

Combination therapy to target the neuronal origin of menopausal symptoms

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Abstract

Menopausal syndrome is marked by an array of psychosomatic as well as vasomotor symptoms such as hot flushes and night sweats. Amongst vasomotor symptoms of menopause, hot flushes are the most common. It consists of sudden sweating and periodic flushing with palpitations, chills, anxiety, choking and nausea. Depletion of estrogen is in part a cause for these symptoms, but not entirely. Neuronal origin of menopausal symptoms is gaining significance for better understanding the pathophysiology of vasomotor symptoms. There is significant change that occurs in the thermoregulation due to menopause. An important neuronal theory is narrowing of thermoneutral zone due to elevated central sympathetic activation. The first line therapy such as lifestyle changes, either alone or combination with dietary isoflavones, do not effectively control the vasomotor symptoms in severe cases. In such individual hormone therapy is inevitable, albeit it's higher risk for coronary artery disease, breast carcinoma and pulmonary embolism. Therefore, it is imperative that the therapeutic target should be directed towards the central origin of symptoms and it should be devoid of these adverse effects. Medicinal plants and complimentary therapies have proved to be of great therapeutic advantage for patients with menopausal syndrome. Amongst medicinal plants studied extensively so far for reduction of menopausal symptoms, *Valeriana Officinalis*, *Passiflora incarnata* and *Humulus lupulus* are particularly important. *Valeriana Officinalis* binds to the beta subunit of the GABA-A receptor which leads to chloride channel mediated anxiolysis. It also decreases the metabolism of GABA thereby potentiating its effect. *Passiflora incarnata* acts by increasing the level of serotonin via modulating the content of mono-amine oxidases. *Humulus lupulus* increases the level of GABA thereby exerting its sedative and anxiolytic effect in menopause. The GABA mimetic action of these three ingredients controls the psychosomatic and vasomotor symptoms of menopause mediated by central sympathetic action. Clinical trials with these three herbs in European post menopausal women have led to active control and reduction in menopausal symptoms. This review delineates their role in the management of menopausal syndrome.

Keywords: Valeriana officinalis, Passiflora incarnata, Humulus lupulus, Menopause.

Introduction

Menopause is an inevitable event in woman's life. It may be physiological or due to a surgical cause. A major part of women's life (about 30%) is being spent post menopause.¹ Post menopausal syndrome comprises of irritability, anxiety, headache and other vasomotor symptoms that greatly affect the quality of her life. More than 75% of post menopausal women are affected by vasomotor symptoms, which can continue to occur up to 10 years from the onset of menopause.² Amongst vasomotor symptoms hot flushes usually affect more than 80% of menopausal women.³ The cause of hot flushes cannot be attributed only to estrogen deficiency. The thermoregulatory change leading to vasomotor symptoms has neuronal origin. One of the widely accepted neuronal theory is narrowing of thermoneutral zone due to elevated central sympathetic activation.

Hot flushes are common during the night as well. It affects the normal sleeping pattern and causes insomnia. In return insomnia causes anger; reduce mental functions, anxiety and restlessness. This predisposes of coronary artery diseases, stress disorders and various other metabolic disturbances.⁴ In day to day practice, it is not uncommon to encounter post menopausal women who are non adherent to therapy, especially hormones. Perceived harm, inappropriate efficacy or various adverse effects are cited as reason for

non compliance. Hence, there is a need for alternative therapy which can improve the compliance. Conversely, many women do not respond to lifestyle changes in combination with dietary isoflavones even if they are adherent to therapy. The immediate next option for them would be hormone therapy in contemporary clinical practice. Hormone therapy carries a higher risk for coronary artery disease, breast carcinoma and pulmonary embolism. Therefore, a therapy targeting the central origin of symptoms that improves adherence and devoid of adverse effects is the need of the hour.

In this review, we selected medicinal plants that have spasmolytic, anxiolytic, and anti inflammatory action. Extracts from *Valeriana officinalis*, *Passiflora incarnata* and *Humulus lupulus*, either in combination or as a single ingredient have the above mentioned properties.⁵⁻⁷ This review suggests an alternative, safe and effective strategy to control the symptoms of menopause.

Valeriana officinalis in Menopause: The term valerian is derived from the term "valer" which implies "good health". Valerian's root and rhizome are effective in the treatment of anxiety, dizziness, insomnia and neuralgias.⁸ Valerinic Acid is the active pharmaceutical ingredient present in the valerian root which leads to GABA-A receptor mediated anxiolysis and ameliorates neurological symptoms of menopause. A Randomized Controlled Trial (RCT) was carried out amongst 68 post menopausal women with the

complaint of hot flushes. These subjects were randomized into two groups i.e. valerian and placebo. The patients in the valerian group received 255mg of the same, thrice daily for 8 weeks. The severity and frequency of hot flushes were recorded via questionnaires at 2 weeks before the therapy, 4 and 8 weeks post therapy. Hot flushes reduced drastically in the valerian group as compared to the placebo group (p value <0.001). Valerian also decreased the frequency of hot flushes in both 4 and 8 weeks post therapy (p value <0.001).⁹

In clinical practice, often post menopausal women complain of varied mental and urogenital symptoms associated with menopause. Naturally quality of life index in these women are diminished. These changes are worsened by decreased ovarian hormone levels during menopause. Amongst other major menopausal symptoms, urogenital disorders are a major complaint. They include vaginal atrophy, dyspareunia, recurrent urinary tract infection, and urinary incontinence.¹⁰ As women approach menopause there is decline in libido, sexual response, and significant increase in vaginal dyspareunia. These symptoms lead to referral of post-menopausal women to health care centers.¹¹ Considering the signs and symptoms that may occur during menopause, complementary medicine is used to eliminate and reduce the symptoms.¹² It was noted that post menopausal women who chose complementary and alternative medicine for the treatment of menopausal symptoms reported lesser adverse effects when compared to those who chose hormone replacement therapy.

Hormone replacement therapy, despite many of its benefits in recent studies, is still faced with a negative attitude.¹³ As per the Women Health Initiative trial, 16000 post menopausal patients were enrolled and administered hormone replacement therapy. Post 5 years of hormone replacement therapy, a significant increase was noted in stroke and heart disease amongst these patients by 41% and 29% respectively.¹⁴ There was also a twofold rise in venous thromboembolic events. Estrogen therapy led to an increase in venous thromboembolic events by 33%. Many gynecologists are using complementary medicine to prevent menopausal symptoms.¹² Reports have shown that women over 40 years are the highest consumers of complementary therapies.¹⁵ Conventional complementary methods include herbal remedies, exercise, relaxation techniques, acupuncture, acupressure, massage, and aromatherapy.¹⁶ According to Izadjoo et al., 60 post-menopausal women between the age of 45 and 60 years were studied for physical mental and urogenital symptoms post administration of valerian capsules twice a day for 8 weeks.

They were evaluated at baseline 1 month and 2 months post administration of the test drug. The results showed that valerian capsules improved the mental, physical and urogenital symptoms of menopause effectively, p value <0.001.¹⁷

Passiflora Incarnata in Menopause: In the year 1569, few Spanish globetrotters discovered *Passiflora incarnata* in Peru. Since then passion flower has been used in a variety of medicines for sedation, relaxation and relieving anxiety. As

the life expectancy of an average woman has increased to 65 years, menopause has undoubtedly become one of the most challenging transitions in a woman's life. A decrease in the level of various ovarian hormones leads to an imbalance of physiological and psychological factors which negatively affect the quality of life index of these women. Passion flower provides a useful supplementary treatment without the risk of adverse effects. *Passiflora incarnata* has Vitexin as the active pharmaceutical ingredient which is responsible for analgesic, spasmolytic and anti-anxiety effects.

Passiflora incarnata was found to be effective in reducing menopausal symptoms in the 3rd and 6th week of the study (P>0.05). *Passiflora* was reported as an alternative treatment for treating menopausal symptoms such as insomnia, depression, anger, headache and other vasomotor symptoms for those having contraindications to hormonal treatment.¹⁸

Passiflora Incarnata acts by increasing the level of serotonin via modulating the content of mono-amino oxidases. Fig. 1 demonstrates its mechanism of action of *Passiflora incarnata* in menopause. There is significant evidence that a decrease in serotonin level aggravates menopausal symptoms. As per Fahami et al, study (2010), the effectiveness of passion flower in 29 post menopausal women was studied. Symptoms of hot flushes, insomnia, depression, anger and headache were attenuated. This study showed that the Passion Flower group had a significant decrease in menopausal symptoms throughout the third and the sixth weeks of study (p < 0.05). Therefore *Passiflora* can be beneficial in alleviating the symptoms of menopause.

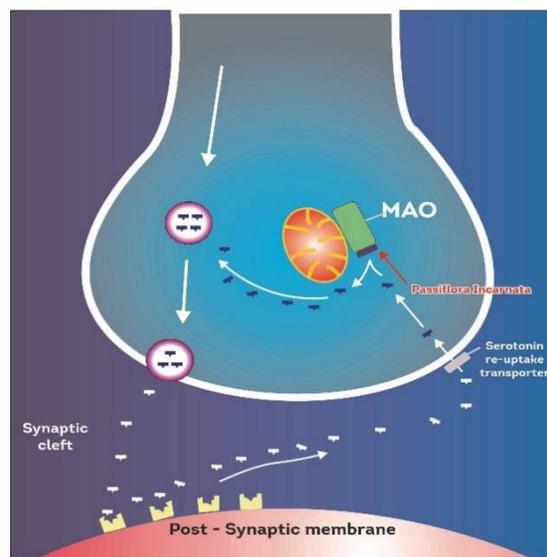


Fig. 1: Mechanism of action on *passiflora incarnata* in menopause

Humulus Lupulus in Menopause: *Humulus lupulus* contains 8-prenylaringenin (8-PN) which is a potent phytoestrogen and the active pharmaceutical ingredient. 8-PN has been confirmed to be able to interact with various estrogen receptors. *Humulus lupulus* is widely used to treat anxiety, headache, sleep disorders and pain. HOPS have

been found to decrease the intensity of hot flushes in post menopausal women. Erkkola et al (2010) and Heyerick et al, found HOPS being effective in reducing vasomotor symptoms of hot flushes, sweating, sleeplessness and palpitation.^{19,20} As per Erkkola et al (2010), post 16 weeks of therapy the HOPS group in comparison with placebo showed significant reductions in menopausal symptoms in terms of the Kupperman Index (P value <0.05), Visual Analogue Scale (P value <0.05) and a marginally significant reduction for Menopause Rating Scale (P value = 0.06). Bowe et al study reported daily subcutaneous administration of 8-PN led to an active control of elevated skin temperatures in post menopausal hot flushes. HOPS extract can strongly bind to ER-alpha and ER-beta receptors, stimulate alkaline phosphate activities in Ishikawa cells and upregulation of presenelin-2.

Herbal medicines, especially those containing oestrogen, can have various favorable effects and alleviate vasomotor symptoms in postmenopausal women. Substantial amounts of 8-prenylnaringenin (8-PN), the strongest known phytoestrogen capable of binding to oestrogen receptors in the human body, are found in *Humulus lupulus* (commonly known as HOPS). As a member of the Cannabaceae family, HOPS contains volatile oils and oestrogenic, resin-based and polyphylic compounds. Owing to its estrogenic, sedative, hypnotic, antipyretic, anti-inflammatory and antiseptic effects, it has found wide medicinal and industrial applications. It is therefore an appropriate herbal medicine for treatment of menopausal symptoms. In a RCT done with 120 menopausal patients, *Humulus lupulus* had significantly lowered the mean Greene score as compared to the placebo group at the end of 4, 8 and 12 weeks.²¹ *Humulus lupulus* had significantly lowered the mean Greene score as compared to the placebo group at the end of 4, 8 and 12 weeks with statistically significant difference, p value=0.001.

Heyerick, 2006 examined the efficacy of a HOPS extract enriched in 8-prenylnaringenin on relief of menopausal symptoms. There was a significant reduction of Kupperman Index after 6 and 12 weeks in both treatment and placebo groups (P = 0.023). A decrease in the hot flush score was statistically significant (P <0.01) in the HOPS group after 6 weeks as compared to placebo. They showed that daily intake of a HOPS extract has favorable effects on vasomotor symptoms. Animal studies have shown that chronic exposure to *Humulus lupulus* has been reported to increase blood sugar levels in diabetics. However, there is no data available on non-diabetic individuals. Rosic et al noticed significant improvements in the physical, psychological and genitourinary symptoms of menopause following the administration of *Humulus lupulus*.²² Currently available clinical evidences show that *Humulus lupulus* has high estrogenic activity and significantly reduce the intensity and frequency of hot flushes in post menopausal women. Hence it can be useful in ameliorating symptoms of estrogen deficiency that occurs during menopause.

Conclusion

The neuronal origin of vasomotor symptoms requires centrally acting therapeutic agents. In our review, we found evidence to effective therapeutic role of herbal extracts of valerian, passion flower and hops. Our analysis of literature points to a synergistic pharmacological action of these three ingredients in menopause. Hence the combination therapy of these ingredients can be recommended in the treatment of menopausal vasomotor symptoms. Owing to the synergistic action, a fixed dose combination of *Valeriana officinalis* 300 mg, *Passiflora incarnata* 80 mg and *Humulus lupulus* 30 mg has potential benefit in the treatment of menopausal vasomotor symptoms.

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Conflict of Interests: None

References

1. Ellen B. Gold. The Timing of the Age at Which Natural Menopause Occurs. *Obstet Gynecol Clin North Am* 2011;38(3):425-440.
2. Pronob K, Manu A. Postmenopausal syndrome. *Indian J Psychiatry* 2015; 57(2):222-232.
3. Ellen W. Freeman, Mary D. Sammel, Hui Lin, Ziyue Liu, Clarisa R. Gracia. Duration of Menopausal Hot Flushes and Associated Risk Factors. *Obstet Gynecol* 2011;117(5):1095-1104.
4. Katharine S. Edwards, Valerie Hoover. Insomnia and Heart Disease. Aug 02, 2016. Available from: <https://www.acc.org/latest-in-cardiology/articles/2016/08/02/07/25/insomnia-and-heart-disease>
5. Hazelhoff B, Malingre TM, Meijer DK. Antispasmodic effects of valeriana compounds: an in-vivo and in-vitro study on the guinea-pig ileum. *Arch Int Pharmacodyn Ther* 1982;257(2):274-287.
6. Grundmann O, Wähling C, Staiger C, Butterweck V. Anxiolytic effects of a passion flower (*Passiflora incarnata* L.) extract in the elevated plus maze in mice. *Pharmazie* 2009;64(1):63-64.
7. Van CM. Hop bitter acids efficiently block inflammation independent of GRalpha, PPARalpha, or PPARgamma. *Mol Nutr Food Res* 2009;53(9):1143-1155.
8. Shaheen EL, Karen F. Nutritional and herbal supplements for anxiety and anxiety-related disorders: systematic review. *Lakhan Vieira Nutr J* 2010, 9:42.
9. Mirabi, Faraz M. The Effects of Valerian Root on Hot Flushes in Menopausal Women. *Iran J Pharm Res.* 2013; 12(1): 217-222.
10. Taavoni S, Ekbatani N, Kashaniyan M, Haghani H. Effect of valerian on sleep quality in postmenopausal women: a randomized placebo-controlled clinical trial. *Menopause* 2011;18(9):951-955.
11. Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? *Fertil Steril* 2001;76(3):456-460.
12. Taibi DM, Vitiello MV, Barsness S, Elmer GW, Anderson GD, Landis CA. A randomized clinical trial of valerian fails to improve self-report, polysomnographic, and actigraphic sleep in older women with insomnia. *Sleep Med* 2009;10(3):319-328.
13. Geller SE, Studee L. Botanical and dietary supplements for mood and anxiety in menopausal women. *Menopause.* 2007; 14(3): 541-9.

14. Suvarna K. Hormone Replacement Therapy: An Update. *Obstet Gynaecol India* 2012;62(3):261–265.
15. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Seminars Integr Med* 2004;2(2):54-71.
16. Morelli V & Naquin C. Alternative Therapies for Traditional Disease States: Menopause. *Am Fam Physician* 2001;66(1):129-134.
17. Izadjoo M. The effect of valerian oral capsules on menopausal symptoms in women. *Int J Rev Life Sci* 2015;5:220–226.
18. Fahami F, Asali Z, Aslani A, Fathizadeh N. A comparative study on the effects of Hypericum Perforatum and passion flower on the menopausal symptoms of women referring to Isfahan city health care center. *Iran J Nurs Midwifery Res* 2010;15(4):202–207.
19. Erkkola R, Vervarcke S, Vansteelandt S, Rompotti P, De Keukeleire D, Heyerick A. A randomized, double-blind, placebo-controlled, cross-over pilot study on the use of a standardized hop extract to alleviate menopausal discomforts. *Phytomed* 2010;17(6):389-396.
20. Heyerick A, Vervarcke S, Depypere H, Bracke M, De Keukeleire D. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. *Maturitas* 2006;54(2):164-175
21. Aghamiri V, Mirghafourvand M, Mohammad CS, Nazemiyeh H. The effect of Hop (*Humulus lupulus L.*) on early menopausal symptoms and hot flushes: A randomized placebo-controlled trial. *Complement Ther Clin Pract* 2016;23:130-135.
22. Semso R, Sulejman K, Muhamed R. Phytoestrogens Impact on Menopausal Symptomatology. *Mater Sociomed* 2013;25(2):98–100.

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