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ORIGINAL ARTICLE

Effect of Korean Red Ginseng as an adjuvant treatment for women with residual symptoms of major depression

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Abstract

Introduction: Around 20% of patients with major depression experience residual symptoms. Ginseng has shown potential antidepressant effects in some animal studies and in patients with stress-related somatic symptoms. Therefore, we investigated the effectiveness and tolerability of Korean Red Ginseng adjuvant treatment in patients with residual symptoms of major depression.

Methods: In this eight-week prospective study, 35 female outpatients aging from 18 to 65 years (45.1 ± 9.5), who were remitted from major depression with residual symptoms, were given Korean Red Ginseng at doses of 3 g/day. The Depression Residual Symptom Scale (DRSS) and Montgomery–Åsberg Depression Rating Scale (MADRS) were administrated to evaluate depressive symptoms. The general severity of symptoms was assessed by a clinician using the Clinical Global Impressions Scale for Severity (CGI-S). The Depression and Somatic Symptom Scale (DSSS) was also used to evaluate somatic symptoms in the subjects. This trial is registered at Clinical.gov, number NCT01496248.

Results: Subjects reported significant decrease in depressive symptoms on the DRSS ($P < 0.05$) and MADRS ($P < 0.01$) decreased significantly over the eight-week period. The scores on the CGI-S, an objective measurement of symptoms, showed significant improvement in the severity of illness ($P < 0.001$). Somatic symptoms on the DSSS also attenuated significantly during the study period ($P < 0.05$).

Discussion: These results suggest that Korean Red Ginseng is efficacious as an adjuvant treatment for patients experiencing residual symptoms of major depression. Future placebo-controlled research is required to confirm our results.

Introduction

Depression is considered as a serious illness, but can be cured as various pharmacological agents become more readily available. In real practical settings, however, only 55% of patients show a response to initial antidepressant treatment, and merely 30% of patients reach a remission state in response to treatment by one antidepressant. (Trivedi *et al.*, 2006) Additionally, it is common for patients to experience various residual symptoms of depression such as fatigue, loss of interest, insomnia, neuromuscular pain, and cognitive dysfunction even after being considered as in a remission state by their clinician. One previous study reported that 26% of patients under remission state experienced at least one residual depressive symptom, and 57% suffered from more than two residual symptoms (Nierenberg *et al.*, 1999). These patients mainly complained of low energy, guilt, sleep disturbance, anxiety, difficulty in the workplace, lack of interest, fatigue, low libidinal energy, etc. Somatic complaints such as low back pain, myalgia, stomachache, and

joint pain are also commonly reported by patients under remission from depression (Opdyke *et al*., 1996; Nierenberg *et al*., 1999; Gasto *et al*., 2003; Carney *et al*., 2007; Merens *et al*., 2008).

Residual depressive symptoms themselves have a negative influence on quality of life and increased the risk of depression recurrence. (Thase *et al*., 1996; Ohayon and Roth, 2003; Dombrovski *et al*., 2008) Moreover, residual depressive symptoms have harmful impacts on the progression of comorbid physical illnesses and consequently increase the utility of medical services and socioeconomic burden. (Horsten *et al*., 2000; Jonas and Mussolino, 2000) As an attempt to overcome the limitations of antidepressants as a usual treatment modality for depression, various therapeutic approaches to residual symptoms have been tried. A number of herbal medicines, including St. John's wort (*Hypercum peforatum*), Nelumbinis semen (*Nelumbo nucifera Gaertn*), and Ginkgo (*Ginkgo biloba*), have been tested as alternative therapies for depression. One other type of herbal medicine, ginseng, usually refers to the extract derived from one of 11 species of plants, belonging to the genus *Panax* of the family Araliaceae. Among these species, Korean Red Ginseng (*Panax ginseng* C.A. Meyer) has shown potential antidepressant effects in the both animal models of depression and some clinical trials. Specifically, several reports have suggested that ginseng may be effective in ameliorating depressive symptoms and can promote stress relief in mice (Saito *et al*., 1974; Choi *et al*., 2009; Kim *et al*., 2011). Additionally, one human study demonstrated that ginseng was effective for managing mood symptoms in postmenopausal women (Tode *et al*., 1999).

Therefore, in the current study, we aimed to examine the efficacy and safety of ginseng administration in patients who were in remission for major depression but who were experiencing residual symptoms after antidepressant treatment. To the best of our knowledge, no study has investigated the effect of ginseng on patients experiencing residual symptoms. Here, we observed added benefits of Korean Red Ginseng in patients who took a daily dose of 3 g of the extract for eight weeks in addition to their regularly prescribed antidepressants.

Methods

Subjects

Subjects were recruited from the female outpatient unit of the Department of Psychiatry at the Korea University Ansan Hospital from June 2011 to August 2012. All subjects were diagnosed with major depressive disorder on the basis of the Diagnostic and Statistical Manual of Mental disorders, fourth edition (DSM-IV) diagnostic criteria (American Psychiatric Association, 1994) Subjects were included in the study if they met the followed criteria: (i) women diagnosed with major depressive disorder and an age ranging from 18 to 65 years; (ii) patients remitted from major depression after antidepressant treatment for at least one month before recruitment. Remission was determined when a patient's symptoms ranked less than 12 on the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) more than two times over assessments given at intervals of one or more weeks; and (iii) patients who reported residual symptoms after their depressive symptoms remitted. Exclusion criteria were as follows: (i) patients who were hypersensitive or allergic to ginseng; (ii) patients who had a history of substance abuse or dependence; (iii) pregnant or breast-feeding patients; (iv) patients whose routine screen test results came back abnormal for liver or renal function; and/or (v) patients who had a history of attempted suicide within one year of study enrollment.

All participants were extensively informed about the study and gave written informed consent before the trial onset. The study protocol with obtaining signed signatures form participating study subjects was reviewed and accepted by the institutional review board of the Korea University Ansan hospital. This trial is registered at Clinical.gov, number NCT01496248.

Medication

Korean Red Ginseng extract was administrated to subjects in capsule form. Aside from ginseng extract, capsules contained ginsenosides, such as Rg1 (3.4 mg/g), Rb1 (7.25 mg/g), Rg3s (0.23 mg/g), Re (2.42 mg/g), Rc (2.9 mg/g), Rb2 (2.75 mg/g), Rd (0.64 mg/g), Rf (1 mg/g), Rh1 (0.17 mg/g), Rg2s (0.32 mg/g), and other minor ginsenosides.

Korean Red Ginseng was administered according to an add-on design where subjects supplemented Korean Red Ginseng to their usual antidepressant treatment. All subjects initially received 2 g of red ginseng on day one, and within four weeks, red ginseng was titrated to 3 g/day on an individual basis, depending on clinical recommendation and tolerability. After titration, subjects maintained red ginseng at doses of 3 g/day for the next four weeks. Importantly, all psychiatric medication taken by the subjects was

fixed during the length of the study period, and the only other treatment allowed during the study period was with benzodiazepines, at a maximum equivalent dose of 4 mg of lorazepam per day.

Tools and schedule of assessments

Psychometric scales were assessed at baseline, week four, and week eight. The Depression Residual Symptom Scale (DRSS), (Bertschy *et al*., 2010) MADRS and the Depression and Somatic Symptom Scale (DSSS) (Hung *et al*., 2006) were assessed by patients. The Clinical Global Impressions Scale for Severity (CGI-S) (Guy, 1976) were measured by a clinician. Additionally, electrocardiography and urine, microbiological, and blood assays were checked at baseline and at week eight.

DRSS

The DRSS consists of 25 items and includes specific residual depressive symptoms such as sadness, anhedonia, lack of energy, psychomotor retardation, and anxiety as well as items reflecting subjective feelings of vulnerability, loss of internal reference points, and increased emotionalism. Patients were instructed to compare the past seven days with the period before the very first symptoms of their most recent depressive episode. Each item was scored as 0 to 3, and total scores ranged from 0 to 75.

MADRS

The MADRS is a 10-item rating scale widely used in patients with depression. Each item is rated from 0 to 6, allowing for a maximum score of 60. The MADRS has been designed to measure severity of depression in clinical samples and is sensitive to changes in symptoms that may occur during antidepressant treatment.

CGI-S

The CGI was originally developed for use in psychopharmacology trials; however, its application has expanded, and it is now a standard primary measure in studies investigating the efficacy of pharmacological treatments for various psychiatric illnesses such as depression, anxiety disorder, and bipolar disorder. The CGI-S rates the severity of a patient's illness on a 7-point scale ranging from 1 (normal) to 7 (extremely ill).

DSSS

The final DSSS was composed of 22 items with two major subscales: the depression and the somatic subscale. The depression subscale had 12 items, including three vegetative symptoms and fatigue, and the somatic subscale had 10 items, including five pain items, which comprised the pain subscale. In calculating the DSSS score, "absent" was scored as 0 points, "mild" as 1 point, "moderate" as 2 points, and "severe" as 3 points.

Statistical analysis

Analyses were performed using the modified intent-to-treat (ITT) approach. The ITT population consisted of all patients who received at least one dose of the study medication and had at least one primary efficacy evaluation of the treatment. The confirmatory statistical analysis for the efficacy of Korean Red Ginseng was performed in the ITT population via an analysis with repeated-measures analysis of variance, with missing data estimated by the last observation carried forward (LOCF) method. The LOCF data set included data recorded at a given visit in the study period; if no observation was recorded at that visit, data were carried over from the previous visit. Baseline demographic and clinical features of the study population were calculated using the appropriate descriptive functions, including means for continuous variables and frequencies for categorical variables. All analyses were conducted using Statistical Package for Social Science software version 12.0 for Windows (SPSS, Inc., Chicago, Illinois, USA). The differences between groups were considered different if *P*-values were smaller than 0.05.

Results

Sociodemographic findings and clinical characteristics of subjects

A total of 35 female patients were enrolled in this study. Patients' characteristics and demographics are shown in Table 1. The mean age of the subjects was 45.1 ± 9.5 years old. The severity of depressive symptoms was 6.7 ± 2.7 on the MADRS and the residual symptoms assessed by the DRSS was 22.8 ± 12.7 at the baseline. The doses of the prescribed antidepressants are shown in Table 2.

The efficacy of ginseng augmentation in patients with residual depression symptoms

Residual symptoms measured by the DRSS improved from baseline (21.8 ± 12.7) to week four (17.3 ±

Table 1. Clinical characteristics of subjects at baseline (N = 35)

Age (years)	45.1 ± 9.5
Education (years)	11.5 ± 2.5
Marital status (with partner)	27 (77.1)
Duration of current antidepressant medication (months)	13.6 ± 20.7
Illness duration (years)	8.1 ± 5.9
MARDS	6.7 ± 2.7
DRSS	22.8 ± 12.7

Data are shown as mean ± standard deviation (SD) and number (%). DRSS, Depression Residual Symptom Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.

Table 2. Currently prescribed antidepressants among subjects (N = 35)

Antidepressants	Number (%)	Dosage range (mg)
Escitalopram	12 (34.3)	5–20
Venlafaxine	7 (20.0)	37.5–225
Paroxetine	5 (14.3)	10–37.5
Duloxetine	4 (11.4)	60
Citalopram	3 (8.6)	20
Bupropion	1 (2.9)	300
Fluvoxamine	1 (2.9)	150
Imipramine	1 (2.9)	25
Trazodone	1 (2.9)	12.5

12.1), and this improvement was still apparent at week eight (17.5 ± 11.1; $P < 0.01$). The mean MADRS score of the subjects at baseline was 6.7 ± 2.7, which gradually decrease to 5.1 ± 3.1 at week four, and further down to 4.4 ± 3.1 at week eight ($P < 0.001$) (Figure 1). The general severity of symptoms among subjects were significantly attenuated on the CGI-S from baseline (16.7 ± 11.1) to week four (13.1 ± 9.6) and week eight (14.1 ± 9.6; $P < 0.001$). Somatic symptoms reported by subjects also significantly improved over the study period ($P < 0.01$): DSSS scores were 16.7 ± 11.1, 13.1 ± 9.6, and 14.1 ± 9.6 at baseline, week four, and week eight, respectively.

The safety of ginseng administration in women with residual symptoms of depression

Gastrointestinal complications ($n = 5$, 14.3%) and headaches ($n = 4$, 11.3%) were the most commonly reported adverse events in subjects with residual symptoms (Table 3). Four subjects dropped out of the study because of adverse side effects, which disappeared within four weeks of ginseng discontinuation. Lastly, no fatalities or irreversible adverse effects were observed during the study period.

Discussion

This study examined the efficacy and safety of the coadministration of ginseng and antidepressants in women with residual symptoms of depression. Our findings indicate that Korean Red Ginseng improved residual symptoms on both subjective and objective measurements of depressive symptoms. Additionally, we found that most subjects were able to tolerate 3 g

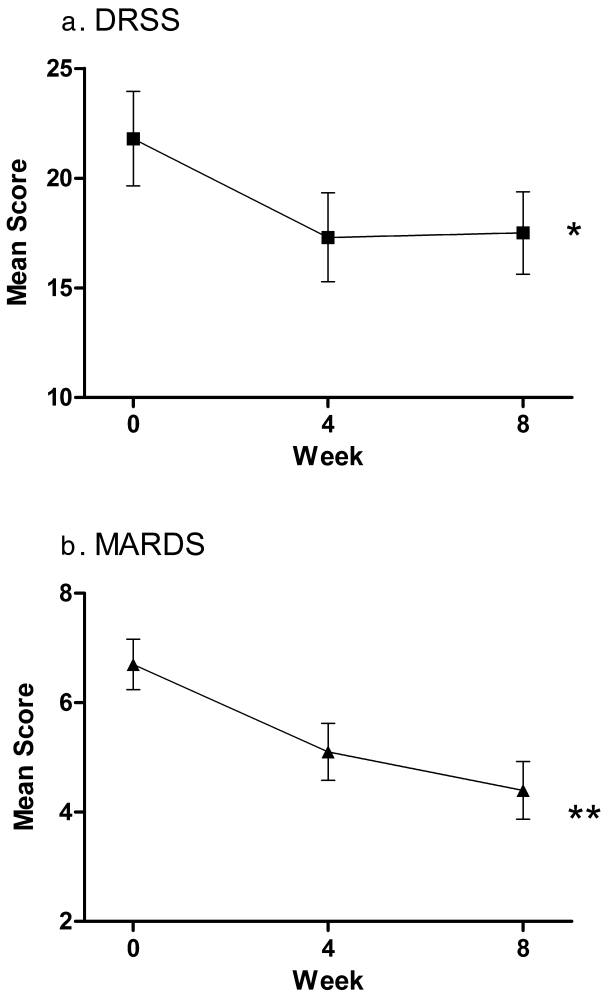

Figure 1. The efficacy of Korean Red Ginseng treatment on patients with residual depression symptoms. Data are mean ± SE, repeated measures ANOVA. *$P < 0.05$; **$P < 0.001$. DRSS, Depression Residual Symptom Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

Table 3. Incidence of adverse events in subjects treated with Korean Red Ginseng for 8 weeks

Adverse events	Number (%)
Gastrointestinal complications	5 (14.3%)
Headache	4 (11.4%)
Insomnia	3 (8.6%)
Hypersomnia	2 (5.7%)
Hair loss	2 (5.7%)
Itching sensation	1 (2.9%)

of Korean Red Ginseng, with only four patients dropping out due to adverse effects.

Around 30–50% of patients with major depressive disorder experience ongoing residual symptoms after remission. Residual symptoms of depression include affective, cognitive, neurovegetative, and various somatic symptoms as well as low energy, guilt, sleep disturbances, anxiety, difficulty in workplace, lack of interest, fatigue, low libidinal energy, and pain. (Opdyke *et al*., 1996; Nierenberg *et al*., 1999; Gasto *et al*., 2003; Carney *et al*., 2007; Merens *et al*., 2008) Our results suggest that red ginseng administration exerts beneficial effects over residual symptoms by improving both affective and non-affective symptoms. Consistent with our findings, many previous studies have reported that ginseng has positive effects on mood and functional somatic symptoms. For example, Tode *et al*. reported that daily oral administration of red ginseng significantly improves fatigue, insomnia, and depressed feelings in postmenopausal women. (Tode *et al*., 1999) Another randomized placebo-controlled study described that adults complaining of various functional somatic symptoms on the Symptoms checklist-90-revised self-report had significantly improved symptoms after taking 3 g of Korean Red Ginseng (Kang *et al*., 2009). Reay *et al*. reported that 400 mg of red ginseng exerts a calming effect on healthy volunteers both 2.5 h and 4 h after administration. (Reay *et al*., 2010) Additionally, *Panax quinquefolius*, the so-called American ginseng, has been reported to have calming properties; (Scholey *et al*., 2010) and, similarly to Asian red ginseng, it contains ginsenosides Rg1, Re, Rb1, Rc, Rb2, and Rd. These studies all suggest that ginseng could prove useful in managing a variety of symptoms in patients with depressive disorders.

There are several plausible explanations as to why Korean Red Ginseng is effective in treating depressive symptoms. First, several studies using animal models have revealed that ginseng modulates the hypothalamus–pituitary–adrenal axis (HPA) response to stress. This can be attributed to the ginsenoside Rb1-mediated inhibition of the stress-induced increase in plasma corticosterone via regulation of nitric oxide production (Luo *et al*., 1993; Kim *et al*., 1998). Another animal study found that wild ginseng suppressed corticotrophin-releasing factor expression and stimulated neuropeptide Y expression in the hypothalamus (Lee *et al*., 2011). Second, ginseng might exert antidepressant effects via interaction with neurotransmitters. Ginoside Rb1 and its metabolite, compound K, have been shown to increase the latency to immobility of ovariectomized mice during the forced swimming test. Interestingly, these antidepressant-like effects disappeared after administration of the 5-HT(2A) receptor antagonist ritanserin (Yamada *et al*., 2011). Another study found that saponin, the active component of Panax ginseng C.A. Meyer, reversed a decrease in norepinephrine, dopamine, and homovanillic acid induced by chronic mild stress (Dang *et al*., 2009). Third, ginseng might exert antidepressant effects by modulating neuroinflammatory responses. It is known that depression leads to the activation of pro-inflammatory cytokines and the suppression of anti-inflammatory cytokines (O'Brien *et al*., 2004). Rb1 has been shown to inhibit pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α; moreover, it can counteract the stimulation of pro-inflammatory cytokines by Rg1 (Joo *et al*., 2005). Fourth, ginseng might exert antidepressant effects by contributing to neurogenesis. Fossati *et al*. (2004) proposed that recurrent depression may enhance the deleterious effects of depression on the structural and functional plasticity of the fronto-limbic area, which includes the prefrontal cortex, cingulate, paracingulate, amygdala, and hippocampus. Additionally, neuroimaging studies have consistently reported hippocampal volume loss in patients with recurrent depression (Eker and Gonul, 2010). These deleterious changes to the brain may be counteracted by ginseng as suggested by studies where crude ginseng saponin-induced neurite outgrowth in cultured rat cerebral cortical neurons (Sugaya *et al*., 1988) and Rb1 potentiated nerve growth factor-mediated neurite outgrowth in cultured chick embryonic dorsal root ganglia (Nishiyama *et al*., 1994).

Our findings have important clinical implications. For one, antidepressants are often not enough to fully control residual depression symptoms. In this study, we found that Korean Red Ginseng treatment for patients with residual depression symptoms seems to be effective and safe. This finding should provide incentive for clinicians to expand their treatment options for residual symptoms of depression and other related disorders. Furthermore, our finding provides the basis for performing future clinical trials to examine the efficacy of red ginseng on patients with newly onset depression, treatment-resistant depression, and in other patients with psychiatric disorder commonly reporting depressive symptoms like schizophrenia, anxiety, and bipolar disorder.

Limitation of the study

In spite of the meaningful implications discussed above, there are some limitations to the current study,

which should be considered. First, Korean Red Ginseng has been purported to boost energy levels for long periods. Because of this, many Koreans still have favorable attitudes toward red ginseng, and these attitudes may have contributed to an increase in placebo effect. Second, our conclusions about the efficacy and safety of ginseng augmentation on residual symptoms of depression are based on a small patient sample without a control group, and our subjects were non-blinded and enrolled in the absence of randomization. Third, we were unable to show whether the improvement in residual symptoms persisted after eight weeks, or how long ginseng augmentation in patients was maintained. Therefore, placebo-controlled research with larger samples and longer follow-ups will be required to confirm our results.

Summary of the study

Our results suggest that a dose of 3.0 g of Korean Red Ginseng is effective and safe in patients experiencing residual symptoms of depression. Ginseng seems to have biologically active antidepressant properties via its influence on the HPA axis, interaction with neurotransmitters, anti-inflammatory actions, and involvement in neurogenesis. Therefore, Korean Red Ginseng could serve as an alternative treatment option for patients with depression and other related disorders.

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The authors have no conflict of interest to declare.

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