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Ehretia Microphylla (*Tsaang Gubat*) versus Loratadine as Treatment for Allergic Rhinitis: A Randomized Controlled Trial

ABSTRACT

Objective: To determine if *Ehretia microphylla* (*Tsaang Gubat*) decoction tea and placebo can improve the symptoms of mild intermittent allergic rhinitis in comparison to loratadine and control tea.

Methods:

Design: Double-Blind, Randomized Controlled Trial

Setting: Tertiary-Government Training Hospital

Participants: Twenty-four patients diagnosed with mild intermittent allergic rhinitis from October 2015 to July 2016 were randomly divided into a treatment group given *Ehretia microphylla* (*Tsaang Gubat*) decoction tea and placebo, and a control group given control tea and loratadine, both taken for 7 days. Patients underwent pre– and post–intervention evaluation by anterior rhinoscopy, Sino-nasal Outcome Test 22 (SNOT 22) Questionnaire and 10-point Visual Analog Scale (VAS). Data were encoded and subjected to statistical analysis using Mann Whitney U test and Wilcoxon Signed Rank test.

Results: Age and gender of the treatment and control group participants were comparable. Prior to intervention, no differences in symptoms were noted between both groups on SNOT 22 and VAS scores. After intervention, no differences in symptoms were noted between the 2 groups on SNOT 22 and VAS scores either. Comparison of pre- (30.4 ± 17.3) and post- (7.2 ± 6.5) intervention mean SNOT 22 scores of the loratadine control group with pre- (32.5 ± 23.7) and post- (7.8 ± 10.4) intervention mean SNOT 22 scores of the *Ehretia Microphylla* treatment group showed significant improvement of symptoms in both groups. Likewise, comparison of pre- and post-intervention mean VAS scores of the loratadine control group and pre- and post-intervention mean VAS scores of the *Ehretia Microphylla* treatment group based on symptoms of sneezing, rhinorrhea, nasal congestion and pruritus showed significant improvement of symptoms in both groups (p-values of < .001).

Conclusion: *Ehretia microphylla* (*Tsaang Gubat*) decoction tea may improve symptoms of allergic rhinitis (sneezing, rhinorrhea, pruritus and nasal congestion) and be taken as an alternative to loratadine in patients with mild intermittent allergic rhinitis. Further clinical trials with more participants may provide stronger evidence for this conclusion.

Keywords: *Allergic rhinitis, tsaang gubat, ehretia microphylla, loratadine*

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Allergic rhinitis is a common health problem affecting all ages with prevalence of 20% among Filipino adults.[1] Patients present with symptoms of sneezing, rhinorrhea, nasal congestion and pruritus. These symptoms result from the inflammatory reaction caused by the interplay of inflammatory cells and mediators due to exposure to allergens. Current treatment guidelines include recommendations for environmental modifications, antihistamines, decongestants, intranasal cromolyn, intranasal anti-cholinergics, intranasal corticosteroids and immunotherapy.[2] Allergic rhinitis carries the burden of impaired quality of life and enormous cost implications.[3] Thus, treatment goals focus on alleviating troublesome symptoms of allergic rhinitis at a viable economical cost.

Ehretia microphylla (*Tsaang Gubat*) is 1 of the 10 medicinal plants approved by the Republic of the Philippines Department of Health to treat different ailments.[4] The leaves are traditionally used for medicinal purposes as an anti-spasmodic, mouthwash and body cleanser, attributed to the effects of different components (phenolic acids, flavonoids, benzoquinones, cyanogenetic glycosides, and fatty acids).[5] It also contains rosmarinic acid and nitrile glucosides which are anti-allergic substances that counter histamine release from mast cells that cause type-1 reactions.[5,6] Unfortunately, to the best of our knowledge, there is still no study detailing the use of this herbal medicine for allergic rhinitis. A PubMED, EMBASE and HERDIN search of the English literature using the keywords "allergic rhinitis," "*tsaang gubat,*" "ehretia microphylla," and "loratadine" did not yield any study on the use of *Ehretia microphylla* for allergic rhinitis.

This study aims to determine if *Ehretia microphylla* (*Tsaang Gubat*) decoction tea and placebo can improve the symptoms of allergic rhinitis in comparison to loratadine and control tea.

METHODS

With Institutional Review Board approval, this double blind, randomized controlled trial was conducted at the Ear, Nose, Throat – Head and Neck Surgery (ENT-HNS) Out-Patient Department of the Jose R. Reyes Memorial Medical Center, a tertiary government training hospital from October 2015 to July 2016.

Participants

The target population were patients aged 18 years old and above who complained of sneezing, rhinorrhea, nasal congestion and pruritus; with pale, edematous, boggy mucosa on anterior rhinoscopy; clinically diagnosed with mild intermittent allergic rhinitis (symptoms <4 times per week or for <4 weeks, with normal sleep, and no impairment in daily activities, sport, leisure, work or school). Excluded were patients with nasal mass, polyp and nasal trauma, those with history, symptoms or signs of *Ehretia microphylla* allergy, and those who could not tolerate ingestion of the tea decoction.

Preparation of *Ehretia microphylla* (*Tsaang Gubat*) decoction tea[7]

Fresh leaves were gathered from Baliuag, Bulacan and authenticated at the University of Santo Tomas – Research Center for Natural and Applied Sciences Herbarium. After washing the leaves thoroughly in running water, one cup (200 ml) of leaves was chopped and boiled per 2 cups (400 ml) of water for 15 to 20 minutes under low heat. The boiled leaves were drained, cooled, transferred to clean plastic containers and refrigerated. The Ehretia Microphylla tea was given to participants in 1L bottles that were refilled every 2 days during the study.

Preparation of control tea

One (1) teabag of Lipton® Yellow Label Tea (Uniliver, Manila) was soaked per 2 cups (400 ml) of water just off the boil for 3 to 5 minutes. The teabag was removed and the tea preparation cooled, transferred to clean plastic containers and refrigerated. The control tea was given to participants in 1L bottles that were refilled every 2 days during the study.

PROCEDURE

Clinical histories were obtained and physical examinations, including anterior rhinoscopy were performed by ENT-HNS resident physicians on duty. Each patient was asked to answer the Allergic Rhinitis Questionnaire[2] as guide for fulfilling inclusion criteria. After obtaining informed consent 24 participants fulfilling these criteria were considered for inclusion in the study. Subjects were assigned to either of the 2 groups via electronic randomizer using Microsoft Excel for Mac 2011, Version 14.5.6 (150930) (Microsoft Corp., Redwood CA, USA).

The treatment group was given *Ehretia microphylla* tea taken by cupful (200 ml) every 4 hours when awake and placebo (flour dummy pill) taken once nightly, for 7 days. The control group was given loratadine 10 mg / tablet taken once nightly and control tea taken by cupful (200 ml) every 4 hours when awake, also for 7 days.

The Sino-nasal Outcome Test 22 (SNOT22) Questionnaire (Washington University, St. Louis, Missouri) and 10-point Visual Analog Scale (VAS) scores per symptom of sneezing, rhinorrhea, nasal congestion and pruritus were obtained before and after intervention by the blinded outpatient resident physician on duty. Data were encoded and tallied in SPSS version 24 (IBM, 64 bit edition). Statistical analysis of different variables, mean and standard deviation were computed and analyzed using Mann Whitney U test, and Wilcoxon Signed Rank test, and p-values were set with 95% confidence interval.

RESULTS

Twenty four participants, 11 males (45.8%) and 13 females (54.2%) with mean age of 44 years (range 18-77) were randomly assigned to two groups of 12 persons each and completed the study with no adverse events reported. There were no significant differences in age and gender between treatment and control groups.

Comparison of scores of individual SNOT 22 items between groups showed that there were no significant differences in symptoms before and after intervention. *(Table 1, 2)*

Comparison of mean SNOT 22 scores pre- (30.4 ± 17.3) and post-intervention (7.2 ± 6.5) in the loratadine control group with mean SNOT 22 scores pre- (32.5 ± 23.7) and post- (7.8 ± 10.4) intervention in the *Ehretia Microphylla* treatment group showed significant improvement of symptoms in both groups (p = .002 and p = .017, respectively) as shown in *Table 3*.

There were no significant differences in the pre–intervention VAS scores of both groups specifically for symptoms of sneezing, rhinorrhea, nasal congestion and pruritus as shown in *Table 4*. Likewise, there were no significant differences in the post-intervention VAS scores of both groups. There was significant improvement noted in the pre- and post-intervention VAS scores (p = .002 and p = .003) for both groups as shown in *Table 5*.

Table 1. Comparison of the Pre-Intervention SNOT 22 Between the Two Groups

SNOT 22	PRE-INTERVENTION		
	Control Group (n=12)	Treatment Group (n=12)	*p-value*
1. Need to blow nose	2	2	.68 (NS)
2. Sneezing	4	4	1.00 (NS)
3. Runny nose	3.5	4	.44 (NS)
4. Cough	1	1.5	.56 (NS)
5. Post-nasal discharge	1	1	.88 (NS)
6. Thick nasal discharge	0.5	1	.69 (NS)
7. Ear fullness	1	1	.86 (NS)
8. Dizziness	1	1	.74 (NS)
9. Ear pain/pressure	0.5	0.5	.78 (NS)
10. Facial pain/pressure	0.5	0.5	.98 (NS)
11. Difficulty falling asleep	1	1	.90 (NS)
12. Wake up at night	0	1	.44 (NS)
13. Lack of a good night's sleep	0	1	.65 (NS)
14. Wake up tired	0	0	.78 (NS)
15. Fatigue during the day	0	0.5	.66 (NS)
16. Reduced productivity	0	0.5	.73 (NS)
17. Reduced concentration	0	0	.71 (NS)
18. Frustrated/restless/ irritable	1	0.5	.44 (NS)
19. Sad	1	0.5	.44 (NS)
20. Embarrassed	0.5	0	.55 (NS)
21. Sense of smell/taste	0	0	.97 (NS)
22. Congestion/ Obstruction of nose	3	4	.54 (NS)

Table 2. Comparison of the Post-Intervention SNOT 22 Between the Two Groups

SNOT 22	POST-INTERVENTION		
	Control Group (n=12)	Treatment Group (n=12)	*p-value*
1. Need to blow nose	0	0	.95 (NS)
2. Sneezing	1	1	.57 (NS)
3. Runny nose	1	0	.18 (NS)
4. Cough	1	1	1.00 (NS)
5. Post-nasal discharge	0	0	.89 (NS)
6. Thick nasal discharge	0	0	.69 (NS)
7. Ear fullness	0	0	.91 (NS)
8. Dizziness	0	0	1.00 (NS)
9. Ear pain/pressure	0	0	.62 (NS)
10. Facial pain/pressure	0	0	.91 (NS)
11. Difficulty falling asleep	0	0	.32 (NS)
12. Wake up at night	0	0	.57 (NS)
13. Lack of a good night's sleep	0	0	.93 (NS)
14. Wake up tired	0	0	.93 (NS)
15. Fatigue during the day	0	0	1.00 (NS)
16. Reduced productivity	0	0	.58 (NS)
17. Reduced concentration	0	0	1.00 (NS)
18. Frustrated/restless/ irritable	0	0	.44 (NS)
19. Sad	0	0	.91 (NS)
20. Embarrassed	0	0	.51 (NS)
21. Sense of smell/taste	0	0	.95 (NS)
22. Congestion/ Obstruction of nose	1	1	.65 (NS)

Table 3. Comparison of the Pre- and Post-Intervention SNOT 22 Mean Scores

Mean SNOT 22	Control Group (n=12)		Treatment Group (n=12)		
	Mean	SD	Mean	SD	***p-value***
Pre	30.4	17.3	32.5	23.7	.843 (NS)
Post	7.2	6.5	7.8	10.4	.671 (NS)
p-value	.002 (S)		.017 (S)		

Table 4. Comparison of Pre- and Post-Intervention VAS Scores per Symptom of Allergic Rhinitis

A. Sneezing	Control Group (n=12)		Treatment Group (n=12)			
VAS	Mean	SD	Mean	SD	*Mann-Whitney*	***p-value***
Pre	7.8	1.8	7.9	1.6	68.0	*0.843 (NS)*
Post	1.1	0.9	1.0	1.0	65.0	*0.713 (NS)*
Wilcoxon	**3.075**		**3.078**			
P-value	*.002 (S)*		*.002 (S)*			

B. Rhinorrhea	Control Group (n=12)		Treatment Group (n=12)			
VAS	Mean	SD	Mean	SD	*Mann-Whitney*	***p-value***
Pre	6.8	1.4	7.2	1.2	58.5	*.443 (NS)*
Post	1.0	1.0	0.4	0.5	46.5	*.143 (NS)*
Wilcoxon	**3.089**		**3.140**			
P-value	*.002 (S)*		*.002 (S)*			

C. Nasal Congestion	Control Group (n=12)		Treatment Group (n=12)			
VAS	Mean	SD	Mean	SD	*Mann-Whitney*	***p-value***
Pre	6.1	2.5	6.7	2.3	61.5	*.551 (NS)*
Post	1.2	1.0	1.1	1.2	68.5	*.843 (NS)*
Wilcoxon	**3.108**		**3.077**			
P-value	*.002 (S)*		*.002 (S)*			

D. Pruritus	Control Group (n=12)		Treatment Group (n=12)			
VAS	Mean	SD	Mean	SD	*Mann-Whitney*	***p-value***
Pre	6.4	1.2	7.4	1.0	38.0	*.052 (NS)*
Post	1.0	0.7	1.3	0.8	54.0	*.319 (NS)*
Wilcoxon	**3.084**		**3.072**			
P-value	*.002 (S)*		*.002 (S)*			

Table 5. Comparison of the Pre- and Post-Intervention VAS Mean Scores

Mean VAS	Control Group (n=12)		Treatment Group (n=12)		
	Mean	SD	Mean	SD	***p-value***
Pre	2.6	1.6	2.8	2.1	.713 (NS)
Post	0.5	0.5	0.5	0.7	.514 (NS)
p-value	.002 (S)		.003 (S)		

DISCUSSION

In this randomized controlled trial, both *Ehretia microphylla* (*Tsaang Gubat*) decoction tea (plus placebo) and loratadine (plus control tea) improved the symptoms of allergic rhinitis. Comparison of the SNOT22 and VAS scores before and after the intervention both for the loratadine control group and *Ehretia microphylla* treatment group showed improvement in sneezing, rhinorrhea, nasal congestion and pruritus.

The leaves of *Ehretia microphylla* (*Tsaang Gubat*) have been investigated for their anti-inflammatory property. The active components, rosmarinic acid and nitrile glucosides[5,6] are claimed to be anti-allergic substances that counter histamine release from mast cells, rosmarinic acid being one of the particularly active principles. *Ehretia microphylla* has been found useful in the treatment of different inflammatory ailments.[7]

Rosmarinic acid is a strong anti-inflammatory agent according to several studies.[5,8] A study by Osakabe *et al.*, found a significant increase in responder rates for itchy nose, watery eyes and total symptoms in patients with seasonal allergic rhinoconjunctivities supplemented with rosmarinic acid.[9] A decrease in the number of neutrophils and eosinophils in the lavage fluid from the same patients was noted with no adverse events recorded.[9]

Improvement of symptoms of sneezing, rhinorrhea, nasal congestion and pruritus in allergic rhinitis may be attributed to the anti-inflammatory effect of rosmarinic acid, by inhibition of histamine release and inhibition of adhesion molecule, chemokine and eicosnoid synthesis.[6,9] In a study by Oh, rosmarinic acid inhibited IgE production, histamine release, inflammatory cytokine production and COX-2 expression.[10]

This study has several limitations. Since *tsaang gubat* was not compared with loratadine alone (loratadine was combined with a tea), possible interactions of tea with loratadine and effects of tea on allergic rhinitis itself were not accounted for in this study. Moreover, *tsaang gubat* can be prepared in various concentrations and administered in various forms, none of which were accounted for in this trial. *Tsaang*

gubat itself may vary in effect depending on where it is sourced (studies have shown such variation for other herbals). It is important to note that the possible active ingredient(s) in *tsaang gubat* that have anti allergic and anti inflammatory properties were not isolated and may be present in varying concentrations as well.

In conclusion, *Ehretia microphylla* (*Tsaang Gubat*) decoction tea may improve symptoms of allergic rhinitis (sneezing, rhinorrhea, nasal congestion and pruritus) and be taken as an alternative to loratadine in patients with mild intermittent allergic rhinitis. Further clinical trials with more participants may provide stronger evidence for this recommendation.

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