
Evaluation of the clinical efficacy and safety of grapeseed extract in the treatment of fall seasonal allergic rhinitis: a pilot study

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Background: Herbal products are widely used by consumers as alternatives to prescription drugs in treating symptoms of allergic rhinitis. However, there have been few placebo-controlled clinical trials that have examined the efficacy or safety of these products. Although grapeseed extract (GSE) is an herbal that is marketed for treating allergic rhinitis, its efficacy is unproven.

Objective: The aim of this study was to compare the efficacy and safety of GSE with placebo in the treatment of seasonal allergic rhinitis (SAR).

Methods: This was a randomized, double-blind, placebo-controlled study of GSE 100 mg, twice daily, versus placebo. Patients with SAR and skin prick test sensitivity to ragweed were randomized to 8 weeks of active treatment or placebo which was begun before the ragweed pollen season. Outcomes included: daily symptom diary scores recorded by patients, rhinitis quality of life scores at baseline and after 4 and 8 weeks of treatment; and requirements for rescue chlorpheniramine. Safety was monitored with routine laboratory studies.

Results: Over 8 weeks of treatment, no significant differences were observed between active and placebo groups in rhinitis quality of life assessments, symptom diary scores, or requirements for rescue antihistamine. No significant laboratory abnormalities were detected.

Conclusions: This study did not show trends supporting the efficacy of GSE in the treatment of SAR.

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INTRODUCTION

Allergic rhinitis is the most common form of all allergic disorders, affecting an estimated 44 million Americans, or 20% of the North American population.¹ During the latter half of the 20th century, the incidence of allergic rhinitis (and asthma) has increased world-

wide, resulting in dramatic escalations in direct and indirect treatments costs. In 1996, direct and indirect costs for allergic rhinitis were estimated at \$7 billion, \$3 billion of which was spent on nonsedating antihistamines.²

Despite steady advances in conventional therapies, herbal supplements are widely used to treat symptoms of allergic rhinitis. Comprehensive reviews of alternative medicines for allergic and asthmatic disorders have been published elsewhere.^{3,4} The extent of utilization of herbal products for allergic rhinitis is unknown. However, a wide variety of herbal supplements are marketed, including: bee pollen, cayenne (red pepper), chamomile flower (composite family), echinacea, euphrasia, fenugreek seeds, grapeseed extract (GSE), goldenseal

roots, licorice, ma huang (ephedra), mullein weed (Europe), and nettle. Eisenberg et al,⁵ in a survey of trends in alternative medicine utilization in the United States, reported that the prevalence of administration of an alternative therapy for allergies had risen from 8.7% in 1990 to 16.6% in 1997.

There are theoretical benefits of herbal products favoring the use of polyphenolic bioflavonoids in the treatment of allergic disorders. Quercetin, a bioflavonoid found in citrus and buckwheat, and oligomeric epicatechins, contained in apples, inhibit allergen-stimulated basophil histamine release and modify intercellular adhesion molecule expression on endothelial cells.^{6,7} GSE is a popular herbal remedy that is rich in catechins and epicatechins as well as proanthocyanidins, polyphenolic bioflavonoid antioxidants.⁸ Many herbal folk preparations consumed in Southeast Asia possess in vitro antiallergic properties including: hi-chum, or an extract of *Siegesbeckia pubescens* (composite) used in Korea⁹; Japanese herbals shoseiryu-to and shosaiko-to^{10,11}; and the Chinese herbal mixtures wu-hu-tang¹² and biminkang.¹³

There have been few published clinical studies examining the efficacy of herbal preparations in allergic rhinitis. Bao et al¹³ reported an observational comparative study of 164 allergic rhinitis cases treated with biminkang mixture (*Artimisia rupestris* folk herb) and 52 control allergic rhinitis patients who received treatment with an ill-defined patent medicine. Efficacy was reported in 94% of patients receiving biminkang versus 69% of the group who

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received the patent medicine. Recently, Walls et al¹⁴ reported the results of a placebo-controlled study examining the efficacy of an herbal Chinese formulation, bimin, in the treatment of perennial allergic rhinitis. The bimin was analyzed and found to be free of antihistamine, steroid, or ephedrine constituents. The herbal preparation was significantly better than placebo in physicians' global evaluation, use of rescue medication, quality of life assessments, and daily symptoms of sneezing. In this study, serum total immunoglobulin E decreased significantly in the group that received active treatment.

GSE is widely promoted as effective in treating 60 to 70% of patients with seasonal allergies and has been touted as a natural antihistamine. Despite these claims, there are virtually no pre-clinical or clinical data that support the use of GSE (and many other herbal agents) in the treatment of immunoglobulin E-mediated disorders. Presumably, this information is based on anecdotal experiences of individual consumers. As mentioned, GSE contains catechin monomers which have been demonstrated to inhibit allergen-induced histamine release in passively sensitized rat peritoneal mast cells.¹⁵ Based on this information, GSE seemed to be an herbal product worthy of objective evaluation for possible clinical efficacy in seasonal allergic rhinitis (SAR). This report describes a 2-month, double-blinded, placebo-controlled pilot study, the purpose of which was to evaluate the clinical efficacy and safety of GSE

versus placebo in prevention of fall SAR symptoms.

METHODS

Study Population

Patients were included who were between the ages of 18 and 75 years, with medical histories compatible with moderate to severe SAR associated with the fall ragweed pollen season for at least 2 previous consecutive years. A positive skin prick test to commercial short ragweed extract (ALK, Wallingford, CT) was required. Patients had to be either asymptomatic or minimally symptomatic for at least 1 month before enrollment. Informed consent was obtained from all participants before initiation.

Pregnant women were excluded as were those women of child-bearing potential not using reliable contraceptive methods. Patients who had received allergen injections during the previous 2 years, or those individuals with hypersensitivity to grapes or grapeseed products were excluded. Other exclusion criteria included: perennial rhinitis; rhinitis medicamentosa; vasomotor rhinitis; nasal structural deformities; hypertrophic rhinitis; or nasal polyps. Patients who had used astemizole or systemic corticosteroids within 3 months before screening or nasal steroids within 15 days were excluded. Patients were excluded with active medical disorders including: cancer, infection, hematologic, renal, hepatic, cardiovascular, metabolic, or gastrointestinal disease.

Study Design

Because the putative onset of action of GSE is not known, treatment was initiated in all subjects 2 to 4 weeks before the onset of seasonal symptoms and the fall ragweed pollen season (Fig 1). Because the possible effective dose of GSE is unknown, a dosage of 100 mg, twice daily, was selected that is twice the manufacturer's daily recommended dose of 50 to 100 mg/day. Two groups of approximately 25 to 30 patients were recruited for randomization to either GSE or placebo approximately 2 to 4 weeks before the onset of ragweed pollination (August 15 to 25). At visit 1, informed consent was obtained and eligibility determined. A complete medical history, physical examination, and laboratory studies were performed in qualified patients. Laboratory studies were performed at visit 1 and repeated after 4 (visit 3) and 8 weeks (visit 5) of treatment. These included: a complete blood cell count with differential and platelet counts; urinalysis; and serum chemistry tests including sodium, potassium, glucose, creatinine, blood urea nitrogen, uric acid, protein, albumin, calcium, total bilirubin, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, and alkaline phosphatase.

At visit 1, qualified patients were randomized to 8 weeks of treatment with either powdered GSE capsules at a daily dosage of 100 mg, twice daily, or to color-matched twice daily placebo GSE capsules, which were supplied by Next Pharmaceuticals, Inc (Irvine, CA), were manufactured by New Enterprizes, Inc (Oakland, CA), and standardized for oligomer content. Procyanidolic value by a calorimetric test was >95 (range 95 to 120) and the extract contained 90% total polyphenols (personal communication). Placebo capsules were indistinguishable from active treatment and contained an inert filler agent.

Patients returned for study visits at 2-week intervals (visits 2 to 5) at which time diary forms were collected and new ones dispensed. At each visit, 30 chlorpheniramine (4-mg) tablets

Week	0	2	4	6	8
	Screen				
Dispense study meds	X	X	X	X	
Dispense rescue meds	X	X	X	X	
Symptom diary cards	X	X	X	X	
RQOL questionnaire	X		X		X
Labs	X		X		X
Global evaluation					X

Figure 1. Study design: flow chart. Study visits at 2-week intervals.

were dispensed as rescue medication which patients were instructed to use as needed for uncontrolled nasal symptoms. At each return visit, unused rescue medication was returned and the number of used tablets recorded.

Subjects were instructed to record 24-hour retrospective nasal symptoms (stuffy, runny nose, itching, sneezing) and non-nasal symptoms (itching, burning eyes, tearing eyes, redness of eyes, itching of ears or palate) on diary cards. Patients rated their reflective symptoms over the previous 24 hours before bedtime on a 4-point severity scale. At the same time, numbers of doses of study and rescue medication were also recorded. On the final visit, investigators evaluated the overall severity of rhinitis on a 4-point scale and the overall response to treatment on a 5-point scale (1 = excellent to 5 = worsening of symptoms). At visits 1, 3, and 5, subjects completed a self-administered Rhinoconjunctivitis Quality of Life Questionnaire (RQOL).^{16,17}

Data Analysis

For each patient, average symptom severity scores were calculated as:

Symptom severity score

$$= \frac{\text{sum of scores during diary period}}{\text{number of days of diary period}}$$

Mean symptom severity scores were calculated for each symptom as well as the overall total symptom score. Data were tabulated as mean values and Wilcoxon rank sum test were used to analyze differences between GSE- and placebo-treated groups. For RQOL, the average scores were calculated for each domain as well as for the overall quality of life. The average scores in each domain and the overall quality of life were evaluated by treatment by evaluating changes at visits 3 and 5 from visit 1. Wilcoxon rank sum test were used to compare the differences between treatment groups. For global evaluation, χ^2 test was used to analyze the association between treatment and the global response to the treatments. All statistical analyses were conducted using SAS (Windows, version 6.12).

Table 1. RQOL Scores at Visit 1 in Placebo and Active Treatment Groups

Domains	Placebo (n = 26)	GSE (n = 25)	P value*
Overall RQOL			
Mean $\pm$ SD	1.04 $\pm$ 1.03	1.18 $\pm$ 1.26	0.75
Activity			
Mean $\pm$ SD	1.23 $\pm$ 1.22	1.43 $\pm$ 1.45	0.73
Sleep			
Mean $\pm$ SD	0.81 $\pm$ 0.86	1.11 $\pm$ 1.47	0.83
Non-hay fever			
Mean $\pm$ SD	1.03 $\pm$ 1.13	1.11 $\pm$ 1.29	0.85
Practical problems			
Mean $\pm$ SD	1.29 $\pm$ 1.40	1.29 $\pm$ 1.42	0.89
Nasal			
Mean $\pm$ SD	1.32 $\pm$ 1.22	1.35 $\pm$ 1.38	0.97
Eye			
Mean $\pm$ SD	0.92 $\pm$ 1.22	1.27 $\pm$ 1.56	0.37
Emotions			
Mean $\pm$ SD	0.74 $\pm$ 0.92	0.85 $\pm$ 1.37	0.95

* Based on Wilcoxon rank sum test.

No significant difference in scores were detected between placebo- and GSE-treated groups.

RESULTS

Twenty-eight subjects were randomized to GSE and 26 to placebo. The mean age was 43 (11 male and 17 female) in the GSE group and 36 (9 male and 17 female) in the placebo group. Of the 28 patients who were begun on GSE at visit 1, 25 returned for visits 2 to 5 and were considered evaluable, as were 26 randomized placebo patients who completed 8 weeks of treatment.

As shown in Table 1, RQOL scores at visit 1 did not differ significantly

between groups. As shown in Table 2, no significant differences were found in mean overall nasal symptom scores and individual symptom scores between GSE- and placebo-treated groups during 8 weeks of treatment. The weekly symptom severity scores, plotted in Figure 2, increased and decreased in both groups parallel to the mean weekly pollen ragweed counts. No weekly differences were seen between GSE and placebo treatment groups either before or during the peaks of ragweed pollination.

Table 2. Mean Symptom Severity Scores Obtained from Daily Symptom Diary Card Data during 8 Weeks of Active Treatment with Placebo and GSE Treatment

Symptoms	Placebo (n = 26)	GSE (n = 25)	P value*
Overall			
Mean $\pm$ SD	5.58 $\pm$ 3.15	5.94 $\pm$ 3.59	0.81
Sneezing			
Mean $\pm$ SD	1.08 $\pm$ 0.54	0.90 $\pm$ 0.45	0.17
Itchy nose			
Mean $\pm$ SD	0.91 $\pm$ 0.62	0.95 $\pm$ 0.64	0.96
Runny nose			
Mean $\pm$ SD	0.91 $\pm$ 0.54	1.04 $\pm$ 0.59	0.36
Stuffy nose			
Mean $\pm$ SD	0.87 $\pm$ 0.56	1.02 $\pm$ 0.72	0.60
Itchy eyes			
Mean $\pm$ SD	0.84 $\pm$ 0.56	0.86 $\pm$ 0.63	0.96
Watery eyes			
Mean $\pm$ SD	0.51 $\pm$ 0.44	0.64 $\pm$ 0.71	0.81
Red eyes			
Mean $\pm$ SD	0.45 $\pm$ 0.47	0.52 $\pm$ 0.61	0.88

* Based on Wilcoxon rank sums test.

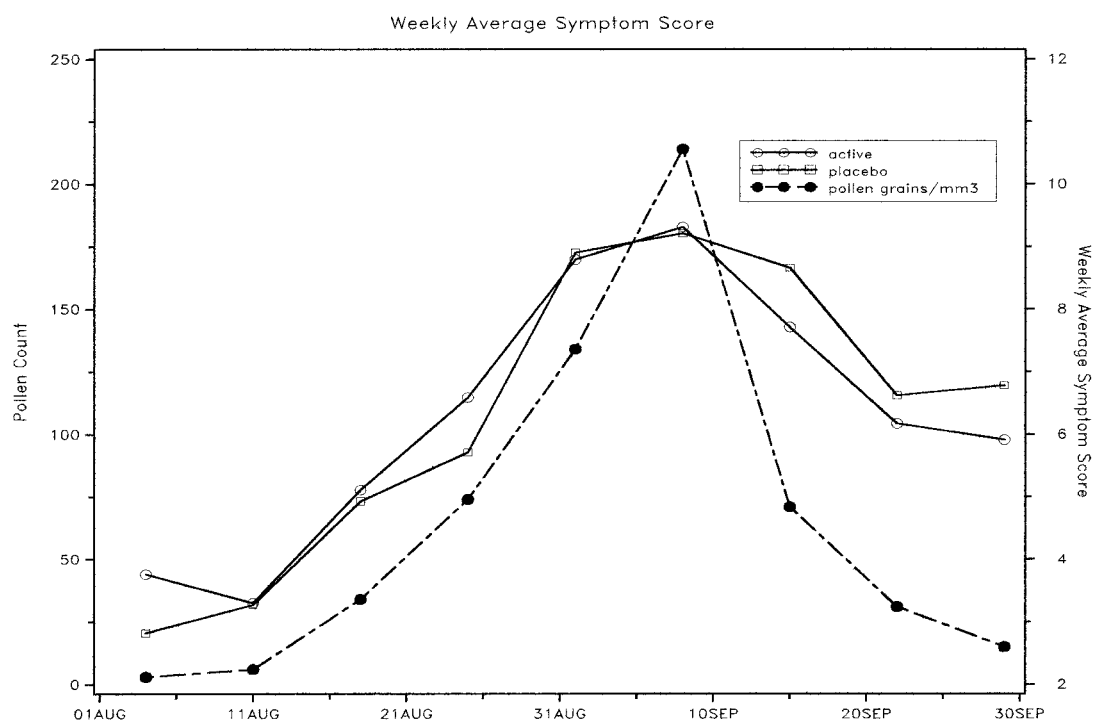


Figure 2. Comparison of mean weekly total symptom scores in placebo- and GSE-treated groups of patients with SAR and weekly average ragweed pollen counts. No significant intergroup differences were observed (Wilcoxon test, $P = 0.81$).

Global physician assessments performed at visit 5 (after 8 weeks of treatment) are shown in Table 3. There were no significant differences between groups. Fourteen of 26 placebo-treated and 13 of 25 grapeseed-treated patients reported moderate or good responses to treatment, with the remainder of patients in both groups reporting no improvement or worsening of symptoms. No subjects in either group reported an excellent response.

The RQOL was administered to all patients at visits 1, 3, and 5. The mean changes in RQOL scores between visits 1 and 3 and between visits 1 and 5 were analyzed for the patients' assessments of the impact of their condition during the previous week on the following quality of life domains: daily activities; sleep; non-nose/eye symptoms (fatigue, thirst, reduced productivity, tiredness, poor concentration, headache, feeling "worn out"); practi-

cal problems (eg, inconvenience of carrying nasal tissues, need to rub or blow nose repeatedly); nasal symptoms; eye symptoms; and the emotional domain (eg, frustration, impatience, irritability). As shown in Table 4, no significant differences were found for these domains between the GSE- and placebo-treated groups over the aforementioned intervals (visit 1 to 3; visit 1 to 5).

Weekly rescue medication requirements are shown in Figure 3 for both GSE and placebo groups. There was no difference between treatment groups in the overall requirement for rescue chlorpheniramine or in the numbers of patients using rescue antihistamines during the 8-week treatment period. No differences between groups were observed, particularly during the weeks representing the peak of the ragweed pollen season.

Common adverse events included headaches, abdominal pain and sore throat, as listed in Table 5. No reported

Table 3. Global Evaluations of Therapeutic Responses by Treatment Group

Treatment	Response to Treatment				Total
	Good	Moderate	Poor	Worsening	
Placebo	7 (26.9)	7 (26.9)	8 (30.8)	4 (15.4)	26
GSE	5 (20.0)	8 (32.0)	3 (12.0)	9 (36.0)	25

$\chi^2 = 4.58$, $P = 0.21$

Excellent: Complete control of allergy symptoms;

Good: Marked improvement of symptoms;

Moderate: Limited improvement in allergy symptoms;

Poor: No appreciable change in allergy symptoms;

Worsening: Worsening or increase in allergy symptoms.

Table 4. RQOL Score Changes from Visit 1 to Visit 3 and Visit 5

Domains	Visit 3—visit 1			Visit 5—visit 1		
	Placebo (n = 26)	Treatment (n = 25)	P value*	Placebo (n = 26)	Treatment (n = 25)	P value*
Overall RQOL						
Mean ± SD	0.27 ± 1.32	0.44 ± 1.42	0.97	0.91 ± 1.70	0.76 ± 1.66	0.54
Activities						
Mean ± SD	0.40 ± 1.89	0.55 ± 1.63	0.90	1.13 ± 2.14	0.71 ± 1.99	0.64
Sleep						
Mean ± SD	0.28 ± 1.23	0.07 ± 1.62	0.40	0.85 ± 1.60	0.68 ± 2.00	0.63
Non-nose/eye symptoms						
Mean ± SD	0.11 ± 1.40	0.48 ± 1.59	0.62	0.47 ± 1.65	0.74 ± 1.37	0.69
Practical problems						
Mean ± SD	0.46 ± 1.91	0.58 ± 1.57	1.00	1.25 ± 2.05	0.96 ± 1.74	0.74
Nasal symptoms						
Mean ± SD	0.36 ± 1.55	0.85 ± 1.40	0.31	1.36 ± 1.90	1.05 ± 1.78	0.57
Eye symptoms						
Mean ± SD	0.45 ± 1.46	0.33 ± 1.74	0.57	0.83 ± 1.81	0.41 ± 2.07	0.38
Emotional						
Mean ± SD	0.04 ± 1.02	0.33 ± 1.41	0.51	0.82 ± 1.72	0.96 ± 1.77	0.80

* Based on Wilcoxon rank sum test.

adverse events were considered to be related to study medication and all resolved spontaneously without intervention. Prevalences of reported adverse events did not differ significantly between treatment groups. In the GSE group, there was one patient who reported nausea on a single visit, which was thought to be possibly related to treatment and resolved by the next visit; this subject was able to complete 8 weeks of active treatment. No clinically significant laboratory abnormalities were observed in subjects in either treatment group.

DISCUSSION

This pilot study was conducted to ascertain if large differences existed in efficacy and side effects between daily treatment with oral GSE and placebo in treating SAR. In this pilot study, no such large differences were observed. We failed to detect any statistically significant benefits and no consistent trends were observed to clearly indicate that GSE was more effective than placebo in reducing nasal symptom scores or requirements for rescue antihistamines. In addition, no significant associations or discernible trends were detected between GSE or placebo treatment with regard to improvements either in RQOL scores or physician global evaluations.

No treatment-related adverse events or abnormal laboratory values were detected. This suggests that short-term administration of GSE was safe at the prescribed dose of 100 mg, twice daily. However, a short-term safety study performed in a small group of subjects does not reliably predict the long-term safety of GSE.

Admittedly, it is difficult to study alternative treatments using conventional study designs that have been used in the evaluation of pharmacologic agents. First, the group sizes needed to conduct parallel controlled studies for any drug must be large enough to detect small differences between treatments. Because of a lack of resources required for a large multicenter study, we conducted a small pilot study to explore the potential efficacy of GSE compared with placebo treatment. Realistically, our goal was to identify possible trends favoring efficacy, but we realized that this approach could not absolutely prove or disprove efficacy of GSE in treating SAR. Second, in considering the overall study design, we chose to initiate treatment before the onset of the ragweed pollen season as opposed to randomizing subjects to treatment after a brief baseline lead-in period at the beginning of the pollen season. Because the onset of action or steady-state phar-

macokinetics of GSE is unknown, we chose to begin treatment at 2 to 4 weeks before onset of seasonal symptoms. Thus, the analyses of symptom data relied on parallel group differences at various intervals rather than between-group comparisons of changes from baseline symptom scores. Finally, although a crossover study would have required fewer subjects, such a design could not be performed during a relatively brief pollinating season. Further, such a design could have been complicated by crossover effects.

Despite these limitations of study design, there was no evidence suggesting superiority of one treatment arm over the other. Although it is acknowledged that the results of this small pilot study does not exclude possible efficacy of GSE, the lack of any trend favoring some effect of GSE effect over placebo would suggest that a larger study using a similar design is unlikely to show clinically important differences. This investigation is a rare example in which an alternative treatment was investigated by a randomized controlled trial. Perhaps, this study will set a precedent among practitioners to investigate alternative and complementary therapies in randomized controlled trials, a theme that has been emphasized by Margolin et al.¹⁸

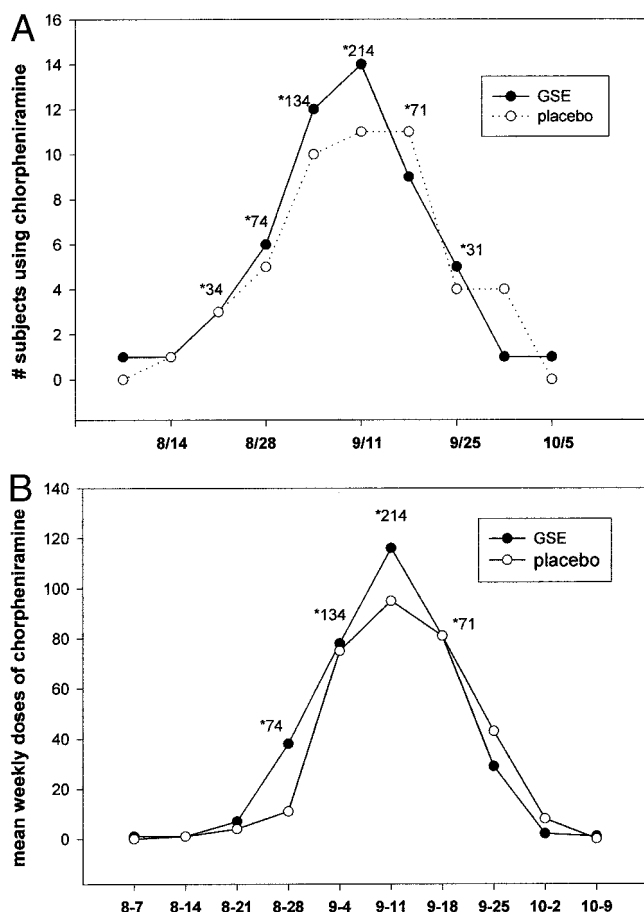


Figure 3. Comparisons of the number of GSE- and placebo-treated subjects (A) requiring rescue chlorpheniramine (Mann-Whitney test, $P = 0.80$); and mean weekly doses (B) of rescue medication in GSE and placebo groups (Mann-Whitney test, $P = 0.80$). Mean weekly pollen counts (*) are shown adjacent to datapoints.

CONCLUSION

There is a clear need to objectively evaluate herbal products for both efficacy and safety. The latter is of some concern because several recent reports of severe adverse effects after

chronic use of certain herbal products that contain hepatotoxins, ephedrine, and mineralocorticoid substances have been published.^{19,20} Because herbal preparations are loosely regulated, it is essential that consumers and their physicians have access to objective clinical data upon which to judge safety and efficacy of these products. This study begins to examine methods by which their safety and efficacy can be investigated in human trials of allergic rhinitis. If regulatory standards for proving safety and efficacy of these products are established in the future, there would be a better rationale for conducting larger clinical trials.

Table 5. Reported Adverse Events

Adverse events	No. (%) GSE-treated patients	No. (%) placebo-treated patients
Headaches	13 (52)	13 (54)
Abdominal pain	3 (12)	3 (13)
Sore throat	3 (12)	2 (8)
Nausea	2 (8)	1 (4)
Cough	1 (4)	2 (8)

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