review. Journal of natural product and plant resources. 2014; 4; 69-80.
78. Real M. et al. Assessment of Hormone-like Activities inGinkgo biloba,Elettaria cardamomum

and Plantago Ovataextracts Usingin Vitroreceptor-specific Bioassays. Food Additives & Contaminants: A. 2015;32 (9); 1531–1541.
79. Radenahmad N. et al. Young Coconut Juice Significantly Reduces Histopathological Changes in the Brain that Are Induced by Hormonal Imbalance: a Possible Implication to Postmenopausal Women. Histol. Histopathol. 2009; 24 (6), 667–674.
80. Kim I. G. et al. Screening of Estrogenic and Antiestrogenic Activities from Medicinal Plants. Environ. Toxicol. Pharmacol. 2008; 25 (1), 75–82.
81. Boue S. M. et al. Evaluation of the Estrogenic Effects of Legume Extracts Containing Phytoestrogens. J. Agric. Food Chem. 2003; 51 (8)
82. Boue S. M. et al. Estrogenic and Antiestrogenic Activities of Phytoalexins from Red Kidney Bean (Phaseolus vulgaris L.). J. Agric. Food Chem. 2011; 59 (1), 112–120.
83. Sreeja S, Anju VS, Sreeja S. In vitro estrogenic activities of fenugreek Trigonella foenum graecum seeds. Indian J Med Res 2010. Jun;131:814-819.
84. Elaine Elisabetsky, Traditional medicines and the new paradigm of psychotropic drug action, Maurice M Iwu, Jacqueline C Wootton, Advances in Phytomedicine, Elsevier. 200; Chapter 11; 1, 133-144p.
85. Jacobs, E., & D'Esposito, M.Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2011;31(14); 5286–5293.
86. Satarkar, S.R., Joshi, M.P., & Desai, V.H. Comparative Study of Central Nervous System Effect of Santalum album Linn. Paste Fragrance v/s Aqueous Extract in Wistar Albino *Rats.* American Journal of Phytomedicine and Clinical Therapeutic. 2013;1; 661-671.
87. Khazal, K. F et al. Effect of an extract of Withania somnifera root on estrogen receptor-positive mammary carcinomas. Anticancer research. 2013; 33(4), 1519–1523.
88. Prabhakara Reddy Nagareddy, M Lakshmana, *Withania somnifera* improves bone calcification in calcium-deficient ovariectomized rats, *Journal of Pharmacy and Pharmacology.* 2006; 58 (4): 513–519.
89. Lowe, D. A., Baltgalvis, K. A., & Greising, S. M. Mechanisms behind estrogen's beneficial effect on muscle strength in females. Exercise and sport sciences reviews. 2010; 38(2); 61–67.
90. Khalid, A. B., & Krum, S. A. Estrogen receptors alpha and beta in bone. Bone. 2016; 87, 130–135.
91. Palacios, S., Mejía, A., & Neyro, J. L.Treatment of the genitourinary syndrome of menopause. Climacteric: the journal of the International Menopause Society. 2015; 18,1; 23–29.
92. Raine-Fenning, N. J., Brincat, M. P., & Muscat-Baron, Y. Skin aging and menopause: implications for treatment. American journal of clinical dermatology. 2003; 4(6); 371–378.
93. Wang, Y. et al. Curcumin in Treating Breast Cancer: A Review. Journal of laboratory automation, 2016; 21(6); 723–731.
94. Callan, N. G. L. et al. Constipation and diarrhea during the menopause transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. Menopause (New York, N.Y.). 2018; 25(6); 615–624.
95. Hendrix S. L. Urinary incontinence and menopause: an evidence-based treatment approach. Disease-a-month: DM. 2002; 48(10); 622–636.
96. Notelovitz M. Estrogen therapy and osteoporosis: principles & practice. The American journal of the medical sciences. 1997; 313(1); 2–12.
97. Davis, S. R. et al. Writing Group of the International Menopause Society for World Menopause Day 2012. Understanding weight gain at menopause. Climacteric: the journal of the International Menopause Society. 2012;15(5); 419–429.
98. Kumari et al. Study of anti-obesity activity of Withania somnifera root and terminalia arjuna bark in MSG-HFD induced mice. 2018.
99. Augustine Amalraj, Sreeraj Gopi, Medicinal properties of Terminalia arjuna (Roxb.) Wight & Arn.: A review,Journal of Traditional and Complementary Medicine. 2017; 7 (1); 65-78.
100. Modi MB, Donga SB, Dei L. Clinical evaluation of Ashokarishta, Ashwagandha Churna and Praval Pishti in the management of menopausal syndrome. Ayu. 2012 Oct; 33(4); 511-6.
101. Deepa S. Patil, Prashanth A.S. A comparative clinical study to access the role of Basti and Virechana Karma followed by Rasayana in post-menopausal Asthikshaya (Osteoporosis). J Ayurveda Integr Med Sci 2020;5; 96-103.
102. Akhila M and Laxmipriya Dei. Ayurvedic management of menopausal syndrome with Vayasthapana gana: A case report. International Journal of Herbal Medicine 2019; 7(6); 43-46.
103. Saad Ahmed et al. (Tribulus terrestris Linn.): Pharmacological actions and therapeutic applications: A Review, International Journal of Herbal Medicine 2020; 8(4); 25-29.
104. Akhtari, E et al. Tribulus terrestris for treatment of sexual dysfunction in women: randomized double-blind placebo - controlled study. Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2014; 22(1), 40.
105. Kasar PL, Kirte MC and Ukey R. Effect of Jatamansi (nordostachys jatamansi) on blood pressure in rajonivritti kala (menopause). World journal of pharmaceutical research. 2018;7, (5): 835-841.
106. Gopal, S. et al. Effect of an ashwagandha (Withania Somnifera) root extract on climacteric symptoms in women during perimenopause: A randomized, double-blind, placebo-controlled study. The journal of obstetrics and gynaecology research. 2021; 47(12); 4414–4425
107. Tandon VR, Sharma S, Mahajan A, Mahajan S. Effect of life-style modification on postmenopausal

overweight and obese Indian women: A randomized controlled 24 weeks preliminary study. J Midlife Health. 2014 Jan; 5(1); 23-8.

108. Meher, Krishna et al. Ayurvedic Approach to Menopause: A Review. International Research Journal of Ayurveda & Yoga. 2022; 05. 167-171.
109. Reynolds P. Smoking and breast cancer. Journal of mammary gland biology and neoplasia. 2013; 18(1); 15–23.
110. Jones, M.E. et al. Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res*.2017, 19 (118).
111. Shield, K. D., Soerjomataram, I., & Rehm, J. Alcohol Use and Breast Cancer: A Critical Review. Alcoholism, clinical and experimental research. 2016; 40(6), 1166–1181.
112. Nazarpour, S. et al. Factors associated with quality of life of postmenopausal women living in Iran. BMC Women's Health. 2020; 20 (104)
113. Afonso, R. F et al. decreases insomnia in postmenopausal women: a randomized clinical trial. New York (N.Y.) 2012; 19(2): 186–193.
114. Chien, L. W., Cheng, S. L., & Liu, C. F.The effect of lavender aromatherapy on autonomic nervous system in midlife women with insomnia. Evidence-based complementary and alternative medicine. 2012; eCAM, 2012, 740813.

*****