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Short Review

The beneficial potential of ginseng for menopause

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ABSTRACT

Korean Red Ginseng (KRG) has long been used not only as a food supplement but also as a treatment for various diseases. Ginseng originated in South Korea, which later spread to China and Japan, has a wide range of pharmacological activities including immune, endocrine, cardiovascular, and central nervous system effects. KRG is produced by repetitions of steaming and drying of ginseng to extend preservation. During this steaming process, the components of ginseng undergo physio-chemical changes forming a variety of potential active constituents including ginsenoside-Rg3, a unique compound in KRG. Pandemic Coronavirus disease 2019 (COVID-19), has affected both men and women differentially. In particular, women were more vulnerable to COVID-related distress which in turn could aggravate menopause-related disturbances. Complementary and alternative medicinal plants could have aided middle-aged women for several menopause-related symptoms during and post COVID-19 pandemic. This review aimed to explore the beneficial effects of KRG on menopausal symptoms and gynecological cancer.

1. Introduction

Ginseng has a wide range of pharmacological activities including immune, endocrine, cardiovascular, and central nervous system effects [1–6]. Numerous prescriptions for drugs containing ginseng can be found in Donguibogam in Korea, and among them, Insamdanggwisan and Insamdanggwisan have records of prescriptions to manage the health of postpartum women. Some side effects such as breast pain or vaginal bleeding, anxiety have been reported with raw ginseng. However, Korean Red Ginseng (KRG) which is processed has been broadly used with less toxicity. In addition, past literature describes that ginseng benefits most for Soeumin (少陰人, SE type) among the four types from 'the Sasang (四象, four Typology or Constitution)' which explains the diverse range of individual variations in behavioral indicators, physical attributes and bio-psychological traits [7,8].

Panax ginseng *Meyer* (*P. ginseng*;PG) and *P. quinquefolious* (American ginseng; AG) are the two most commonly consumed ginseng worldwide. Collectively PG and AG are among the most extensively studied alternative medicines for pharmacological activities, including antioxidative, antidiabetic, anti-inflammatory, anti-cancer, neuroprotective, immunomodulatory, and prophylactic effects. The most important bioactive components contained in PG and AG are ginseng saponins called ginsenosides. Ginsenosides have shown immense pharmacological and physiological benefits, which include anti-cancer and anti-inflammatory properties [9–13]. Among the ginsenosides, Rb1 and Rg1 are the most plentiful ginsenosides. The contents of ginsenoside Rb1, Re, and Rd in AG are higher than those found in PG. Further, PG exhibits greater concentrations of Rg1, Rb2, and Rc in comparison to AG. The ratio of Rg1 to Rb1 was greater in PG than in AG [14].

KRG is produced through iterative processes of steaming and drying ginseng, initially intended for prolonged preservation [15]. The concentration of malonyl-ginsenoside (Rg1, Rb1, Rb3, Rc, Rd, Rb2) and amino acids were decreased during the steaming process. In contrast, Rh1, 20(S)-Rg2, 20(S, R)-Rg3, and Maillard reaction products were

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Table 1
Overview of clinical studies of ginseng on postmenopausal women.

Population size (age)	Ingested length	Dosage	Main outcomes	Ref
62 (52.9 ± 53.5; 53.5 ± 4.1)	4 weeks	500 mg/ b.i.d	Improved FSFI, QoL and menopausal symptoms	[38]
82 (54.33 ± 2.52; 53.86 ± 3.21)	12 weeks	3 g/day	Increased serum SOD	[41]
72 (52.98 ± 3.04; 55.01 ± 3.67)	12 weeks	3 g/day	Improved KI, TC, carotid intima-media thickness	[42]
28 (51.2 ± 4.1)	8 weeks	3 g/day	Improved FSFI in the sexual arousal domain	[33]
63 (58.7 ± 4.2; 59.7 ± 4.2)	8 weeks		Improved antioxidant status, mitochondrial DNA number. Decreased fatigue	[32]

either generated or increased in their concentrations [16]. Since its inception in South Korea, KRG has been utilized not only as a dietary supplement but also as a remedy for a variety of ailments. This practice later spread to China and Japan. Unique to KRG is the ginsenoside Rg3 component [17]. In addition to the saponin components mentioned above, ginseng also contains various active ingredients such as polysaccharides, proteins, peptides, amino acids, nucleic acids, alkaloids, and polyacetylenes, all of which serves as pharmacologically significant active ingredients [18]. As an example, there are numerous reports on the anticancer activity [19], anti-inflammatory activity [20], hyperlipidemia inhibition [21], and immune activity [22–24] in acidic polysaccharide of KRG. The Korean Food and Drug Administration (KFDA), approved that KRG is effective on seven major symptoms including fatigue relief, circulation improvement, memory enhancement as well as antioxidant activity [12], immune boosting, and the easing the symptoms of menopause, based on several experimental studies as well as clinical trials [25].

Pandemic Coronavirus disease 2019 (COVID-19), which now ended have affected tremendously in several aspects of our lives. Various studies have shown that biological differences between men and women differentially affected the COVID-19 infection. Women have been hit especially hard and reported to experience greater COVID-related distress [26,27]. In addition, menopause-related changes in hormone levels decrease immune function and reduce angiotensin-converting enzyme 2 expression correlated with COVID-19-related mortality by regulating viral entry [28,29]. These findings indicate that COVID-19 could aggravate menopause-related disturbances and complementary and alternative medicinal plants could have aided middle-aged women for several menopause-related symptoms during and after the pandemic [28]. Based on these reports, this review aimed to discuss and summarize the beneficial effects of KRG on menopausal symptoms and gynecological cancer based on the available clinical studies and evaluations.

2. Effects of KRG for menopause syndrome

The beneficial effects of KRG on menopausal symptoms were evaluated as early as 1999 by a Japanese group based on a report of its efficacy in treating gynecological diseases [30,31]. This first comparative clinical study of KRG on menopause involved 12 postmenopausal women, 8 without menopause syndrome who received 6 g/day of KRG for 30 days [30]. KRG relieved psychological symptoms such as fatigue and anxiety related to menopause [32,33]. The androgen decline observed with hormonal therapy was not observed with KRG, indicating that KRG did not affect dehydroepiandrosterone - sulfate (DHEA) levels, which affect decline of androgen with age [30]. Recent systemic review of 15 randomized clinical trials of ginseng relieving menopausal symptoms reported no effect on hormone biomarker levels, sexual function, or endometrial thickness despite the low level of evidence [34]. These clinical trials demonstrated a promising effect of KRG on post-menopausal syndrome. Although the mechanism for these effects is not clearly understood the positive effects might be due to the various valuable functions of ginseng such as adaptogenic, immune-modulatory [35–37], strong cognitive [38], anti-inflammatory [39,40] and anti-oxidative effects. Further, the authors also assessed the current clinical evidence of ginseng for women's health care [34]. The data indicated that ginseng is a functional supplement for middle-aged women with notable effects on female sexual function. Out of the 15 trials reported in the systemic review, we pulled out 5 double-blind, placebo-controlled (RDP) clinical trials as listed in Table 1. These studies found beneficial effects in menopausal women who took KRG (1–3 g/day) for 4–12 weeks.

Lee et al., conducted two consecutive clinical trials of 72 postmenopausal women and of 82 postmenopausal women using the KRG provided by Korea Ginseng Corporation [42,41]. The latter study further showed that KRG supplementation significantly increased serum superoxide dismutase activity [41]. The results of this study provide evidence that KRG has positive effects on mid-aged menopausal women, including the alleviation of menopausal symptoms, reduction of cardiovascular risk factors, and anti-oxidative effects. However, serum estradiol levels were not influenced by KRG. Interestingly, the majority of postmenopausal symptom clinical trials utilizing KRG were conducted in Japan and Korea. However, recent clinical trial conducted in Iran also demonstrated the efficacy of PG in alleviating menopausal symptoms among a sample of 59 married postmenopausal women aged 45–60 years [38]. In their study, the ginseng group showed significant improvements in all domains of the female sexual function index compared to the control group ($p < 0.001$). Significant improvements in all dimensions of the quality of life (QoL; psychosocial, vasomotor, sexual, and physical) were observed in the treated group ($p < 0.001$) [38].

In another recent clinical studies, the authors reported that KRG improves sterol metabolism by decreasing cholesterol and 7-hydroxycholesterol levels in menopausal women specifically with hypercholesterolemia [42,43]. The study included 63 participating women aged 46–69, and administered with 2 g of KRG per day showed that KRG significantly increased mitochondrial DNA copy number, total anti-oxidant status, and improvement of fatigue status demonstrating efficacy of KRG on biological aging and antioxidant activity [32]. The mode of action for the clinical effects of KRG on menopause is currently vague. KRG treatment had no effect on uterine weight, which is one of the most direct measurement to assess *in vivo* estrogenic activity [44]. Female hormonal levels were not affected by KRG treatment from the animal studies. However, KRG reduced the circulating levels of free fatty acids, serum cholesterol and decreased both high-density/low-density lipoprotein (HDL/LDL) levels, and triglycerides, and normalized the hyperinsulinemia and hyperglycemia caused by ovariectomy (OVX) [2,45]. These data support the clinical study, indicating that KRG exhibited cardiovascular protective effects associated with menopause.

Estrogen receptors are widely distributed in the brain region responsible for memory performance and cognitive function. Estrogen functions in neuroplasticity, neuroprotection, and cognition [46], and its levels are positively correlated with learning speed [47]. This accounts for the cognitive disturbances experienced by perimenopausal women whose estrogen levels decrease [48,49], emphasizing the need for strategies to prevent cognitive disturbances after menopause. Research has indicated that ginseng use can help alleviate the cognitive decline. Healthy adults who consumed 1 g/day of KRG for 8 weeks showed an increase in gray matter volume of the left parahippocampal gyrus and improved combined cognitive function, including execution, attention, and memory, compared to the control group (mean age = 40 years, female 76 %) [50]. It is currently unclear if long-term consumption of ginseng can compensate for cognitive deficits caused by low estrogen levels in late life following menopause. While there are no studies exclusively targeting women, research involving the elderly, suggests that ginseng may have complementary functions in enhancing cognition.

Table 2
Studies of ginseng conducted in OVX animal models.

Ingredient	Animals model	Ingested length	Dosage	Main outcomes	Mechanism	Ref
KRG	8-week-old female C57BL/6J n = 24	15 weeks	5 % w/w	Regulation of obesity and metabolic disorders	Increase blood vessel density, reduced MMP activity in adipose tissue. Reduced mRNA levels of CD68, TNFα, MCP-1, reduced both serum insulin and glucose levels	[45]
KRG	9-weeks-old female Sprague-Dawley rats n = 48	5 weeks	0.2 g/day	Cholesterol-reducing effects of KRG in menopausal women	Decreased serum cholesterol, HDL and LDL, atherogenic indices, HDL/TC ratio	[44]
Ginseng	Female Wistar rats n = 50	6 weeks	100,300 mg/kg/day	Protection in TAA-induced liver injury in OVX rats	Reduced levels of MPO, TNF-α and NF-kβ p65,	[54]
Ginsenoside Rb_1	9-week-old Female ICR albino mice n = 24	14 days	100, 200, 400 mg/day	Antidepressant-like activity	Reduced immobility time	[55]
Ginsenoside Rb_1	Female Swiss-Hauschka mice N = 56	120 min	20 mg/kg	Neuroprotective effects	Reduced 5-HIAA/5-HT ratios, increased accumulation of 5-HTP^{+}	[56]
	Female Swiss-Hauschka mice N = 56	7 days	10 mg/kg/day, ip (twice a day)			
ginsenoside Rg1	10-week-old Female Wistar rats N = 96	6 weeks	5, 10, 20 mg/kg/day, ip	Enhanced learning and memory	Improved learning and memory, and reduce $A\beta_{1\text{-}42}$ generation	[57]
Ginsenoside Rc	6–8weeks old female C57Bl/6 mice N = 60	3 months	25, 50 mg/kg/day	Promoting Bone Formation	Increase BMD, RUNX-2, COL-1, OCN, ALP,	[58]
Ginsenoside Rg3	8-week-old female Sprague–Dawley rats N = 36	5 weeks	20 mg/kg, every 2 days	Effective alleviation OVX-induced bone loss and abnormal changes of trabeculae *in vivo*	Increase ALP, OCN, OPN, COL1A1, RUNX-2, AMPK/mTOR	[59]

In a population-based prospective cohort study of Korean elders to investigate the impact of cumulative ginseng intake on cognitive function (N = 6422; mean age = 70.2 years, female = 56.8 %), the high-use group (ginseng intake for ≥5 years at baseline) showed higher cognitive scores than the no-use group. This implies that ginseng consumption for more than five years may positively affect cognitive function in late life [51]. In another study on long-term ginseng intake and cognitive function, consumption of ginseng for five or more years starting in middle age (<65 years) showed a positive effect on delayed episodic memory of APOE4-negative older adults (N = 160, mean age = 72.53 years, female = 69.38 %) [52]. Ginseng appears to reduce physiological stress responses and positively affect cognitive function. In a double-blind, placebo-controlled trial involving individuals with high stress levels (stress response inventory ≥81 points) and depression (Beck depression inventory ≥10 points) (N = 62, 57 % female, mean age = 40.4), the intake of KRG at 2 g per day for 6 weeks significantly reduced epinephrine levels and improved cognition compared to placebo intake [53]. In conclusion, research suggests that ginseng may play a beneficial role in preserving cognitive function, which can be compromised by reduced estrogen levels in women after menopause. These studies provide and supports the clinical results that ginseng is beneficial on menopause.

3. Effects of ginseng from OVX animal studies

Evidence suggests that OVX rodents causes increase in body weight, increased lipid accumulation and deteriorated blood lipid profiles. However, KRG administration *ad libitum* to OVX 8-week-old female C57BL/6 mice (n = 8/group) at a dose of 5 % (w/w) in high-fat diet (5 g of KRG mixed with 1 kg high fat chow [45], demonstrated a 19 % lower body weight with concomitant reduced adipose tissue weight than that of untreated control group. Ginseng reduced the circulating levels of free fatty acids and triglycerides, and normalized hyperinsulinemia and hyperglycemia caused by OVX. Triglycerides values for sham control group were 98 ± 9 mg/dl. With the surgery and treatment, triglycerides concentration was 135 ± 12 mg/dl for OVX group and reduced to 83 ± 8 mg/dl for ginseng treated group ($p < 0.05$ versus ovariectomized group). Cholesterol level was not examined in this study. Overall, these data support the clinical study, indicating cardiovascular protective effects associated with menopause.

In another study, the association of the improvement of menopausal symptoms with female hormones were evaluated in OVX rats [44]. KRG (0.2 g with olive oil) was administered with oral gavage for 5 weeks. KRG treatment had no effect on uterine weight, which is one of the most direct measurement to assess *in vivo* estrogenic activity. This is in line with the clinical studies that the hormonal levels were not affected by ginseng treatment. KRG treatment caused considerable reductions in serum cholesterol and decreases both HDL and LDL, although not to the statistically significant level. Other studies of ginseng or ginsenoside conducted in OVX animal models are summarized in Table 2 [54–59].

Antihypertensive effects of ginseng may occur through the promotion of vascular endothelial cell-derived nitric oxide (NO) secretion. Constitutively produced NO further triggers cyclic guanosine 3′,5′-monophosphate (cGMP) production, a cellular mediator of vascular smooth muscle relaxation, causing vasodilation and lowering of blood pressure, thereby normalizing vascular flow in hypertensive individuals [64–67]. Total ginseng saponin can enhance the contractile responses evoked by stimulation of adrenergic α1-receptor and the membrane depolarization in the isolated rat aortic strips, which seems to be associated to calcium influx [68]. Mechanisms in NO production of ginsenoside such as Rb1 and Rg3 are also being studied. These studies support the notion that the beneficial effect of ginseng on menopause is exerted through adaptogenic and tonic effect.

4. Effects of KRG on gynecological cancer

Estrogen-dependent cancer is one major concerns with the complementary phytochemicals for menopausal symptoms. A few *in vitro* studies showed that nuclear hormone receptors are the cellular targets of ginsenosides which are the major pharmacological constituents of ginseng. However, it should be pointed that direct binding or measurement of ginsenoside-occupied receptor was not shown. Additionally, evidence from our earlier study demonstrated no *in vivo* estrogenic response, alterations in the synthesis of estrogen and testosterone in animal experiments, and no steroidogenic activity linked to KRG,

Table 3
Overview of clinical studies of ginseng on gynecological cancer patients.

Population size (age)	Ingested length	Dosage	Main outcomes	Ref
30 Epithelial ovarian cancer (52.9 ± 10.1; 55.9 ± 12.1)	12 weeks	3 g/day	Improved health-related quality of life, no effect on ovarian cancer	[60]
55 Premenopausal women after gynecologic cancer (49.42 ± 4.91; 48.58 ± 5.04)	12 weeks	3 g/day	No absolute relief of menopausal symptoms but effective in reducing sexual complaints	[61]
30 Non-metastatic breast cancer (44.0 ± 2.1; 43.3 ± 1.6)	22 weeks	1 g/day	Protect against doxorubicin-induced cardiac toxicity enhance health-related quality of life	[62]
48 Non-Metastatic Breast Cancer (44 (31–54) 46 (33–65))	8–11 weeks	1 g/day	Enhancing Health-Related Quality of Life	[63]

suggesting that KRG does not disturb the hypothalamic-pituitary-gonadal axis [69]. Several *in vitro* and animal studies have shown the protective effects of ginseng and its components against ovarian cancer and breast cancer at the cellular level [60,70–73]. A recent open-label, single center, randomized phase-II study from Japan showed that ginseng with *Japanese angelica* root combined with the other 10 herbs (Ninjin'yoeito; NYT) showed efficient improvement on preoperative fatigue and anxiety in addition to the recovery from anemia on patients with gynecologic disease [74]. Cancer Fatigue Scale and Visual Analogue Scale for Anxiety scores were significantly decreased in treatment group [74]. Interestingly, significant improvements were not observed in the iron supplementation group, while fatigue significantly improved and anxiety disappeared in the NYT group, which suggests the usefulness of combining NYT with iron supplements to treat anemia before patients are scheduled for surgical treatment of gynecological diseases [74]. Table 3 summarizes reported randomized double-blind clinical trials with ginseng on gynecological cancer.

Ginseng protected doxorubicin-induced cardiac toxicity in a study from 30 non-metastatic breast cancer patients. It implied that prophylactic PG supplementation may protect against doxorubicin-induced early cancer therapeutics-related cardiac dysfunction and early decline in left ventricular ejection fraction in breast cancer patients [62]. Epithelial ovarian cancer is one of the most lethal malignant cancer for females. Most of the patients are failed to be diagnosed at early stages due to lack of screening method. A recent study with 30 patients showed that red ginseng improved health-related QoL and reduced genotoxicity in epithelial ovarian cancer patients who received chemotherapy after surgery [60]. However, no effect was shown on overall survival from this short 3-month study. Most recent report of the double-blind, randomized, placebo-controlled trial on the effects of reducing menopausal symptoms after treatment with KRG were assessed in premenopausal women of climacteric disturbance after oophorectomy due to gynecological surgery. No differences or statistically meaningful results were observed from the blood chemistry analysis. Although no statistical difference was observed over placebo-control in Menopause Rating Scale (MRS) score, KRG treatment showed better outcome for exhaustion, cardiac complaints, and sexual function. Comparison of 11 MRS symptoms between the two groups demonstrated that the KRG group seemed to be superior to the placebo group on the sexual complaints [61]. Consistent with above three double-blind, randomized controlled trials, KRG alleviated menopausal symptoms on menopausal women but did not affect the levels of hormones such as prolactin and estrogen, and no side effect or risk of developing breast cancer were found [33,42,75,76]. In a meta-analysis, well-studied phytoestrogen isoflavone showed little risk of breast cancer. Among the 16 studies, 11,169 breast cancer cases and 648,913 participants were identified and included in the data analysis. The meta-analysis indicated that women with a high dietary intake of soy foods might experience a statistically significant reduction in breast cancer risk [77]. However, an extensive examination of the effects of ginseng use on breast and gynecologic cancers will become accessible when more clinical research is conducted.

5. Conclusion

The clinical trials carried out in Japan, Korea and as well as in Iran demonstrated a promising effect of KRG on post-menopausal syndrome. Not only for middle-aged women, ginseng has been shown to be beneficial for prostate health in men, including reducing inflammation in the prostate gland and inhibiting the growth of prostate cancer cells. Several studies suggested that ginseng inhibits development of testosterone propionate-induced benign prostatic hyperplasia in male Sprague Dawley rats without serious side effects [78]. Ginseng including Korean black ginseng has been proven to be effective for improving symptoms of andropause, also known as male menopause [79]. It awaits a large scale randomized clinical trials to prove that KRG plays beneficial role in climacteric disturbance for both male and female.

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