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Complementary And Nature Based Treatment For Menopausal Women- A Better Approach

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ABSTRACT

The end of menstrual cycle in a woman marks the beginning of menopause. Menopause is caused as a part of aging in women but can also occur due to surgery, hysterectomy and damage to the ovaries due to chemotherapy. During menopause transition, there are drastic changes in the hormonal concentration. The wide range of symptoms like hot flashes, mood changes, fatigue, stress, tiredness, vaginal dryness and itching associated is a result of decreased estrogen and progesterone in the body. Some disorders in the immune system can result in premature ovarian failure, where in menopause happens before the age of 40. Many associated symptoms occur due to decrease in inhibin b which is the initiator of menopause. Decrease in estrogen causes the risk of CVS diseases and osteoporosis. The decrease in estrogen and progesterone leads to lack of binding of these substrates to the receptor present in urogenital track causing irritation, itching and burning sensation. The increased estradiol level is associated with mood changes and distress. Various treatments are given in order to provide relief from the symptoms of menopause. Menopause hormone therapy is one of the most common modes of treatment but has many side effects. So natural alternatives like herbal supplements and plant products are widely used. Phytoestrogens and Bioidentical hormones are also popular mode of treatments. Practicing yoga asana and breathing techniques is highly recommended as it calms and relaxes the mind.

Keywords: Endocrinology, Pituitary-ovarian axis, Inhibin, Estradiol, Premature Ovarian Failure, Follicle Stimulating Hormone, Phytoestrogens

INTRODUCTION

Menopause also called as climacteric, is a natural part and significant event in a woman's life when ovaries stop producing estrogens and releasing eggs. Henceforth the menstrual periods stop permanently. The four major hormones involved in menstrual cycle are follicle-stimulating hormone, luteinizing hormone, estrogen, and progesterone whose production decreases during menopause. The low level of estrogen causes various symptoms in the body and affects the health of a woman. It usually commences between the ages of 45 and 55, but can develop before or after this age range. After this the endocrinology of pituitary ovarian axis changes along with selective rise in follicle stimulating hormone (FSH) and luteinizing hormone (LH) leads to accelerated loss of primordial follicles from the ovaries. There is also a rapid decrease in sex hormones.

*DIFFERENT PHASES OF MENOPAUSE ARE:

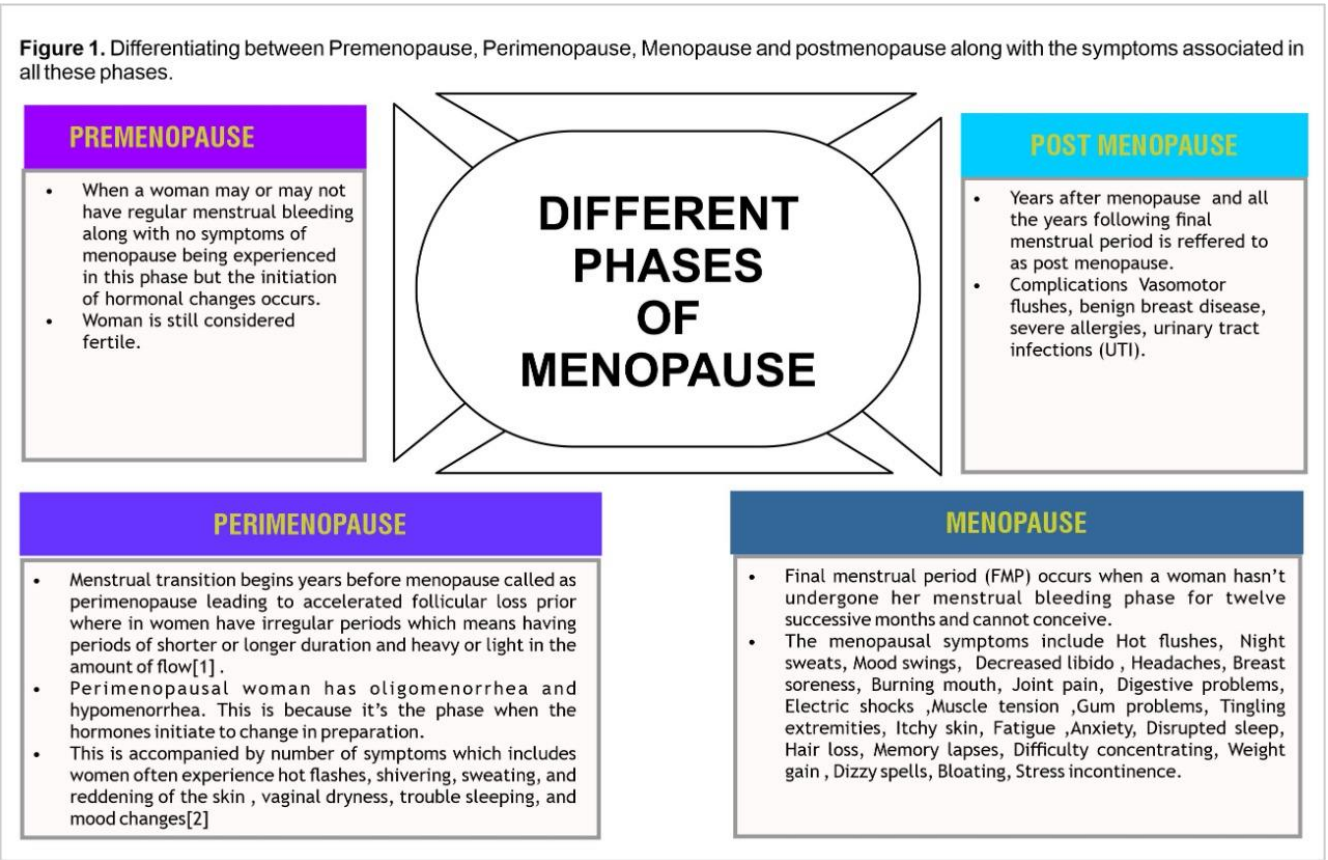

Figure 1. Differentiating between Premenopause, Perimenopause, Menopause and postmenopause along with the symptoms associated in all these phases.

Only 1 percent of the women has their climacteric before the age of 40 and is referred as premature menopause or primary ovarian insufficiency.

*__LABORATORY TESTS THAT CONFIRMS MENOPAUSE:__A blood test known as the Pico AMH Elisa diagnostic test approved by food and drug administration to detect menopause as many adverse health impacts like cardiovascular disease, cognitive changes, fractures and many more that are associated with the menstrual transition phase. Loss of ovarian function causes reproductive ageing in women which results in decreased level of inhibin B and antimullerian hormone (AMH) [3]. During the early phase, there is increase in follicle stimulating hormone (FSH) due to decreased level of inhibin B and hence this maintains the folliculogenesis and estradiol secretion. Therefore FSH in the blood fluctuates during this phase[4]. After FMP the estradiol level stabilises at very low level. So a blood test that measures the level of the hormones FSH and Estradiol can be used to determine menopause. Biochemical parameters that confirms menopause in women includes[5]

- Thyroid function tests
- Blood lipid profile
- Liver function tests
- Kidney function tests
- Testosterone
- Progesterone

- Prolactin
- Chorionic gonadotropin (hCG) tests[6].

***BIOCHEMICAL TEST PARAMETERS**[7][8]

NAME OF TEST	PERIMENOPAUSE	MENOPAUSE	POSTMENOPAUSE
Anti-mulerianhormone (AMH) Test	Starts decreasing than the normal range	Almost Undetectable	Undetectable
Salivary Test	High cortisol	High cortisol	High cortisol
Urine Test	*Estradiol -80–400 pg/ml *Progesterone -15–23 ng/ml	Estradiol -80–400 pg/ml *Progesterone-15–23 ng/ml	Estradiol -80–200 pg/ml Progesterone-2–8 pg/ml
Thyroid Function Test	T3 : High T4: Low	T3 : High T4: Low	T3 : High T4: Low
Lipid profile Test	TC Cholesterol :Little elevated LDL Cholesterol: Little elevated VLDL Cholesterol: Low	TC Cholesterol : More elevated LDL Cholesterol: Little elevated VLDL Cholesterol: Lower	TC Cholesterol :Highly elevated LDL Cholesterol : Highly elevated VLDL Cholesterol: Lowest
DHEA	Normal	Low	High
	Normal serum HCG	Normal serum HCG	Elevated serum HCG
Liver Function Test	ALT :Elevated AST :Elevated	ALT :Elevated AST :Elevated	ALT :Elevated AST :Decrease

Table 1. Different tests that confirm menopause in women.

The various clustering symptoms at the same time largely affect the quality of life of a woman. Therefore treatments are given when the symptoms are severe. One very common therapy includes menopausal hormone replacement therapy[9].

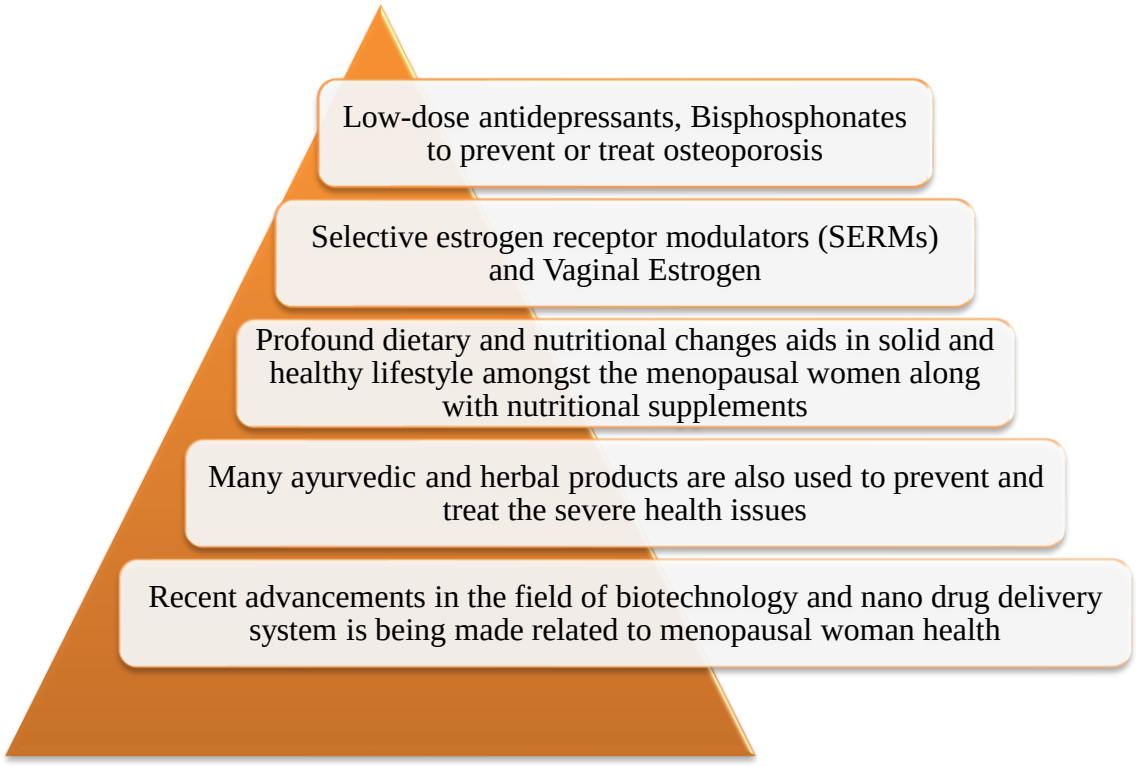

Figure 2. Other mode of treatments to curb menopause symptoms and advancement related to menopausal women health.

***VARIOUS STAGE TERMINOLOGIES:**

Stage terminology	Menstrual cycle	FSH level	LH level	Menopause symptoms
Early reproductive	Variable → Regular	Normal	Normal	None
Peak reproductive	Regular	Normal	Normal	None
Late reproductive	Regular	↑	Normal TO ↑	Slightly
Early menopausal transition	Variable length	↑↑	↑↑	vasomotor 15-20% vaginal —
Late menopausal transition	≥ 2 skipped cycles + interval of amenorrhea of ≥ 60 days	↑↑	↑↑	vasomotor 20-30% vaginal —
Early post menopause	Menopause = 12 months amenorrhea FMP = none	↑↑↑	↑↑↑	vasomotor 35-55% vaginal 10-30%
Late post menopause	None	↑↑↑	↑↑↑	vasomotor 30%& declining vaginal 35-47%

Table 2. Duration of menstrual cycle and level of FSH and LH in different phases of women's life along with the symptoms faced in that phase.

***VARIATIONS IN HARMONES DURING MENOPAUSAL TRANSITION:**

There are drastic changes in the concentration of various hormones during this menopausal transition. There is significant increase in LH and FSH during perimenopause due to loss of ovarian inhibin B with aging[10].. There is consistent rises and falls in the estrogen levels[11].. A clinically frustrating aspect of menopause is the fluctuation in the level of estradiol which is the most potent natural estrogen and the decrease in level of progesterone is directly associated with this hormone[12].. There is production of 25% of circulating testosterone, 60% of circulating androstenedione, and about 20% of circulating DHEA but this total androgen level decrease after menopause. Therefore the various changes in the concentration of different hormones during perimenopause and after menopause are depicted below.

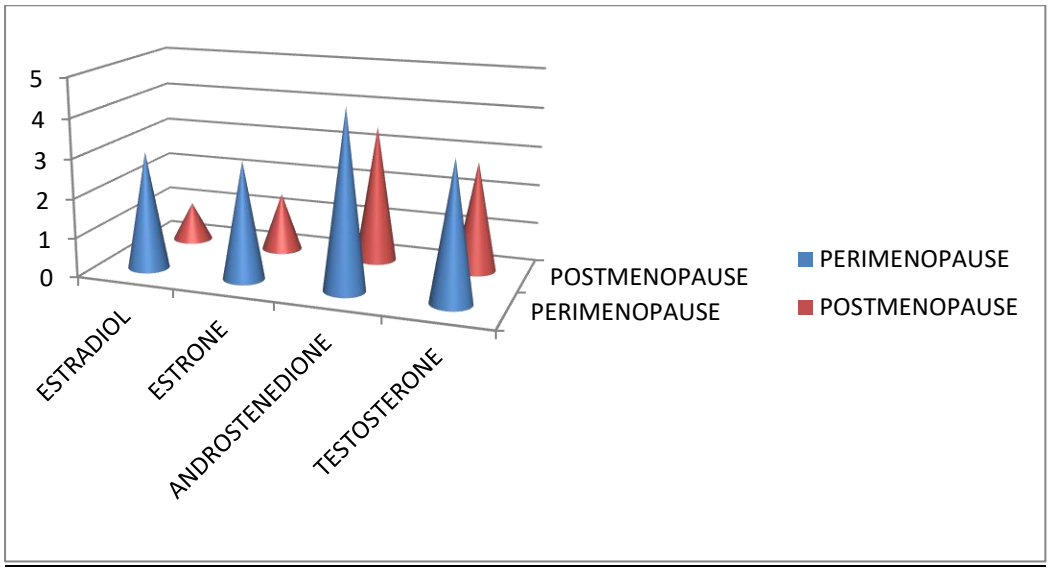

Figure 3. Concentration of different hormones in perimenopause and post menopause period.

EPIDEMIOLOGY:

A number of factors like demographic, menstrual cycle, reproductive phase and lifestyle pattern of a woman altogether are responsible to determine at which age a woman will have menopause and when all the symptoms associated with menopause commence. The mean age of menopause in urban women ranges from 46 to 51 years while in rural women it is from 48 to 50 years. Natural menopause rate is higher in rural women whereas the rate of surgical menopause is higher in urban women. Premature menopause is common in urban woman while there are almost no cases of premature menopause in rural women. There are variations in the symptoms experienced in women of rural and urban areas and urban women experience more menopause symptoms as compared to the rural woman. Hot flushes, night sweat, depression, osteoporosis and cardiovascular diseases are the predominant symptoms. The average median age of menopause in India and Philippines is 44 years, while in United States and Australia is 51 years, in United Kingdom is 52 years and in Ireland it is 50years. In tribal and rural India, women have simple and stress free lives resulting in almost no menstrual problems. Women in countries where there is less stress physical exertion and a diet of

fresh foods, grains and spices with estrogenic effects rarely face any perimenopause and menopause symptoms[13].

***PREMENOPAUSAL PHYSIOLOGY:**

The reproductive cycle of female is known as menstrual cycle and each cycle is of approximately 28 days. The first menstruation is called menarche. One ovum is released during the middle of the cycle as secondary oocyte from the mature Graffian follicle and is called as ovulation. The menstrual cycle begins with the Menstrual phase in which the menstrual flow lasts for 3-5 days due to the breakage of endometrial lining of the uterus and the blood vessels. This occurs when fertilization does not take place. Other factors like stress, poor health or pregnancy may also be responsible. This phase is followed by Follicular phase. Due to changes in the pituitary and ovarian hormone, the secretions of LH and FSH increases gradually. This causes the primary follicles to grow in size and become fully mature graffian follicle. At the same time the endometrial lining of the uterus regenerates through proliferation .Both the LH and FSH attains a peak in the middle of cycle resulting in LH surge causing the release of the ovum (ovulation). The follicular phase is followed by luteal phase in which the remaining part of graffian follicle is transformed to corpus luteum. This corpus luteum secretes progesterone which is required to maintain the endometrial lining in case fertilization took place[14]. Further again the disintegration of endometrial lining marks the beginning of a new cycle and the above events continues.

***SYMPTOMS AND PHYSICAL CHANGES DURING MENOPAUSE**

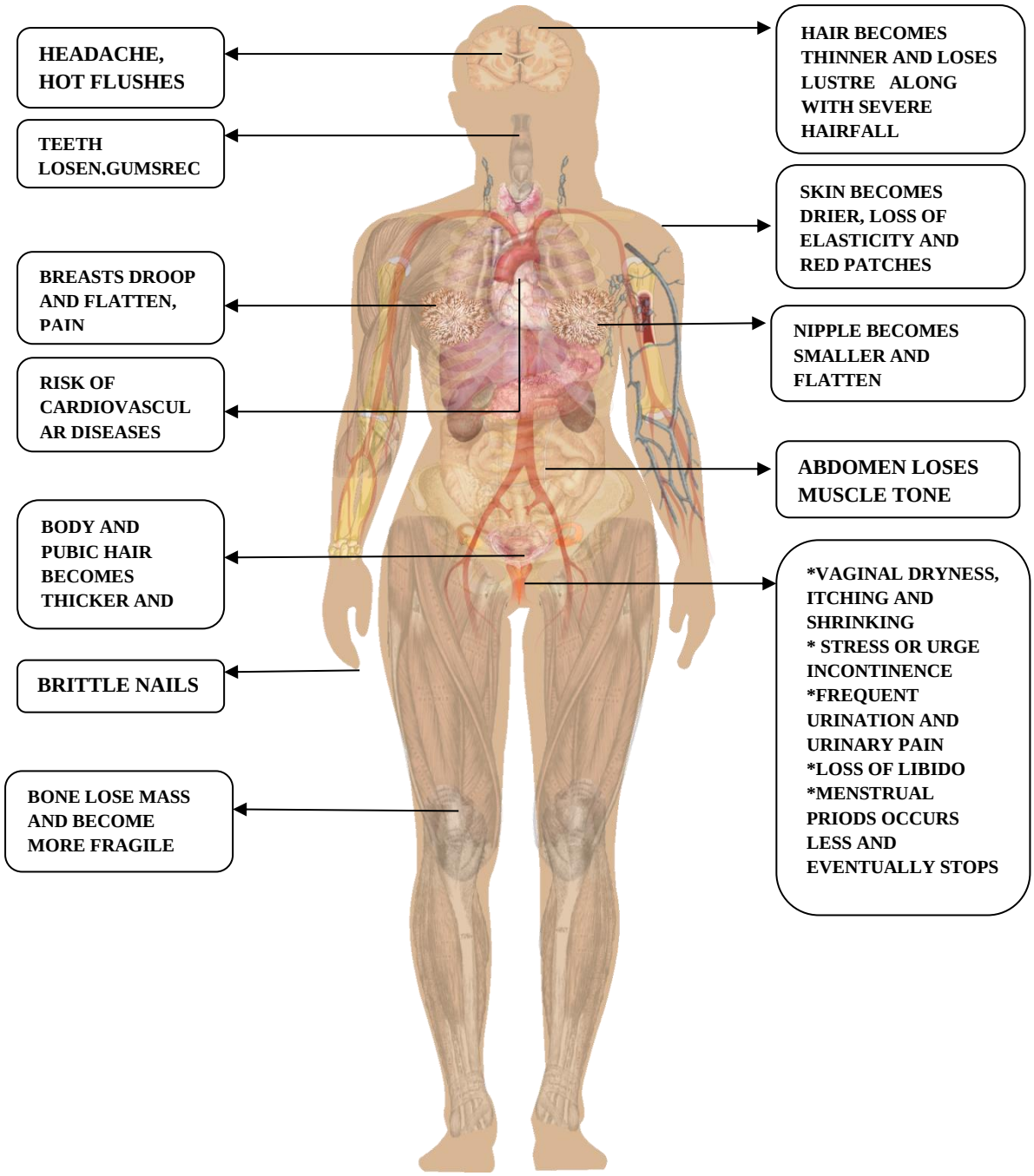

Figure 4. Different signs and symptoms occuring during menopause and their effects on vaious parts of the body.

***PATHOPHYSIOLOGY OF MENOPAUSAL TRANSITION:**

Ovarian senescence begins with primordial follicle activation, maturation and regression due to changes in the production of estrogen, progesterone, FSH and LH[15].. As the reproductive ageing continues only fewer follicles are left. In order to produce a good egg and respond to follicles there is a rise in FSH level. Simultaneously LH level rises causing a decrease in both estrogen and progesterone. These sex hormones drop gradually causing irregular menstrual cycles and at menopause there is a significant drop in their level. All this happens due to the decrease in the level of inhin b which is the primary initiator of menopause whose normal function is to negatively inhibit the anterior pituitary

from secretion of FSH in the beginning of the menstrual cycle[16]. Inhibin is a member of TGF-βfamily and is composed of two heterodimeric protein. The decrease in inhibin b causes increase in FSH during the early cycle as negative inhibition is removed. In response to increase FSH the ovaries secrete high level of estradiol. A combination of elevated estradiol and serum FSH in turn increase the aromatase activity which converts the testosterone to estradiol[17]. The corpus luteum is formed during the luteal phase to secrete progesterone which also decreases due to decreased inhibin b .Thus the ovaries become unresponsive to the increased FSH as all the follicles are depleted from the ovaries .

Human ovaries have accepted the concept of degeneration of primordial follicles is not constant during ageing and it decreases significantly at an accelerated rate after the age of 37. During puberty 60,000-80,000 primary follicles are present in each ovary which declines to only 1000 primordial follicles in the ovary at the age of 51 which causes natural menopause[18]. The reasons behind this accelerated degeneration of follicles are decrease in one or more inhibitors and increase in one or more stimulators.

***PATHOPHYSIOLOGY OF MENOPAUSE TRANSITION:**

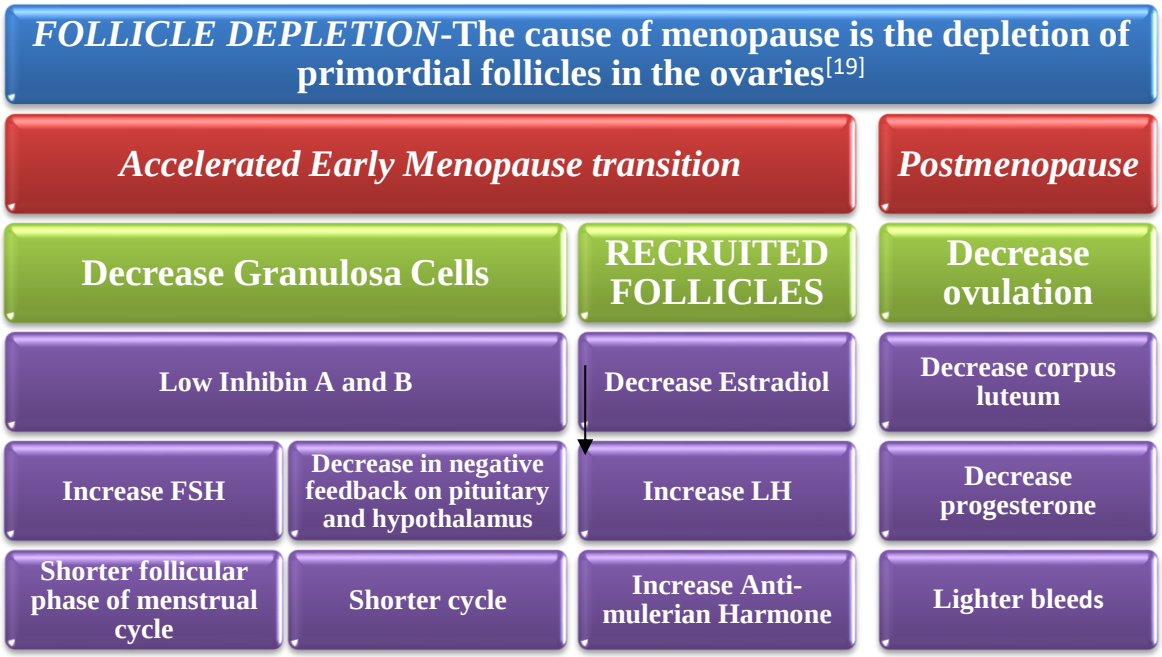

Figure 5. Physiological process associated with menopause

***PATHOPHYSIOLOGY OF ORGAN CHANGES IN MENOPAUSE:**

- During menopause there is hormonal transition in ovaries which also affects the other organs of the body. Different changes in the organs are as follows[20]:
- Post menopause there is many changes in the ovaries due to ovarian senescence which includes lack of follicular cysts, increased atretic follicles, and persistent corpora albicans[21]:
- Estrogen also known as cardio protective because it increases the level of high density lipoprotein and decreases the level of low density lipoprotein[22]:. Hence post menopause the risk of cardiovascular disease increases absence of estrogen [23]:

- In urogenital tract, estrogen and progesterone receptors are distributed throughout the tract[24]. Post menopause there is lack of these substrates which leads to decreased vascularity which in turn decreases epithelial lining, increases fatty deposits along with decreased blood flow in vaginal epithelium and decreased glycogen production. Thus weakening the walls of vagina[25]. Therefore causing itching sensation, burning and irritation in the urinary tract. This subsequent vaginal atrophy leads to tissue trauma and bleeding.
- Ductal and Lobular structures of breast are affected by estrogen and progesterone respectively. Lack of both of these serum post menopause leads to loss of volume as there is change of dense breast tissue with soft adipose tissue.
- Thinning and loss of elasticity of skin due to decreased collagen content as there is absence of estrogen which aids in prevention of skin ageing and maintains the level of skin collagen, skin dryness occurs due to decreased sebaceous gland secretion and hormonal changes which also leads to sagging of skin especially around the neck, jawline, and cheeks[26].
- Menopause causes many significant changes in the bones. Dearth of estrogen increases osteoclast formation. This increase leads to predominance of bone resorption over bone formation. Hence increasing the risk of osteoporosis which leads to defect in bone mineral density as trabecular bone is highly affected[27].
- Menopause leads to extreme cognition and mood changes. High and erratic estradiol levels relate to emotional distress along with emotional distress due to fluctuation in the level of estrogen[28].

***AYURVEDIC PATHOLOGY OF MENOPAUSE:**

Ayurveda explains the symptoms of menopause are due to the ageing phenomena. Ayurveda defines ageing Nishpratikriya and Swabhavabal Roga. All the symptoms of menopause are due to disturbed Vata Dosha which is the element of air and space. According to ayurveda, menopause demarks the transition from the Pitta stage of life to Vata state of life[29]. According to ayurveda there is decline in the qualities of body like Dosha, Dhattu, Malla, Agni and Oja which correlates to the various symptoms of menopause and ageing.

***CAUSES OF MENOPAUSE:**

❖ AGE AND INTRACRINOLOGY:

- There are various cyclic changes in the adult ovaries due to production and variation in the level of steroidal hormones, Estradiol, progesterone and key regulatory proteins like inhibin[30].
- The main event in the menopause is the disappearance of primary follicle in the ovary that is loss of ovary reserve[31].
- Ovarian primordial follicles decreases with age from birth but this decrease is not constant and it gets accelerated at the age of 37[32].
- When the loss in ovary reserve is accelerated, the level of plasma FSH increases which corresponds to the time that fecundity drops and there is decrease in inhibin A and B[33].
- The increase in plasma FSH coincides directly with the accelerated loss in the ovary reserve[34].
- The α subunit protein present in the follicles dimerize to form activin which is an autocrine /paracrine regulator of prenatal folliculo- genesis and accelerates the loss of ovary reserve. [35].

- Hence age –related decrease in the production of ovary inhibin which corresponds to monotropic rise in FSH which finally results in accelerated loss of ovary reserve.
- According to traditional mechanism, the estrogens secreted by the ovaries are distributed throughout the bloodstream to all the tissues and cells of the body.

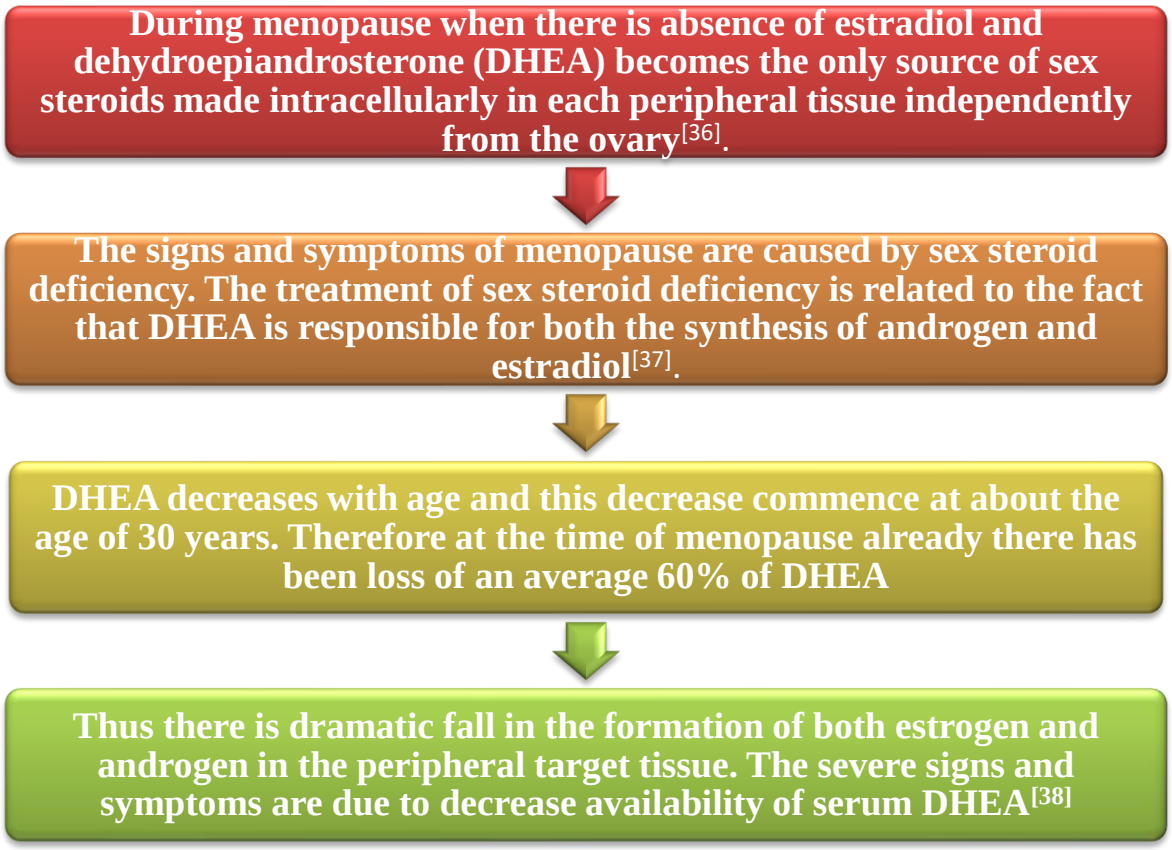

Figure 6. Intracrine hormone changes that causes menopause.

❖ **PREMATURE OVARIAN FAILURE:**

It is also called as premature ovarian insufficiency (POI) is a condition when there is cessation of menses or the ovaries stop functioning prior to or at the age of 40.This can be diagnosed by high blood level of FSH (follicle stimulating hormone) or LH (Luteinizing hormone) .The two main reasons are follicle depletion in which there is lack of follicles due to inadequate primordial follicles, lack of folliculogenesis. Hence lack of ovarian estrogen production .The other reason is follicle dysfunction which implies that follicles are present but they are not functional in steroid production. Follicle depletion occurs due to X chromosome disorder like Turners Syndrome, Fragile X Syndrome Permutation, and Somatic chromosome disorder like galactosemia, auto immune cause, ovarian toxins and thyroid disorders. Follicle Dysfunction occurs due to intraovarian modulator abnormalities, steroidogenic enzyme abnormalities and Gonadotropin receptor abnormalities. Early menopause can also be due to smoking, higher body mass index or cancer of the reproductive organ.

❖ **SURGICAL MENOPAUSE:**

Cessation of menopause by removal of ovaries (Oophorectomy) is defined as surgical method of inducing menopause[39]. Surgical treatments may cause the periods to stop along with sudden drop in the hormone resulting in severe symptoms like hot flushes[40].

❖ **OVARIAN AGEING:**

Decreased inhibin feedback post hysterectomy along with reduced blood supply to the ovaries leads to ovarian ageing. Uterine artery embolisation also contributes for the same. Endometrium of the uterus contains some endocrine factors which yields endocrine feedback, elimination of these factors is also responsible for ovarian ageing. The impaired DNA repair mechanism causing the accumulation of double stranded DNA is responsible for the depletion of ovarian reserve.

***COMPLICATIONS DURING MENOPAUSE AND POST MENOPAUSE:**

Starting from perimenopause to menopause , the body starts experiencing various signs and symptoms due to decreasing DHEA but its post menopause when the symptoms subside and various complications arises.

❖ **VASOMOTOR SYMPTOMS :HOT FLUSHES**

Hot flushes are the most common and troublesome physiological manifestation experienced during menopause due to decrease in estrogen[41]. It starts by ascending flush of upper body caused by vasodilatation resulting in feeling of warmth. The blood pressure is normal but there is alteration in heart rate[42]. Vasodilatation causes decrease in body temperature which leads to shivering[43]. This usually occurs at night and causes insomnia, night sweats, fatigue and irritability[44]. Neurotransmitters like catecholamine and catechol estrogen controls the thermoregulatory centre situated in the hypothalamus[45]. .The estrogen that is distributed in the blood when combines with catecholamine to produce catechol estrogen[46]. During menopause, when there is lack of estrogen, an imbalance arises between catecholamine and catechol estrogen along with reduction in serotonin level which further regulate the 5-hydroxytryptamine receptor in the hypothalamus[47]. When additional serotonin is released, there is activation of the 5-HT_{2A} receptor by itself which results in hot flushes[48]. Regular exercising, muscle relaxation and biofeedback helps in curing the symptoms[49]. If the women is suffering from severe hot flushes and night sweat the Menopausal replacement therapy (estrogen – androgen replacement therapy) provides relief[50][51]. Tiboline a synthetic tissue-specific sexual steroid is very useful in reducing vasomotor symptoms and is an effective alternative to Menopausal hormone replacement therapy[52].

❖ **THYROID DISODER:**

Thyroid disorders, especially subclinical hypothyroidism and subclinical hyperthyroidism are very common in postmenopausal women. Menopause and thyroid disease may be present with similar symptoms like sweating, heart palpitations, insomnia and mood swings. There is Reduction of thyroid iodine uptake, free thyroid hormone synthesis and catabolism of free thyroxin (FT4). Also the level of reverse triiodothyronine (rT3) level increases[53]. Changes in thyroid hormones are related with bone mineral density and fracture. Despite hypothyroid patient show higher bone density, there is still high risk of fracture amongst the hypothyroid patients. Subclinical hypothyroidism is linked with risk of Coronary heart disease (CHD), heart failure and atherosclerosis.

❖ **ESTROGEN EFFECT ON COGNITION:**

Estrogen level impacts the brain chemistry and morphology by affecting the short term and long term memory[54]. Decrease in estrogen affects the verbal memory and the capacity to learn new things. Women experience delay in recalling visual materials, paragraphs or digital span scores[55]. They face

difficulty in remembering names, verbally told information, face challenges in organising and planning things. Estrogen supplementation or estrogen replacement therapy can help in curing this crisis. Administration of estrogen showed changes in the mood along with serotonin transmission.
Estradiol administration interacts with cholinergic system thereby affecting the cognition and verbal memory. This gives cholinergic benefit by enhancing better cognition[56].

❖ **CARDIOVASCULAR DISEASE:**

This is leading cause of death in women[57]. Post menopause there is an increase in total cholesterol, LDL cholesterol, together with Apolipoprotein B, an increase in triglycerides, and a decrease in HDL cholesterol and Apo lipoprotein A1. There is oxidation of LDL[58]. Metabolism changes in glucose and insulin is also observed in postmenopausal women. The abnormalities of lipids, lipoproteins, glucose, and insulin metabolism lead to an increase in the blood pressure. Coronary heart disease and myocardial infraction are one of the most prevalent ailments among the postmenopausal women[59]. The fluctuation of estrogen level which begins from perimenopause phase contributes towards the risk of cardiovascular disease. A high plasma LDL is associated with carotid atherosclerosis among women[60]. There is positive correlation between prolactin and arterial blood pressure[61]. Prolactin accelerates arterial stiffness during early menopause. There is also fluctuation in the blood pressure of women due to changes in the hormones. There is prevalence of both hypotension and hypertension in post menopause women[62].

❖ **BENIGN BREAST DISEASE :**

This includes all the benign breast changes that occur in women. Progesterone insufficiency in postmenopausal women induces benign breast disease[63]. Progesterone has protective function against breast cyst, carcinoma, antianxiety agent but its deficiency initiates the disease[64]. The main etiology behind this is the imbalance in the ratio of estradiol and progesterone ratio in luteal phase. Progesterone induces Estradiol induced mitosis and proliferation and causes cell differentiation[65].

❖ **MENOPAUSE SYMPTOMS IN BREAST CANCER SERVIVORS:**

Breast cancer women experience various menopause symptoms include hot flushes , Vulvovaginal atrophy , osteoporosis , dispareunia and the problem enhances when these symptoms trigger brain fog in them which includes reduced cognition , difficulty in concentration , multitasking and challenges related to memory[66]. Hormonal supplementation is the most effective method in reducing these symptoms. Premenopausal women have higher risks of recurrence of breast cancer than the older women. Menopause symptoms are very common among the breast cancer survivors and can adversely affect the quality of life[67]. Wide range of treatments focussing on nonhormonal mode is available so that menopause after breast cancer is not an unsolved crisis along with any recurrence of breast cancer in the survivors[68].

❖ **Genitourinary Syndrome of Menopause and Vulvovaginal Atrophy:**

This includes symptoms like vaginal drying, itching, discomfort, pain, burning, and irritation; sexual symptoms such as lack of lubrication, discomfort, and urinary symptoms such as urgency, dysuria, and recurrent urinary tract infections[69]. Urinogenital tissues are extremely sensitive towards estrogen and its fluctuation during menopausal transition makes them fragile. In addition to vaginal atrophy, there is narrowing and shortening of vagina along with uterine prolapsed. These symptoms unlike vasomotor symptoms cannot be cured over time. Treatment is required. Menopausal hormonal

therapy or administration of low doses of estrogen is useful. This helps because the whole urinary tract contains estrogen receptor and needs substrate for binding .The novel SERM ospemifene is an alternative to hormonal treatment to vulvovaginal Atrophy[70]. Ospemifene was initially used in the treatment of osteoporosis. SERM have antiestrogenic or neutral effects on the breast which is demonstrated by clinical trials with tamoxifene and raloxifene. Hence ospemifene can be considered as a safe treatment option for breast cancer survivors suffering from Vulvovaginal Atrophy[71]. According to recent research, Postmenopausal women facing severe Vulvovaginal Atrophy symptoms and application of micro ablative fractional CO2 laser is found very effective in treating vaginal atrophy[72].

❖ **DEGENERATIVE ARTHRITIS:**

There is prevalence of basal thumb osteoarthritis in post menopausal women. 25% of women suffer from carpometacarpal osteoarthritis while only 2% suffer from scapho-trapezial osteoarthritis. 55% of the women suffer from both types of arthritis.

❖ **DEMENTIAAND ALZHEIMER'S DISEASE:**

Women having Down syndrome experiences both menopause and Alzheimer at the same time. Reduction in the estrogen level is associated with Alzheimer's disease[73].The women who have early menopause that is before the age of 46 years has the risk of developing Alzheimer disease than those who have late menopause. The bioavailable estradiol is related with causing dementia[74].

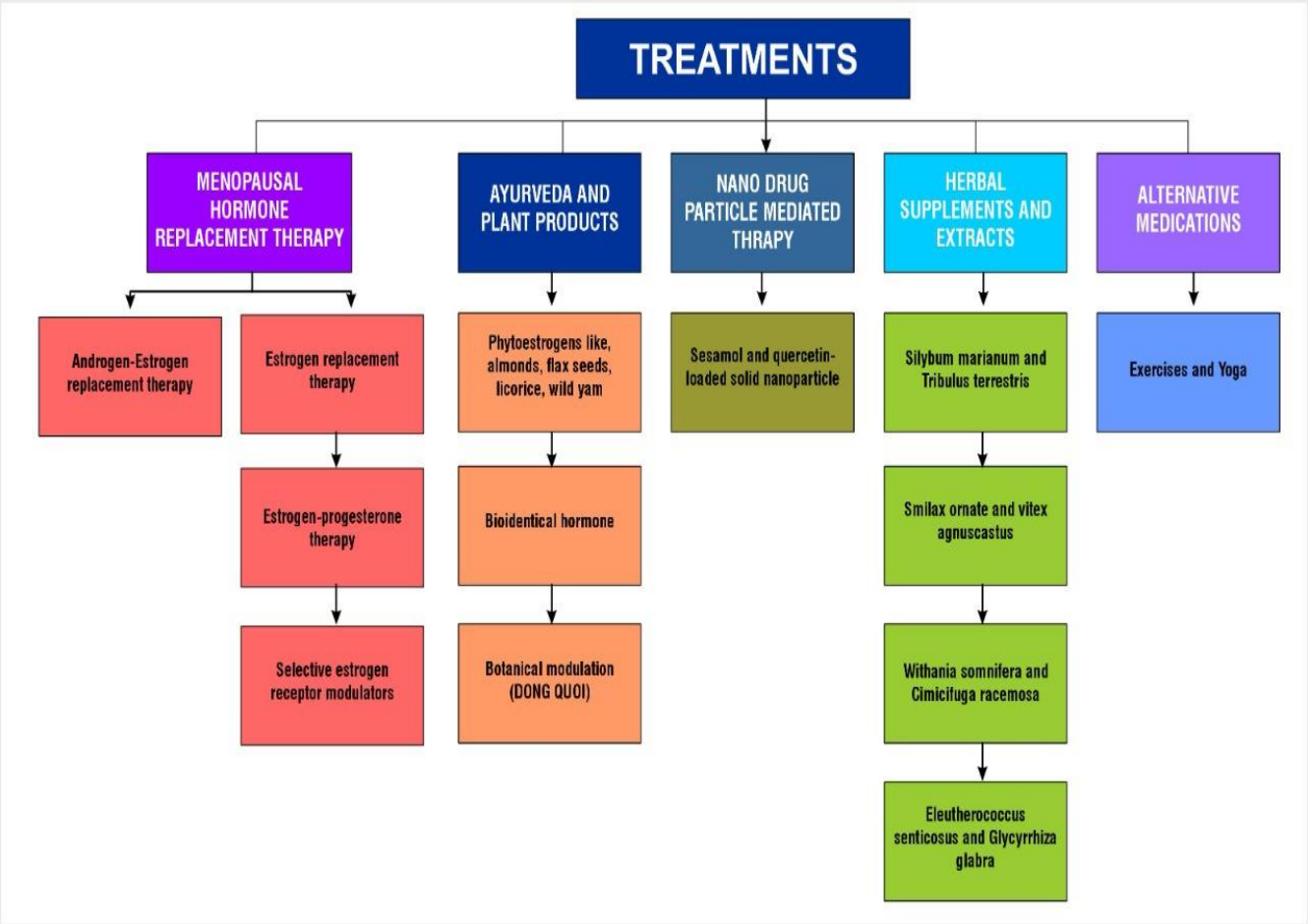

Figure 7. Various modes of treatments related to menopause symptoms and adverse effects caused due to menopause.

❖ **OSTEOPOROSIS:**

There is high risk of women aged 50 years to suffer Osteoporotic fracture which includes vertebral fractures, Distal Forearm(wrist) Fractures, Humerus Fractures and Hip Fractures[75]. The incidents of vertebral fracture commence five years after the menopause. Osteoporosis is denoted by low bone mass, deterioration of bone tissue making it fragile and susceptible to fracture. Due to decrease in estrogen, there is more bone resorption as compared to bone formation[76]. Treatment with parathyroid hormone decreases the risk of vertebral and non vertebral fractures and henceforth increasing the total bone mineral density. This is because parathyroid hormone increases bone formation and bone mass. Calcitonin, vitamin D, and calcitriol are the various other treatments of postmenopausal osteoporosis[77].

TREATMENTS:

❖ **HORMONE REPLACEMENT THERAPY:**

This mode of treatment is very effective and commonly used to get relief from vasomotor symptoms like hot flushes, insomnia, vaginal dryness and osteoporosis[78].This therapy is also used to prevent from many chronic disorders like ischemic heart disease[79].. The dose is given for 2-3 months but if the symptoms still persists then the dosage of estrogen is increased[80]. The Management of therapy includes decrease in estrogen dose, change of the type of the progesterone, or change in the route of administration[81]. The estrogen – androgen replacement therapy showed better results in curing the symptoms as compared to estrogen replacement therapy alone[82][83].

❖ **MANAGING MENOPAUSE : THE AYURVEDIC WAY :**

According to aayurveda, the various menopause symptoms are result of imbalance of Vata approaching the Vata stage of life .Vata pacifying diet and herbs are best for treating the underlying symptoms. Incorporating healthy diet, oils, avoiding caffeinated beverages and spicy foods along with minimizing stress help prevent the symptoms of menopause.

- **SUPPLEMENTS:**

The common herb which mimics estrogen includes saw palmetto, red clover, motherwort, Dong quai, vitex, blue cohosh, black cohosh, shatavari and licorice .The nourishing herbs for menopause includes aloe vera gel, ashwagandha, brahmi, saffron and amalki.

1. ½ tablespoon of ashwagandha , shatavari , vidari powder and ¼ tablespoon of ginger powder taken together and mixed with honey to draw into fine paste and taken twice a day with warm water provides relief from various symptoms.
2. Boil one cup of organic milk and immerse 10 strands of saffron thistles .Then add ½ tablespoon of shatvari powder and 1 teaspoon of ghee .Taken for six months to make feel better during menopause.

- **DONG QUOI (Angelica sinensis):**

Lau et al., (2005) reported the water extract of dong quoi is used in the treatments of perimenopause and menopause treatments in breast cancer survivors by stimulating the growth of MCF-7 cells which shows weak estrogen agonistic activity along with 17β-estradiol and suppression of 4-hydroxytamoxifen. This estrogen like activity of dong quoi can be used as herbal treatment for both estrogen-sensitive and insensitive breast cancer. This should be avoided by women fibroids or blood-clotting problems.

- **Black cohosh (Actaea racemosa, Cimicifuga racemosa):**

One of the most effective herbs used in treatment of menopausal hot flushes and has a good safety record. It is a member of buttercup family and has been used in the treatment of arthritis, muscle pain and liver problems. Fukinolic acid is an active constituent found in Black cohosh has estrogen like properties that can help treat hot flushes, night sweats, mood swings and vaginal dryness. Maki et al., (2017) reported this is very beneficiary herb as most of the symptoms of menopause are due to age – related decline in the estrogen levels. Remifemin which is an ethanolic extract of Black cohash have significantly reduced the FSH levels but not LH, used in curing symptoms of menopause caused by elevated FSH. This herb is proclaimed as natural alternative to hormone therapy[84].

- **Red clover (Trifolium pratense):**

Just like Black cohash, the leaf extract of Red clover gives relief from menopausal symptoms especially hot flushes. Red cloves report to have least slide effects with almost no serious health concerns but can show harmful effects on hormone sensitive tissues. Red cloves have been effectively used in case of skin cancer, skin burns, eczemas and psoriasis. Red clove contains isoflavones which is a kind of phytoestogen having chemical makeup similar to estrogen. It's also useful in case of bone density loss and balancing high/low cholesterol which is very quotidian trouble faced by menopausal women (Narul et al., 2018)

- **Ginseng (Panax ginseng or Panax quinquefolius):**

It is very helpful in curing the sleep discomforts and mood swings experienced due to menopause, thereby improving the overall sense of well being. Recent studies have shown that this herb is useful in reducing the risk of cardiovascular disease in post menopause women. Ginseng functions as 'adaptogen' which is an agent that provides shield against internal stresses and improves physical and mental fitness. Ginsenosides, which is the principle active component of Ginseng, exerts estrogen like actions. Ginsenoside Rg3 increases nitric oxide (NO) production and Ginsenoside Re stimulates cardiac potassium channels. Ginseng can show estrogenic properties by two ways either by directly binding with estrogen receptors or indirectly activating estrogen receptors on the symptoms of menopause (Kim et al., 2013)

- **Kava (Piper methysticum):**

Cagnacci et al., (2003) reported Kava provides comfort from stress and extreme anxiety caused to women post menopause. The disadvantage of Kava is that is has potency to cause liver damage. Kava-Kava extract/therapy is used as an excellent therapeutic tool along with hormone therapy to resolve

all the psychological conflicts along with that this does not diminish the therapeutic action of estrogen on the organic disease like osteoporosis and cardiovascular diseases.

- **Evening Primerose Oil (oenothera biennis):**

This has shown its effectiveness in healing hot flushes but has many side effects such as nausea, inflammation, problems with blood clotting and the immune system. It contains high levels of gamma-linolenic acid (GLA) and linolenic acid, which are contains omega-6 fatty acids which is excellent for brain health and bone.

- **Sage (Salvia officinalis):**

This is very useful in treating hot flushes, night sweats and its mode of action is very fast as difference is observed in only two to three intakes. The hot flushes occur due to stressed hypothalamus caused by changes in the hormones during menopausal transition. Due to this the body cannot regulate the temperature and hence leads to night sweats. Sage aids in restoring this imbalance caused in the hypothalamus and retunes it back [85].

- **Danggui Liuhuang (DLH) decoction:**

Jun et al., (2018) reported DLH decoction consists of seven herbs which are Angelicae Gigantis Radix, Astragali Radix, Coptidis Rhizoma, Rehmanniae Radix Crudus, Rehmanniae Radix Preparata, Phellodendri Cortex, and Scutellariae Radix. This traditional herbal medicine is widely used to treat menopausal symptoms in East Asia. Various menopausal symptoms including night sweats, fever, red face, distress, dry mouth, and constipation can be healed using this compound.

- **PHYTOESTROGENS:**

This is a class of compound which is found in plants. They resemble similar to the structure of estrogen and hence helps in hormonal balance in the body. Phytoestrogens can be consumed either in concentrated herbal form or extract formulas. Dietary soy, wheat, cashew, almonds, flax seeds, licorice, wild yam are examples of phytoestrogen.

- **BIOIDENTICAL HORMONES :**

Bioidentical hormones are synthesised from natural source and hence better than hormone replacement therapy because the latter has many side effects .The bioidentical hormones have the same molecular makeup and structure like that of human hormones. Since the structure of the hormone is similar like that of humans, it binds with the same receptor and responds like human hormone. Another advantage of bioidentical hormone is that it can be compounded for each individual thus ensuring that each individual gets an appropriate dose for the specific hormones, symptoms and health. Bioidentical hormones are available in many different formulations: oral, transdermal, sublingual, and injectables unlike the synthetic ones which are usually formulated in the form of tablets or pills. Thereby products of synthetics hormones yield many toxic substances which results in risk of blood clots, heart diseases, strokes and elevated blood pressure[86].

HERBAL TREATMENTS :

1. **Estrogen excess : Perimenopausal symptoms-**

a) Diet support:

Increase intake of fibres, lower intake of caffeine, alcohol and sugar, avoidance of xenoestrogen.

b) Herbal supplements:

- Vitex agnus-castus: It is commonly used herb for female hormonal imbalance. It is also known as pituitary balancer which directly affects the production and release of pituitary hormone. Vitex stem increases the progesterone production which helps regulate the menstrual cycle and inhibiting FSH. It is very effective in decreasing all the symptoms of perimenopause women. Hypericum perforatum in combination with vitexagnus-castus is being studied to show better result for the treatment of symptoms. The standardised extract to be used is 200 mg, once or twice a day on a regular basis depending upon the symptoms.
- Silybum marianum: This is not only a hormonal influencer but also help in detoxification of liver which ultimately aids in the metabolism of excess estrogens. The standardised extract to be used is 160mg, once or twice daily.
- Taraxacum officinalis: This also promotes detoxification of liver and metabolises the excess estrogen which would otherwise build up resulting in estrogen –excess symptoms. The standardised extract to be used is 2g daily.

2. **Estrogen deficiency :Hot flushes ,insomnia:**
   a) Diet supplement:

Avoid eating spicy foods, decrease in consumption of alcohol and caffeine. Induce soy products in your diet.

b) Herbal supplements:

- Medicago sativa: This is considered to have chemical make up like that of estrogen. It is an herb which is capable of producing estrogenic effects in the body and promoting estrogen production. The standardised intake is 3-6 g daily. It also supports bone density and is used in treatment of neurovegetative menopausal symptoms.
- Tribulus terrestris: This is effective in modulating the level of estrogen and aid in reducing the symptoms of menopause. The standardised extract to be used is 200-400mg daily.

3. **Progesterone deficiency: Insomnia, irritability –**

a) Diet supplements:

Increase intake of fibres and decrease in consumption of caffeine, alcohol and sugar.

b) Herbal supplement:

- Smilax ornate: The roots of this herb are very useful for reducing the symptoms and are considered to mimic progesterone activities. The standardised extract to be used is 1-2 g daily.

- Vitex agnus-castus: This is very effective as it promotes the production of progesterone and also increases LH levels thereby reducing the symptoms. The standardised extract to be used is1-2 gm daily.

4. **Cortisol excess: Anxiety, stress and irritability:**

a) Diet supplement:

Increase in consumption of protein and decrease in consumption of alcohol, caffeine and sugar.

b) Herbal supplement:

- With ania somnifera: This is crucial for adrenal imbalances and considered as adrenal adaptogen. This can bring adrenal back to its normal function. Ashwagandha is considered to decrease the cortisol production. The standardised extract to be used is 600mg, twice a day.
- Passiflora incarnate: It is a strong anxiolytic ideal herb for people with excess cortisol facing problems sleep-onset and sleep-maintenance insomnia. The standardised extract to be used is 500mg twice a day.
- Scutellaria lateriflora: It is antixiolytic herb which is used to decrease anxiety, stress and all cognitive issues due to high cortisol level. The standardised extract to be used is 600mg, twice a day.

5. **Cortisol deficiency: Fatigue, brain fog**

a) Diet supplement:

Increase in protein and decrease in sugar

b) Herbal supplements:

- Glycyrrhiza glabra: This is a well known herb for adrenal support and is considered to bind with the cortisol receptors to increase the half life of cortisol. The standardised extract to be used is 500mg, twice daily.

6. **Low thyroid problem : Fatigue , weight gain :**

a) Diet supplement:

Increase intake of carbohydrates and vegetables like Brassica. Avoid consumption of glutten and dairy products.

b) Herbal supplements:

- Withania somnifera: This increases the production of both T4 and T3.This is a powerful thyroid-balancing hormone. The standardised extract to be used is 600mg, twice daily.

7. **DHEA deficiency**: Poor concentration and all the symptoms arise due to this-

a) Diet supplements:

Increase protein consumption and decrease intake of caffeine and sugar.

b) Herbal supplements:

- Glycyrrhiza glabra: This is well known for increasing the production of DHEA deficiency. The standardised extract to be used is 500mg, twice daily.
- Withania somnifera: If the level of DHEA is too low then ashwagandha will promote adrenal hormone production to bring back DHEA to its normal level. The standardised extract to be used is 600mg, twice daily.

❖ **BOTANICAL MODULATION** :

Hormone replacement therapy is considered as pioneer technique that helps in reducing the most troubling symptoms of menopause but at the same time is associated with various side effects. One of the major side effects is the chances of having breast cancer. So in order to prevent these side effects natural, efficacious and safe methods such as botanical supplements are used in practice. The mechanism of action of various botanicals includes estrogenic, progesterone and serotonergic pathways.

Botanicals having estrogenic properties are red clove, kudzu, hops and rhubarb. Chaste berry and yam have progesterone properties while dong quoi and kava have 5-HT_7 ligands or inhibit the serotonin reuptake are considered to have potential serotonergic activities.

❖ **SELECTIVE ESTROGEN RECEPTOR MODULATOR:**

These are either produced synthetically or derived from botanical sources. They exhibit agonist as well as antagonist interactions on the estrogen receptors. Raloxifen and tamoxifen are the examples. Raloxifen shows agonist activities on bone and lipid, thus preventing vertebral fractures in post menopausal women while shows antagonist activities in the breast and endometrium[88].

❖ **NANODRUG PARTICLE MEDIATED THERAPY:**

- The delivery of sesamol – loaded solid lipid nanoparticle as therapeutic agent for central nervous system is used to improve the emotional , depressive and all the cognitive problems like difficulty in remembering verbal messages due to deficiency of estrogen. It has solubility of 38.8mg/mg along with an average particle size of 122nm and entrapment efficiency of 75.9 ± 2.91%.[89].

- Quercetin- loaded solid nano parcticle which has high bioavailability is used in preventing osteoporosis in post menopausal women[90].

❖ **ALTERNATIVE MEDICATION:**

Cognitive behaviour therapy can be used to provide relief from vasomotor symptoms like hot flushes[91].Mind and body practices such as acupuncture, hypnosis, meditation, and yoga generally are safer along with no side effects being recorded. Exercises and yoga are considered to be one of the best remedies for the treatment of the symptoms of menopause in natural and safe way. Squats, Seated row and T'ai chi are few examples of exercised which are very effective. Acupuncture is considered to provide relief to the various symptoms of menopause. It is considered as a reasonable alternative to hormone therapy. Mindful deep breathing causes calming and soothing effects.

***CONCLUSION**

The menopause transition in a women's life is one of the major and challenging phase wherein the hormones of the body undergoes various significant changes thereby altering physical and psychological system of the body. Not only is the ovaries but there drastic change in the complete reproductive system of the females. The hallmark of menopausal transition is the change in menstrual cycle pattern that is the length of each cycle and the bleeding. There are many symptoms associated with this including hot flushes which is the most frequently occurring symptom in all the women, night sweat, psychological conflicts. Fluctuation in the hormones along with transition in androgen and GH/IGF-1 levels are common symptomatology of the menopause. Various treatments are there to deal with the symptoms but the challenge faced is due to the lack of neatly organised transition period[92]. It is crucial to understand the symptoms experienced by women in different transition phase and their need of treatment. Cardiovascular disease, recurrence of breast cancer in breast cancer survivors and metabolic syndrome represents a time for amelioration of risk factors that may affect quality of life. Hormone replacement therapy is one of the most widely used mode of treatment but prolong use of it can have many adverse effects like stroke, dementia, and mild cognitive impairments. To prevent this alternative methods and natural methods are encouraged.

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