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Short Communication

Efficacy of hydroalcoholic extract of *Rheum ribes* L. in treatment of major depressive disorder

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Traditionally *Rheum ribes* L. has been used in Iran as sedative and mood enhancer. This study investigated the efficacy and safety of a hydroalcholic extract of *R. ribes* in treatment of mild to moderate major depression disorder 33 patients were randomly assigned to receive either Rheum ribes hydroalcoholic extract (1200 mg/day) or placebo in a 6-week, double blind and parallel-group trial. Patients were assessed before the study and during weeks 1, 2, 4 and 6 by the Hamilton Rating Scale for Depression (HAM-D) and a score sheet on adverse effects.In week 4 and 6, the extract showed a significant superiority over placebo in reducing depressive symptoms. There was no significant difference between the 2 groups in terms of adverse effects. The results suggest that Rheum ribes hydroalcoholic extract has some anti depressive effects. However, further studies are needed to confirm these findings.

Key word: *Rheum ribes*, depressive disorder, clinical trial.

INTRODUCTION

Rheum ribes belongs to Polygonaceae family (Zargari, 1997). It grows in Iran and Turkey (Tozlac, 1991). *R. ribes* L. (Polygonaceae) is a hardy perennial, cultivated in some temperate countries for its edible red leaf stalks (Zargari, 1997; Dehkardy, 2002). Its Persian name is “Rivas” (Zargari, 1997). Stem, leaf and stem form of flowers of this plant are edible raw and cooked (Ssharifi, 2005) (Bowen, 1995). Traditional herbal medicine stem and root dry plant for the treatment of anemia, anorexia, weakness, anxiety, depression and diabetes (Moemen, 1967). These plant vitamins A, B, C are seen in abundance (Heshmat et al., 2008). Content of this plant is: Chrysophanol, Physcion, Rhein, Aloe-emodin, Physcion-8-O-glucoside, Aloe-emodin-8-O-glucoside, Sennoside A and Rhaponticin, Flavonoids (Tozlac, 1991; Octay et al., 2007). The problems in the treatment of psychiatric diseases in developing countries, price is high and complications of these medicine (Sayyah et al., 2006). Traditional herbal therapy in the treatment of psychiatric disorder is being increased day by day. Limited studies in the field of anti-depressive effects of herbal medicines particularly in case of *R. ribes* have been made. So in the present study we decided to review the effect of *R. ribes* on mild to major depression disorder.

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MATERIAL AND METHODS

Participants and setting

Participants were patients who referred to the outpatient clinic of Imam Khomeini Hospital, Joondi Shapoor University of Medical Sciences, with complaint of depressed mood. Participants were eligible for the study if they met DSM-IV-TR criteria for mild to moderate major depressive disorder (American Psychiatric Association, 2000). Patients must have baseline score 18 or higher on the Hamilton Rating Scale for Depression (HAM-D17) (Hamilton, 1967) and not receiving psychiatric medication during the 2 weeks prior to referring to the clinic, with age between 18 and 60 years are included in the present investigation. They gave written consent for participation in the study. Subjects were disqualified if they had psychotic symptoms or suicidal tendency, concomitant other psychiatric or neurological disorder, significant cardiac, renal or hepatic disease, a history of sensitivity to medications with plant origin, pregnant or breast-feeding, or mentally retarded. The study was conducted from October of 2007 to June of 2008, in the outpatient clinic of Imam Khomeini Hospital. Patients could withdraw their participation at any time and transfer to a conven-

tional treatment. Those completing the trial were also guaranteed transfer to a conventional treatment. The study was conducted in accordance with the Declaration of Helsinki and Tokyo for humans and was approved by the ethical committee at Joondi shapoor university of Medical Sciences.

Preparation of medication

The fresh stalks of the plant were collected from Shahrood (Semnan Province, Iran) in June 2006. The plant was identified by the Herbarium of Ferdowsi University, Mashhad, Iran and voucher specimens were deposited. Different parts of plant were cleaned from debris, air-dried and finally grounded to a coarse powder. Stalks were cleaned from debris, washed and then cut into small pieces before drying. Powdered plant materials (50 g) were extracted with methanol (300 ml) by the aid of a Sohxlet apparatus for 12 h. After filtration, the solvent was removed under reduced pressure using a Rotavapor - RE to give a concentrated extract and the residue was refrigerated until use.

In order to preserve the double blind condition, *R. ribes* extract and placebo were dispensed in capsules of identical appearance. *R. ribes* capsules were filled with 400 mg of the extract and talcum powder while placebo capsules were only filled with talcum powder.

Procedures

After giving written informed consent, participants entered a parallel group, randomized, double blind, fixed-schedule, 6-week clinical trial. Patients were randomly assigned to treatment with the extract (1200 mg/day) or placebo, using a computer-generated list of random numbers. All patients received one oral capsule 3 times daily. The dosage regimen was selected based on the report about the safety of *R. ribes* (Heshmat et al., 2008) treatment course. Efficacy was assessed using the Hamilton Rating Scale for Depression (HAM-D17) (Hamilton, 1967). Treatment-induced adverse effects were assessed systematically at each visit by a score sheet designed for the present study. A psychiatrist (Mehdi Sayyah) who was trained in the usage of the scales performed all clinical research measurements.

Statistical analysis

Data was examined using intention-to-treat analyses. Missing data were replaced by a last-observation-carried forward approach. Repeated measures analysis of variance (ANOVA) was used to assess the effects of treatment (2 study group), time (weeks of visit) and interaction of treatment and time. Significance of difference in mean scores in each visit was assessed by un-paired Student's t test. The frequency of treatment-induced adverse effects in the study groups was analyzed by Fisher's exact test. All statistical tests were 2-sided and were considered significant at $P < 0.05$.

RESULT

Demographic characteristics

33 patients were enrolled in the study; 17 were assigned to the extract group and 16 to the placebo group. The characteristics of the 2 study groups are summarized in Table 1. The 2 groups were well matched and there were no statistically significant differences between the groups in demographic.

Table 1. Demographic data of the patients.

Characteristic		Extract	Placebo
Age (years, means ± S.D.)		27 ± 32	28 ± 87
Sex	**Women**	10	9
	Men	7	7
Marital status	**Single**	54.65%	51.13%

Retention in treatment

31 patients completed the 6-week trial, while 2 patients discontinued treatment for consent withdrawal. The treatment retention did not differ between the 2 groups in demographic.

Effect on HAM-D scores

As shown in Figure 1, the mean HAM-D scores gradually declined in the both study groups during the trial. ANOVA revealed significant effect of time [$F (1, 4) = 37.4$, $P < 0.01$].The effect of treatment was significant [$F (1, 4) = 23.15$, $P = 0.03$]. Time-by-treatment interaction was significant [$F (1, 4) = 8.5$, $P < 0.02$]. In week 4, patients treated with the extract had significantly lower scores (17.31 ± 2.31) than the placebo-treated patients (24.31 ± 1.43) ($t = 2.51$, $P = 0.02$). In week 6, the mean HAM-D score was significant in the extract group (16.75 ± 2.32) compared to the placebo group (25.41 ± 1.67) ($t = 3.15$, $P < 0.00$).

Adverse effects

No patient discontinued treatment for adverse effects. There was no significant difference between 2 groups regarding the incidence of adverse effects. 2 patients in extract group and one patient in placebo group received oxazepam for insomnia. However, the difference between 2 groups was not statistically significant.

DISCUSSION

Major depressive disorder is currently the fourth leading worldwide cause of disability and burden of diseases. Projections for the year 2020 suggest that this disorder will rise to become the second most important cause of disability-adjusted life years, behind only ischemic heart disease (World Health Organization, 2001). Current antidepressant medications, however, have the disadvantage of limited efficacy and significant side effects (sayyah et al., 2006). Therefore, there is a compelling demand for new types of antidepressants.

The present study was aimed at assessing the putative antidepressant effect of the extract of *R. ribes* L. The re-

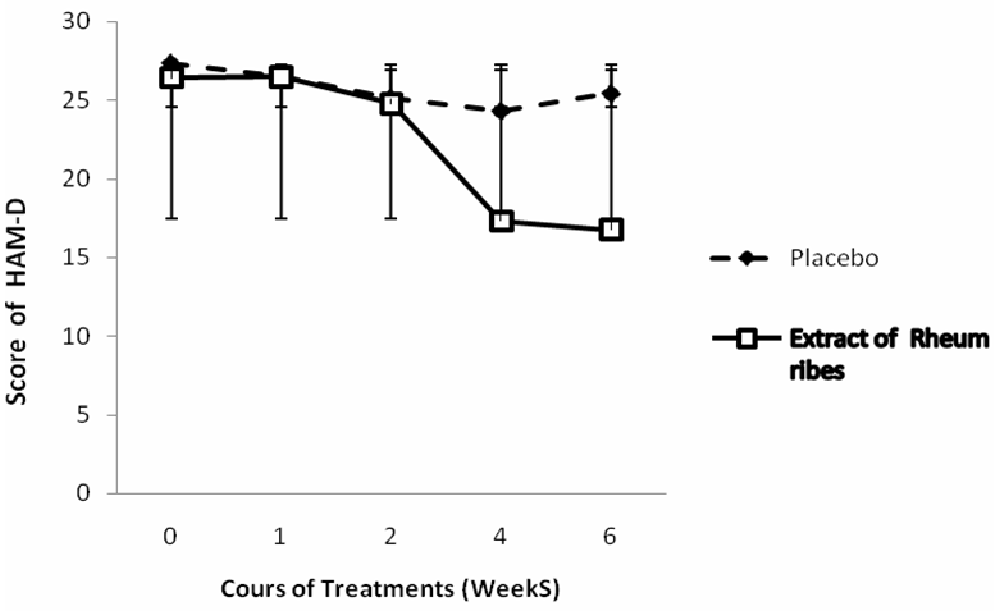

Figure 1. Effect Rheum ribes extract on score of Hamilton Rating Scale for Depression (HAM-D).

results showed that the extract might have some antidepressant effect. The extract was generally well tolerated.

Preliminary phytochemical screening of the *R. ribes* L. contains flavonoids (Oktam et al., 2002). It has been demonstrated that some flavonoids have antidepressant activity in mice and this effect is comparable to that of fluoxetine and imipramine (Anjaneyulu et al., 2003). Furthermore, it has been suggested that the flavonoids of St. John's Wort are involved in its antidepressant action (Butterweck et al., 2004). It seems that the antidepressant effect of *R. ribes* L. extract, observed in the present study may be related in part to flavonoids present in the plant.

The results of this study should be viewed in light of its methodological limitations. Firstly, the study had a small sample size. Further studies with larger sample size are needed to verify the results of this study. Secondly, we preferred using a relatively low dose (1200 mg/day) to increase the safety profile. The safe profile of the extract shown in this study may indicate that higher doses should be used in the future studies. Thirdly, the patients were treated and assessed for a short period of time. Longer trials are needed to assess the long-term safety and efficacy of the extract. Finally, an active control group consisting of patients receiving a conventional antidepressant drug would help in comparing the efficacy of the extract with typical antidepressant medications.

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