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Review article

Ginseng as a Complementary and Alternative Medicine for Postmenopausal Symptoms

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Abstract : Ginseng is a popular herbal medicine that has been used for thousands of years. A number of its components have been isolated and characterized, including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids. The lipophilic characteristics of ginsenosides have raised the possibility of their efficacy as steroid hormones. Several *in-vitro* studies have reported their pharmacological function as steroid hormones, especially estrogen, but no human study to date has confirmed their efficacy as alternatives to synthetic estrogen.

Key words : ginseng, complementary medicine, postmenopausal symptoms

INTRODUCTION

Ginseng has been used for over 2000 years in oriental countries as a tonic,[1-3] to fight to enhance stamina and immune function, where it has been suggested to have pharmacological activities in the cardiovascular, endocrine, immune, and central nervous systems.[4] Its use has expanded to Western countries, and continues to rise with the increasing popularity of complementary and alternative medicine. It is one of the best-selling herbs in the United States with gross retail sales of $US62 million in 2000 with current sales being estimated to be over $300 million US per year.[5,6] In the United States, ginseng is used as an alternative herb for postmenopausal women, as are black cohosh (*Cimicifuga racemosa*), chaste tree berry (*Vitex agnus-castus*), dong quai (*Angelica sinensis*), evening primrose oil (*Oenethera biennis*), motherwort (*Leonurus cardiaca*), red clover (*Trifolium pratense*), and licorice (*Glycyrrhiza glabra*).[7] Here in this review, the reports on ginseng usages targeting post-menopusal symptonms is discussed.

1. Hormone replacement therapy

Menopause is known as the cessation of menstrual periods and normally occurs at a mean age of 51.4 years in healthy women.[8,9] The failure of the ovaries to produce estrogens results in hot flushes and/or sleep disturbances in many women, as well as accelerated bone loss, increased risk of colon cancer, and weight gain accompanied by shifts in plasma lipoprotein cholesterol profiles associated with a higher incidence of cardiovascular disease.[9] Hormone replacement therapy is used to prevent or combat heart disease, stroke, osteoporosis, Alzheimer's disease, and postmenopausal symptoms such as hot flashes and depression.[10] However, such uses of synthetic estrogens and progesterones are associated with side effects, increased risks of uterine and breast cancer (perhaps ovarian cancer as well) and clotting disorders[10] as was demonstrated in The Women's Health Initiative Study, which was abruptly ceased in 2002 because of an increased incidence of breast cancer, and increases in cardiovascular complications such as coronary heart disease, stroke, and venous thromboembolism.[11] Owing to these problems, public interest in alternative medicines for hormone replacement therapy has increased, which is believed to carry less risk when associated with the management of menopausal symptoms.

As stated, the most commonly used alternative herbal medicines for estrogen replacement are soy, black cohosh, dong quai, chastetree berry, and ginseng.[4] Phytoestrogens that include isoflavones, lignans, and coumestans are found in some of these herbs.[12,13] This is assumed to be one reason for the lower prevalence of menopausal symptoms in countries like Korea, Japan, and China, where

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consumption of soy is high.[14] Although accumulating studies suggest important potential health benefits, both the clinical efficacies and mechanisms of action of these herbs are still not fully known.

2. Experimental Ginseng studies in animals and in vitro

The major pharmacologically active components of ginseng are ginsenosides, which are steroidal saponins comprising 3-6% of ginseng.[15] It has been shown that ginsenosides decrease the levels of total cholesterol and triglyceride via cAMP production, and inhibit the accumulation of calcium ions in liver cells.[16] Ginsenosides potentiate analgesia and inhibit analgesic tolerance.[17] The cardioprotective action of ginsenosides is due to effects on vasodilation via nitric oxide (NO) release.[18,19] Other activities, such as anticarcinogenic and neurologic effects, have also been reported for ginsenosides.[20,21] In addition to the above beneficial effects, triterpene saponin has been hypothesized to be a type of phytoestrogen, which is a plant-based compound with estrogen-like activity. Accumulating evidence suggests that ginseng contains either direct or indirect estrogenic activity.[22] Ginseng extracts activate estrogen-responsive genes and regulate the growth of human breast cancer cells.[23] Recent studies by Chan *et al.* showed that picomolar ginsenoside-Rg1 from *Panax notoginseng* activated ER-mediated transcription without direct receptor interaction mediated by mitogen-activated protein kinase pathway.[24,25] Two ginsenosides with estrogenic activity, ginsenoside-Rb1 and -Rh1, had been identified previously by screening panel of ginsenosides by our group.[26] Cho *et al.* showed that ginsenoside-Rb1 activated both ERa and ERb, leading to the transactivation of estrogen-responsive genes. However, this activation occurred in the absence of direct receptor binding, as examined using receptor competition assays. This indicated that ginsenoside-Rb1 activates ER via a mechanism or mechanisms other than that of classical, hormone-mediated activation. The results from other studies in different systems indirectly suggest the regulation of estrogen-responsive genes by ginsenoside-Rb1 as well. It was shown to decrease cardiac contraction in adult rat ventricular myocytes, in part through an increase in NO production.[18] While a correlation between the increase in NO and ER activation was not evaluated, estrogen is known to enhance NO production.[27] Ginsenoside-Rb1 also regulates adrenal tyrosine hydroxylase,[28] which is known to be under estrogen regulation.[29] These in vitro studies provide a scientific foundation for potential clinical development. However, it should be noted that, as with other phytoestrogens, these reported ginsenosides contain biologic activities that are independent of ER, such as antioxidant, antiproliferative, and antiangiogenic effects.[30,31] Although, these approaches are essential to provide a scientific rationale for using ginseng for estrogen-related symptoms, but more comprehensive data are needed to adequately evaluate this activity.

3. Human ginseng studies on postmenopausal symptoms

There are several published randomized trials of phytoestrogen and menopause symptoms.[32-38] One recent randomized controlled clinical trial showed that only black cohosh had a beneficial effect on postmenopausal hot flashes.[7,39] However, recent data showed that black cohosh increased metastatic mammary cancer in transgenic mice expressing c-erbB2.[40] This indicates that black cohosh should be cautiously used. Although, various in vitro studies have indicated that ginseng has estrogenic activity, no clinical trials have demonstrated real efficacy as an estrogen-replacement therapy.[10]

A placebo-controlled multi-centre randomized trial of 384 post-menopausal women with 200 mg of ginseng per day showed ginseng had no significant effect in reducing the frequency of hot flushes after 4 months.[41-45] However, the study noted ginseng had a favorable effect on psychological well-being. A further trial did not show ginseng to be effective for improving in mood. Although in vivo experiments have suggested that ginseng does not have estrogenic activity, its use is not recommended in the presence of breast cancer. However, it should be noted that no claimed phytoestrogen has been demonstrated to be effective against postmenopausal symptoms. There are insufficient data to confirm its inefficacy. Well designed, in vitro data based large scale studies are needed to develop herbal products targeting female-related diseases.

CONCLUSION

There is no convincing evidence for any herbal medical product in the treatment of menopausal symptoms as well as ginseng. More research is required to clearly define the pharmacological effects of ginseng as dietary phytoestrogen. Considering well reported anticancer effects of ginseng, if proven to be effective as a phytoestrogen, it will greatly benefit menopausal women suffering from postmenopausal symptoms without increasing the risk of breast cancer.

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REFERENCES

1. Joo HK, Lee SK, Kim HS, Song YJ, Kang G, Park JB, Lee KH, Cho EJ, Lee JH, Seong IW, Kim SH, Cho CH, Jeon BH. Korean red ginseng extract inhibits tumor necrosis factor-alpha-induced monocyte adhesion in the human endothelial cells. J Ginseng Res. 3: 244-249 (2008)
2. Lee JH, Choi SH, Nah SY. Study on life span extension efficacy by korean red ginseng. J Ginseng Res. 4: 210-216 (2007)
3. Saiki Ikuo. In vivo anti-metastatic action of Ginseng Saponins is based on their intestinal bacterial metabolites after oral administration. J Ginseng Res. 1: 1-13 (2007)
4. Attele AS, Wu JA, Yuan CS. Ginseng Pharmacology: Multiple constituents and multiple actions. Biochem .Pharmacol. 58: 1685-1693 (1999)
5. Yuan CS, Wu JA. Ginsenoside variability in American ginseng samples. Am J. Clin. Nut.. 75: 600-601 (2002).
6. Xing YZ, Shang HC, Gao XM, Zhang BL. A comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiment and clinical trials. Phytother Res. 22: 851-858 (2008)
7. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann. Intern. Med. 137: 805-813 (2002)
8. Hoffman GE, Zup SP. Good versus evil: changing the approach to hormone replacement therapy. Endocrinology. 144: 468-4699 (2003)
9. Turgeon JL, McDonnell DP, Martin KA, Wise PM. Hormone therapy: physiological complexity belies therapeutic simplicity. Science. 304: 1269-1273 (2004)
10. Woo J, Lau E, Ho SC, Cheng F, Chan C, Chan AS, Haines CJ, Chan TY, Li M, Sham A. Comparison of Pueraria lobata with hormone replacement therapy in treating the adverse health consequences of menopause. Menopause. 10: 352-361 (2003)
11. Writing group for the women's health initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA. 288: 321-333 (2002)
12. Lee YJ, Gorski J. Estrogen-induced transcription of the progesterone receptor gene does not parallel estrogen receptor occupancy. Proc Natl Acad Sci U S A. 93: 15180-15184 (1996)
13. Cos P, De Bruyne T, Apers S, Vanden Berghe D, Pieters L, Vlietinck AJ. Phytoestrogens: recent developments. Planta. Med. 69: 589-599 (2003)
14. Cassidy A. Potential risks and benefits of phytoestrogen-rich diets. Int J .Vitam. Nutr .Res .73: 120-126 (2003)
15. Yoon M, Lee H, Jeong S, Kim JJ, Nicol CJ, Nam KW, Kim M, Cho BG, Oh GT. Peroxisome proliferator-activated receptor alpha is involved in the regulation of lipid metabolism by ginseng. Br J. Pharmacol. 138: 1295-1302 (2003)
16. Park KH, Shin HJ, Song YB, Hyun HC, Cho HJ, Ham HS, Yoo YB, Ko YC, Jun WT, Park HJ. Possible role of ginsenoside Rb1 on regulation of rat liver triglycerides. Biol. Pharm. Bull. 25: 457-460 (2002)
17. Nemmani KV, Ramarao P. Ginsenoside Rf potentiates U-50,488H-induced analgesia and inhibits tolerance to its analgesia in mice. Life Sci. 72: 759-768 (2003)
18. Scott GI, Colligan PB, Ren BH, Ren J. Ginsenosides Rb1 and Re decrease cardiac contraction in adult rat ventricular myocytes: role of nitric oxide. Br J Pharmacol. 134: 1159-1165 (2001)
19. Chen X. Cardiovascular protection by ginsenosides and their nitric oxide releasing action. Clin Exp Pharmacol. Physiol. 23: 728-732 (1996)
20. Ernst E, Cassileth BR. How useful are unconventional cancer treatments? Eur J. Cancer. 35: 1608-1613 (1999)
21. Choi S, Jung SY, Ko YS, Koh SR, Rhim H, Nah SY. Functional expression of a novel ginsenoside Rf binding protein from rat brain mRNA in Xenopus laevis oocytes. Mol. Pharmacol. 61: 928-935 (2002)
22. Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause. 9: 145-150(2002)
23. Duda RB, Zhong YZ, Navas V, Li MZC, Toy BR, Alavarez JG. American ginseng and breast cancer therapeutic agents synergistically inhibit MCF-7 breast cancer cell growth. J. Surg. Oncol. 72: 230-239 (1999)
24. Chan RY, Chen WF, Dong A, Guo D, Wong MS. Estrogen-like activity of ginsenoside Rg1 derived from Panax notoginseng. J. Clin. Endocrinol. Metab. 87: 3691-3695 (2002)
25. Lau WS, Chen WF, Chan RY, Guo DA, Wong MS. Mitoen-activated protein kinase (MAPK) pathway mediates the oestrogen-like activities of ginsenoside Rg1 in human breast cancer (MCF-7) cells. Br J. Pharmacol. 156: 1136-1146 (2009)
26. Lee Y, Jin Y, Lim W, Ji S, Choi S, Jang S, Lee S. A ginsenoside-Rh1, a component of ginseng saponin, activates estrogen receptor in human breast carcinoma MCF-7 cells. J. Steroid. Biochem. Mol. Biol. 84: 463-468 (2003)
27. Farhat MY, Lavigne MC, Ramwell PW. The vascular protective effects of estrogen. FASEB. J. 10: 615-624 (1996)
28. Kim HS, Zhang YH, Fang LH, Lee MK. Effects of ginsenosides on bovine adrenal tyrosine hydroxylase. J. Ethnopharmacol. 66: 107-111 (1999)

29. Ivanova T, Beyer C. Estrogen regulates tyrosine hydroxylase expression in the neonate mouse midbrain. J. Neurobiol. 54,638-647 (2003)
30. Mishra SI, Dickerson V, Najm W. Phytoestrogens and breast cancer prevention: what is the evidence? Am J. Obstet. Gynecol. 188: 66-70 (2003)
31. Glazier MG, Bowman MA. A review of the evidence for the use of phytoestrogens as a replacement for traditional estrogen replacement therapy. Arch. Intern. Med. 161: 1161-1172 (2001)
32. Warnecke G. Influencing menopausal symptoms with a phytotherapeutic agent: successful therapy with cimicifuga monoextract. Med. Welt. 36: 871-874 (1985)
33. Stoll W. Phytopharmacon influences atrophic vaginal epithetlium: double-blind study: cimicifuga versus estrogenic substances. Therapeutikon. 1: 23-31 (1987)
34. E Lehmann-Willenbrock E, Riedel HH. Clinical and endocrinologic studies of the treatment of ovarian insufficiency manifestations following hysterectomy with intact adnexa. Zentralbl. Gynakol. 110: 611–618 (1988)
35. Jacobson JS, Troxel AS, Evans J. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J. Clin. Oncol. 19: 2739-2745 (2001)
36. Liske E, Wüstenberg P. Therapy of climacteric complaints with Cimicfuga racemosa: a herbal medicine with clinically proven evidence. Poster Presentation. North American Menopause Society (1998)
37. Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): a six-month clinical study demonstrates no systemic estrogenic effect. J. Womens Health Gend Based .Med. 11: 163–174 (2002)
38. Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 versus conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas. 44: S67-S77 (2003)
39. Viereck V, Emons G, Wuttke W. Black cohosh: just another phytoestrogen? Trends. Endocrinol. Metab. 16: 214-21 (2005)
40. Davis VL, Jayo MJ, Ho A, Kotlarczyk MP, Hardy M.L, Foster WG, Hughes CL. Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2. Cancer. Res. 68: 8377-83 (2008)
41. Wong VC, Lim CE, Luo X, Wong WS. Current alternative and complementary therapies used in menopause. : Gynecol. Endocrinol. 25: 166-74 (2009)
42. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group.: Int J. Clin. Pharmacol. Res. 19: 89-99 (1999)
43. Tode T, Kikuchi Y, Hirata J, Kita T, Nakata H, Nagata I. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J. Gynaecol. Obstet. 67: 169-74 (1999)
44. Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. Arch. Intern. Med. 166: 1453-65 (2006)
45. Hartley DE, Elsabagh S, File SE. Gincosan (a combination of Ginkgo biloba and Panax ginseng): the effects on mood and cognition of 6 and 12 weeks' treatment in post-menopausal women. Nutr. Neurosci. 7: 325-33 (2004)