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A randomized, double-blind placebo-controlled study of intranasal standardized cinnamon bark extract for seasonal allergic rhinitis

Eleanor Steels[a], Elizabeth Steels[a,b,*], Pallavi Deshpande[c], Prasad Thakurdesai[c], Satish Dighe[d], Trudi Collet[d]

[a] Evidence Sciences Pty. Ltd., Brisbane, QLD 4001, Australia
[b] The University of the Sunshine Coast, Sippy Downs, QLD 4556, Australia
[c] Indus Biotech Private Limited, 1, Rahul Residency, Plot Nos. 6 & 7, Off Salunke Vihar Road, Kondhwa, Pune, 411048 Maharashtra, India
[d] Innovative Medicines Group, Queensland University of Technology, Brisbane, QLD 4001, Australia

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ABSTRACT

Objectives: The aim of the study was to assess the safety and efficacy of a nasal spray containing a polyphenol-rich standardized extract of cinnamon bark (*Cinnamomum zeylanicum*) (IND02) for the treatment of seasonal allergic rhinitis (SAR).
Methods: This study was a randomized, double-blind, placebo-controlled study conducted in otherwise healthy men and women, aged between 18 and 75 years old, who were experiencing acute SAR symptoms. Participants were randomized in a 1:1 ratio to a nasal spray containing either IND02 (100 μg/100 μL) or matching placebo in each nostril, twice a day, for seven days.
Results: The outcome measures were the rhinoconjunctivitis quality of life questionnaire (RQLQ), the total daily symptom score comprising of day-time nasal, day-time eye, and night-time nasal symptom scores, the Work Productivity and Activities Impairment (WPAI:SHP), the Pittsburgh Sleep Quality Index (PSQI), the Perceived Stress Scale (PSS) and laboratory clinical parameters.
Results: The IND02 group showed a statistically and clinically significant reduction in total RQLQ and the sub-domains; activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function. There was a significant reduction in the total daily symptom score and sub-domains of total day-time nasal, total day-time eye and total night-time nasal symptoms scores, and total work impairment and regular activity impairment in the IND02 group compared with the placebo group after treatment. The laboratory clinical parameters remained within healthy normal reference range.
Conclusion: The use of a nasal spray of a standardized extract of cinnamon bark (IND02) over seven days reduced symptom severity and improved quality of life, work productivity and regular daily activities in participants experiencing SAR.

1. Introduction

Allergic rhinitis (AR) is considered the most common chronic airway disease in the world, affecting between 10% to 30% of the global population[1] and is associated with significant economic and healthcare costs.[2,3] AR is driven by an Immunoglobulin E (IgE)-mediated mast cell degranulation and subsequent histamine release in the nasal mucosa in response to allergen exposure.[2–5] AR manifests symptomatically with nasal symptoms of rhinorrhoea, nasal congestion, sneezing and pruritus and non-nasal symptoms including lacrimation, itchy eyes and eye redness. Other symptoms include headache, post-nasal drip, fatigue, cognitive impairment and sleep disturbance. AR is also associated with asthma, sinusitis and sleep apnoea.[2–5]

Dietary plant-derived polyphenols influence multiple biological pathways and immune cell functions in the allergic immune response and may be effective in the management of allergic disorders.[6,7] Previous research has identified therapeutic polyphenols such as epicatechin (in green tea[8]), caffenic acid (in coffee beans[8]), flavonoids (such as resveratrol and quercetin[9,10]), proanthocynidins (in apples,[11–13] grape seed,[14] and cinnamon bark[15]), and polyphenolics (in blackberry[16]).

The aim of this randomized double-blind clinical study was to assess the safety and efficacy of a nasal spray containing a polyphenol-rich standardized extract of cinnamon bark extract (IND02), in reducing

* Corresponding author at: P.O. Box 1193, New Farm, Brisbane, QLD 4005, Australia.
E-mail address: e.steels@usc.edu.au (E. Steels).

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nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) and improving quality of life.

2. Materials and methods

2.1. Study design

This was a randomized double-blind clinical study to determine the efficacy of a nasal spray containing polyphenol-rich standardized cinnamon (*Cinnamomum zeylanicum Syn: Cinnamomum verum*) bark extract (IND02) in reducing symptoms of SAR in otherwise healthy individuals. It was conducted in Brisbane, Australia in 2018, during the peak pollen season (January–March). The study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by Ethics Committees of Bellberry Pty. Ltd. (Trial No. 201710747) and the Queensland University of Technology (Trial No. 1900000031). It was registered with the Australian New Zealand Clinical Trial Registry (Trial No: 12618000030279) and the Therapeutic Goods Agency.

2.2. Interventions

The investigational products were 15 mL nasal spray bottles with a metered dose of 100 μg/100 μL solution of either cinnamon bark (*Cinnamomum zeylanicum*) (IND02) in saline or matching placebo -without IND02. Both investigational products contained menthol, so the products were identical for blinding purposes and couldn't be identified. IND02 was characterized as per reported procedure.[17] Each nasal spray (100 μL) contained 100 μg of IND02 standardized to total polyphenols not less than 40 μg. Participants were instructed to take two sprays in each nostril per day, once in the morning and once in the evening for seven days. The extract was supplied by Indus Biotech Private Limited, Pune, India.

2.3. Study population

The study population included 60 male and female participants, aged 18–75 years, medically diagnosed with SAR[5] and currently experiencing acute symptoms. They were recruited through clinical trial databases and the public media. Participants provided written informed consent and ceased using all anti-histamines and nasal irrigation sprays for the duration of the study. The exclusion criteria was as follows: those with a history of asthma (other than mild intermittent) and taking asthma medications, or nasal disorders (such as deviated septum, nasal polyposis or chronic rhinosinusitis), acute or significant sinusitis or upper respiratory tract infections and those with an existing serious medical condition (e.g., severe emphysema); those on allergen immunotherapy, suffering with any uncontrolled chronic diseases, acute or chronic infections, had cancer within the last five years, or on prolonged (≥6 weeks) medication with corticosteroids, anticholinergics, or any other drugs that may have an influence on the outcome of the study. Women were excluded if they were pregnant or breast-feeding.

2.4. Randomization and blinding

Randomization (single block, in a 1:1 ratio of investigational products) was performed independently of the investigators using computer generated Random Allocation Software. Nasal spray bottles were numbered sequentially from 1 to 60 and provided to the researchers at commencement of the study. Eligible participants were allocated to the next sequenced numbered study product by the investigators as they were enrolled. Both participants and investigators were blinded to randomization and therefore did not know allocation to active treatment or placebo group (double-blind).

2.5. Study process

Participants attended a pre-study interview for an initial health assessment including lifestyle questions, current medications, medical history and physical assessment. Enrolled participants completed the seven day pre-treatment (run-in medication-free) phase, abstaining from any anti-histamines and recording their SAR symptoms in a daily participant diary. To be eligible for randomization, participants had to have a total daily symptom score of > 12 for at least four consecutive days. Participants also had a blood test to assess total IgE levels ((ImmunoCAP®, Phadia AB, Uppsala, Sweden) and the presence of specific allergens i.e. a grass pollen mix (couch, timothy, johnson, rye, paspalum, and meadow), house dust mite (*Dermatophagoides pteronyssinus*), an animal dander mix (cat, dog, horse and cow), and a mould mix (penicillium, cladosporium, alternaria and aspergillum). The eligible participants completed the following assessments at baseline and completion of treatment (day eight); the Rhinoconjunctivitis quality of life questionnaire (RQLQ),[19] the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP),[20] the Pittsburgh Sleep Quality Index (PSQI),[21] the Perceived Stress Scale (PSS)[22] and completed a blood test for the laboratory clinical parameters (hematological and biochemical) for safety assessments.

Participants were provided with a numbered nasal spray bottle (from 1 to 60) and instructions for administering the investigational product. They were instructed to maintain abstinence from the use of anti-histamines and record their SAR symptom severity as well as medication use, changes to current medications and any illnesses or adverse reactions experienced in the participant symptom diary.[23] At the end of the study (day eight), participants completed the same assessments as that of baseline and returned the participant diary. The nasal spray bottles were also returned and remaining volume noted for compliance assessment.

2.6. Outcomes measures

2.6.1. Primary outcome measures

The RQLQ contains 28 questions in seven domains which assess the impact of allergy symptoms (activity limitation, sleep problems, nose symptoms, eye symptoms, non nose/eye symptoms, practical problems and emotional function). Participants were asked to respond to each question on a 7-point scale from 0 (not impaired at all) to 6 (severely impaired) and recall how bothered they were by their allergy symptoms during the previous week. The overall RQLQ score was calculated as the total of all 28 responses of RQLQ and the individual domain scores are the total of the items in those domains.[19]

The participant symptom diary included three domains of (1) day-time nasal symptoms; nasal congestion, rhinorrhoea, nasal pruritus and sneezing; (2) day-time eye symptoms: tearing (tears), itching, redness and puffy eyes; and (3) night-time nasal symptoms; difficulty going to sleep, night-time awakenings and nasal congestion. Each individual symptom was evaluated on a four-point rating scale ranging from 0 (no symptom) to 3 (severe symptoms) each morning and evening. The total score of each of the three domains (day-time nasal symptoms, day-time eye symptoms and night-time nasal symptoms) and the grand total symptom diary score was calculated.[23]

2.6.2. Secondary outcome measures

The WPAI:SHP questionnaire[20] is comprised of six questions and measures the effect of symptoms on the participants ability to work and perform daily activities. It also evaluates the impact of SAR on missed working hours due to allergy or other reasons, number of hours actually worked, overall work productivity and regular daily activities. Participants are asked to answer each question on a Likert scale of 0 (no effect) to 10 (prevention of activity).

The PSQI questionnaire assesses sleep quality and disturbances

using 19 individual questions grouped into seven domain scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, with the sum of scores giving a total global score.[21]

The PSS is a perceived stress scale, which is a measure of the degree to which situations in a person's life are appraised as stressful. There are 10 questions that ask how unpredictable, uncontrollable, and overloaded respondents find their lives and direct queries about current levels of experienced stress. Participants respond to each question on a 4-point scale of "how often" with 0 being "never" to 4 being "very often", to determine if a person was classified as low, moderate or high stress.[22]

2.6.3. Safety outcome measures

The safety outcome measures were the physical assessments and laboratory clinical parameters (biochemical and hematological analysis). Blood specimens were collected and analysed by Queensland Medical Laboratories, an independent testing facility. Physical examinations (blood pressure and body weight) were assessed at baseline and at completion of the treatment. Tolerability was assessed by recording adverse events in the participant symptom diary and during clinic visits.

2.7. Statistical methods

The sample size of 60 participants was based on a power of 80%, a two tailed *T*-test with $p < 0.05$, calculated a sample size of 24 participants per group, with an allowance for a potential drop-out rate of 20%. Analyses were conducted on an intention to treat (ITT) population basis. Data was analysed using SPSS software (IBM, USA). Depending upon normality test and resultant distribution, data was either parametric (age, weight, height, body mass index (BMI), blood pressure, RQLQ, diary symptom scores and laboratory parameters) or non-parametric (gender and lifestyle parameters and family history of allergies, the number of identified allergen groups, the difference between specific environmental allergens, WPAI:SHP and PSQI scores of individual questions and the total PSS scores) tests. A priori between group differences from baseline to the end of treatment, was undertaken applying independent *t*-tests. Demographic parameters (age, weight, height, BMI and blood pressure) was measured by unpaired *t*-tests. Gender and lifestyle parameters and family history of allergies were analyzed by two-sided Fisher's Exact test for proportion. The number of identified allergen groups was analysed by Chi-square, and the difference between specific environmental allergens was evaluated by the two-sided Fisher's Exact test for proportion for each type of allergy. The RQLQ and diary symptom scores were normally distributed and statistical significance for the total scores and of each domain and change from baseline for total score and of each domain was analysed using unpaired *t*-tests. The minimal clinically important difference (MCID) is defined as the smallest change of a treatment effect that is clinically important.[24] For the RQLQ, the MCID was reported to be 0.5 for both overall and individual domain scores[19] while the diary symptom score of 0.55 was considered as MCID.[24] The WPAI:SHP and PSQI scores of individual questions and the total PSS scores were analysed by Mann-Whitney *U* test. The laboratory clinical parameters data were analysed using unpaired *t*-tests. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographics

Initially, 82 potential participants were screened for eligibility, with 60 men and women aged between 18 and 75 years enrolled in the study (Fig. 1, Table 1). The two groups were evenly matched for age (42.8 ± 14.82 years, IND02 group; 43.7 ± 14.19 years, placebo group) and other indices of health including weight and lifestyle factors, with the majority of participants exercising regularly (n = 19, IND02 group; n = 21, placebo group), habitual coffee drinkers (n = 23, IND02 group; n = 22, placebo group) and reported imbibing of alcohol in a social setting (n = 17, IND02 group; n = 21, placebo group). All participants were non-smokers. A known family history of allergy-related health conditions was reported by 75% of the study cohort (n = 24, IND02 group; n = 21, placebo group) (Table 1).

3.2. Total and individual IgE IG levels of participants

There was a wide range in IgE responses with a similar distribution (range) of total Ig E levels in both groups; IND02 group, range 5–1138 K/L (mean, 150; SD, 252 K/L) and placebo group, range 5–949 K/L, (mean 202, SD 241 K/L). In this study, 76% of participants were sensitive to multiple allergens, with 50% (n = 21) sensitive to two allergen groups, 22% (n = 13) sensitive to three allergen groups and 13% (n = 8) being sensitive to all four allergen groups. Only four (4) participants (IND02 group, n = 3; placebo group, n = 1) had known allergies to grasses that were not included in this test panel. The groups were evenly matched for the number of allergen groups associated with raised IgE levels.

3.3. Effects on RQLQ and SAR symptoms

There was no difference in RQLQ total or subdomain scores for the IND02 and placebo group at baseline (Table 2). However, there was a significant reduction ($p < 0.001$) in RQLQ total score after treatment in the IND02 group (54.0%, 93.17–42.82) compared to the placebo group (15.6%, 89.30–75.33). A significant difference ($p < 0.01$) in the IND02 group compared to the placebo group after treatment for activity limitation (reduction of 41.8% compared to 8.0%), sleep ($p = 0.01$) (46.0% compared to 3.6%), nose symptoms ($p < 0.001$) (reduction of 47.7% compared to 7.0%), eye symptoms ($p < 0.001$) (50.9% reduction compared to 8.8%), non nose/eye symptoms ($p < 0.001$) (50.5% reduction, compared to a 3.3% increase), practical problems ($p < 0.001$) (44.8% reduction, compared to 8.4%) was observed. There was a non-significant reduction in emotional function ($p = 0.156$) between the groups after treatment (IND02, 33.1%; placebo, 7.7%). The change from baseline score to end of treatment (decrease in score from baseline) between both groups was statistically significant ($p < 0.001$) in favour of the IND02 group compared to the placebo group for total RQLQ. The clinically important difference (CID) was also calculated as per reported procedures.[25] Any difference between two comparative groups in a clinical study is considered clinically significant if MCID is achieved (Table 3).

The participants rated the severity of (1) daytime nasal symptoms: nasal congestion, rhinorrhoea, nasal pruritus and sneezing; (2) daytime eye symptoms: tearing (tears), itching, redness and puffy eyes; and (3) night-time nasal symptoms; difficulty going to sleep, night-time awakenings and nasal congestion in the daily symptom diary. There was a significant reduction in the IND02 group for daytime and night-time nose congestion ($p < 0.01$), itchy eyes ($p < 0.01$) and nasal pruritus ($p < 0.05$) after 24 h of treatment and not in other subdomains as compared to placebo group. There was a significant reduction in total daily symptom score from day one to day seven of treatment in favour of the IND02 group compared to the placebo control group ($p < 0.001$) (Table 4). This was reflected in a significant reduction in day-time nasal symptoms ($0 < 0.001$), day-time eye symptoms ($p < 0.05$) and night-time nasal symptoms ($p < 0.05$) for the IND02 group compared to the placebo group. The change from baseline (decrease from baseline) and the CID were also calculated for each individual symptom (Table 5). There was a significant reduction in the total day-time nasal symptoms ($p < 0.001$), nasal congestion ($p = 0.001$), rhinorrhoea ($p < 0.001$), nasal pruritus ($p < 0.05$) and sneezing ($p < 0.05$), in favour of the IND02 group. Similarly, there was a significant difference in total daytime eye symptoms ($p = 0.001$) and

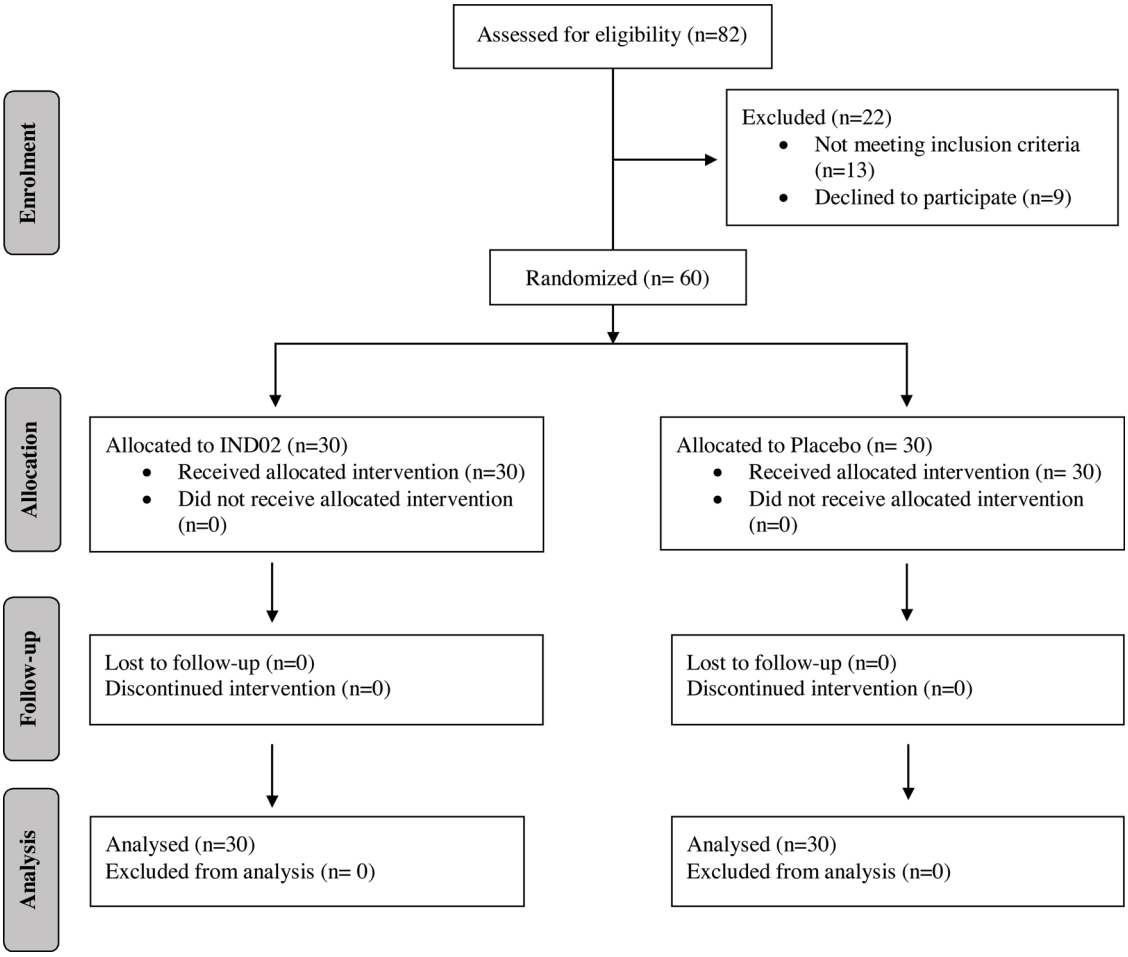

Fig. 1. CONSORT flow chart of the participants.

Table 1
Summary of participant demographics.

Parameters	Placebo (N = 30)	IND02 (N = 30)	p value
Male	12	11	> 0.99
Female	18	19	
Age (years)	43.70 ± 14.19	42.80 ± 14.82	0.81
Weight (kg)	80.19 ± 14.87	79.20 ± 18.95	0.82
Height (cm)	171.70 ± 7.68	170.27 ± 9.82	0.53
BMI (kg/cm^2)	27.13 ± 4.30	27.18 ± 5.32	0.97
Systolic blood pressure (mmHg)	124.87 ± 5.77	124.87 ± 6.53	1.00
Diastolic blood pressure (mmHg)	84.00 ± 5.28	83.33 ± 4.11	0.59
Lifestyle			
Drink Alcohol (n)	21	17	0.42
Drink Coffee (n)	22	23	> 0.99
Exercise (n)	21	19	0.78
Smoking (n)	0	0	> 0.99
Family history of allergies	21	24	0.55

N = 30 in each group. Data is represented as mean ± SD. Data was analysed by Unpaired '*t*' test for each parameter (age, weight, height, BMI, systolic blood pressure and diastolic blood pressure). Data was analysed by two-sided Fisher's Exact test for proportion (contingency table) for each parameter (gender, alcohol drinking, coffee drinking, exercise, smoking and family history of allergies).

the individual symptoms of itching eyes ($p < 0.05$), redness ($p < 0.01$), and puffy eyes ($p < 0.01$), but no difference in tears ($p = 0.425$) in IND02 group as compared to placebo group. The IND02 group recorded a significant improvement in total night-time nasal symptoms ($p < 0.05$), and the individual symptom of night-time awakenings ($p < 0.05$) with a trend to positive improvement in night-time nasal congestion ($p = 0.059$). There was no difference observed in the IND02 and placebo group for difficulty going to sleep ($p = 0.798$).

The study groups were evenly matched in terms of participant numbers in paid work; IND02 group ($n = 20$) and placebo group ($n = 23$) as assessed by the WPAI:SHP. The hours of work and time missed from work was similar between groups. There was a significant increase (improvement) in overall work productivity ($p < 0.05$) and a significant decrease in regular daily activity impairment ($p < 0.001$) in favour of the IND02 group post treatment. (Table 6). There were no statistical differences in the PSQI or the PSS between the groups either at baseline or following treatment.

3.4. Effects on laboratory clinical parameters and health indices

The clinical parameters included complete blood count, liver function tests, renal function, lipids and blood glucose (Table 7). For the duration of the study, all parameters remained within the normal healthy reference range. There was a significant decrease in total white blood cells and neutrophil counts in the IND02 group compared to placebo post-treatment ($p < 0.01$). There were no changes in blood pressure and body weight in either group after treatment. There were reports of worsening of SAR symptoms in two participants in the IND02 group (headache, swollen bottom lip) and two participants in the placebo group (bleeding right nostril, itchy skin). There were no serious adverse events reported.

4. Discussion

The results of this present study demonstrated that the intranasal

Table 2
Comparison of RQLQ total and subdomain scores between groups at baseline and completion of treatment.

Parameters	Baseline			Completion		
	Placebo	IND02	p value	Placebo	IND02	p value
Total RQLQ	89.30 ± 25.18	93.17 ± 30.02	0.591	75.33 ± 24.93	42.83 ± 24.26	< 0.001
Activity limitation	9.67 ± 3.94	10.53 ± 3.63	0.379	8.90 ± 3.80	6.13 ± 3.14	< 0.01
Sleep problems	8.27 ± 4.93	8.83 ± 4.23	0.634	7.97 ± 5.13	4.77 ± 4.06	=0.01
Nose symptoms	15.23 ± 4.56	14.77 ± 4.97	0.706	14.17 ± 4.79	7.73 ± 4.52	< 0.001
Eye symptoms	12.50 ± 5.12	13.03 ± 6.00	0.712	11.40 ± 5.11	6.40 ± 5.04	< 0.001
Nonnose/eye symptoms	21.33 ± 8.61	22.83 ± 8.31	0.495	22.03 ± 8.13	11.30 ± 7.53	< 0.001
Practical problems	11.87 ± 3.63	11.77 ± 4.70	0.927	10.87 ± 4.00	6.50 ± 4.24	< 0.001
Emotional function	10.43 ± 4.38	11.40 ± 5.29	0.444	9.63 ± 4.82	7.63 ± 5.91	0.156

N = 30 in each group. Data is represented as mean ± SD. Data was analysed by Unpaired '*t*' test for total score of each domain.

Table 3
Comparison of RQLQ scores between groups at baseline and completion of treatment.

Parameters	Change from baseline		p value	CID	MCID achieved?
	Placebo	IND02			
Total RQLQ (score)	13.97 ± 14.95	50.33 ± 21.85	< 0.001	36.37	Yes
Activity limitation (score)	0.77 ± 2.47	4.40 ± 3.93	< 0.001	3.63	Yes
Sleep problems (score)	0.30 ± 3.00	4.07 ± 2.39	< 0.001	3.77	Yes
Nose symptoms (score)	1.07 ± 2.57	7.03 ± 4.46	< 0.001	5.97	Yes
Eye symptoms (score)	1.10 ± 2.95	6.63 ± 3.74	< 0.001	5.53	Yes
Non-nose/eye symptoms (score)	−0.70 ± 4.37	11.53 ± 6.24	< 0.001	12.23	Yes
Practical problems (score)	1.00 ± 2.44	5.27 ± 3.76	< 0.001	4.27	Yes
Emotional function (score)	0.80 ± 2.43	3.77 ± 3.80	=0.001	2.97	Yes

N = 30 in each group. Data is represented as mean ± SD. Data was analyzed by Unpaired '*t*' test for total score of each domain, Change from baseline (decrease in score from baseline) was calculated as difference between before starting the treatment and last day of treatment. CID = clinically important difference. CID - clinically important difference, MCID – Minimum clinically important difference.

Table 4
Comparison of daily symptom scores between groups at baseline and completion of treatment.

Parameters	Baseline			Completion		
	Placebo	IND02	p value	Placebo	IND02	p value
Total day-time nasal symptoms	11.03 ± 4.80	9.30 ± 5.15	0.183	12.37 ± 4.77	6.90 ± 4.63	< 0.001
Total day-time eye symptoms	6.57 ± 5.09	5.67 ± 5.35	0.507	7.33 ± 4.92	4.60 ± 4.23	< 0.05
Total night-time symptoms	3.47 ± 2.62	2.97 ± 2.43	0.447	3.50 ± 2.29	2.13 ± 1.78	< 0.05
Total diary symptoms	21.07 ± 10.46	17.93 ± 11.83	0.282	23.20 ± 9.96	13.63 ± 8.92	< 0.001

N = 30 in each group. Data is represented as mean ± SD. Data was analysed by Unpaired '*t*' test for each parameter for each day.

Table 5
Change scores for total and individual symptoms for both groups.

Symptoms (score)	Change from baseline		p value	CID	MCID achieved?
	Placebo	IND02			
Nose congestion (score)	0.00 ± 1.08	0.97 ± 1.07	= 0.001	0.97	Yes
Rhinorhoea (score)	0.20 ± 0.92	1.13 ± 0.90	< 0.001	0.93	Yes
Nasal pruritus (score)	0.47 ± 1.14	1.17 ± 0.99	< 0.05	0.70	Yes
Sneezing (score)	0.33 ± 1.15	1.03 ± 0.89	< 0.05	0.70	Yes
Total day-time nasal (score)	1.90 ± 4.11	8.57 ± 4.58	< 0.001	6.67	Yes
Tears (score)	0.30 ± 1.09	0.50 ± 0.82	0.425	0.20	No
Itchy eyes (score)	0.30 ± 1.49	1.10 ± 1.16	< 0.05	0.80	Yes
Red eyes (score)	−0.10 ± 1.24	0.77 ± 1.01	< 0.01	0.87	Yes
Puffy eyes (score)	−0.10 ± 1.00	0.63 ± 0.76	< 0.01	0.73	Yes
Total day-time eye (score)	0.97 ± 6.43	6.33 ± 4.96	= 0.001	5.37	Yes
Difficulty going to sleep (score)	0.27 ± 0.91	0.33 ± 1.09	0.798	0.07	No
Night time awakenings (score)	0.03 ± 0.93	0.63 ± 1.27	< 0.05	0.60	Yes
Nose congestion at night (score)	0.33 ± 1.24	0.90 ± 1.02	0.059	0.57	Yes
Total night-time nasal (score)	0.57 ± 2.30	1.87 ± 2.70	< 0.05	1.30	Yes
Total diary symptoms (score)	3.43 ± 11.16	16.33 ± 9.91	< 0.001	12.90	Yes

N = 30 in each group. Data is represented as mean ± SD. Change from baseline was calculated as difference between before starting the treatment (evening score of last day of pre-treatment phase) and last day of treatment (evening score of last day of treatment). Data was analysed by Unpaired '*t*' test for each parameter for each day, CID = Clinically important difference, MCID – Minimum clinically important difference.

Table 6
Comparison of WPAI:SHP between groups at baseline and completion of treatment.

Parameters	Baseline			Completion		
	Placebo	IND02	p value	Placebo	IND02	p value
Currently employed (number)	23	20	0.567	23	20	0.567
No. of working hours missed due to allergy	0.61 ± 2.04	0.30 ± 1.13	1.000	0.44 ± 2.09	0.00 ± 0.00	0.340
No. of working hours missed due to other reasons	0.35 ± 1.67	0.95 ± 2.35	0.350	0.35 ± 1.67	0.15 ± 0.67	0.973
No. of hours actually worked	35.00 ± 15.80	32.30 ± 15.23	0.410	35.26 ± 14.56	33.20 ± 17.24	0.543
Effect on work productivity (score)	5.00 ± 2.93	4.85 ± 2.89	0.712	4.65 ± 3.02	2.65 ± 2.06	0.017
Effect on regular daily activities (score)	5.13 ± 2.35	5.17 ± 2.69	0.921	5.20 ± 2.66	2.83 ± 2.32	0.001

Data is represented as mean ± SD. Data was analysed by Mann-Whitney *U* test on scores of individual questions.

Table 7
Comparison of laboratory parameters between groups at baseline and completion of treatment.

Parameters	Baseline			Completion		
	Placebo	IND02	p value	Placebo	IND02	p value
Hemoglobin (g/L)	141.77 ± 15.34	137.00 ± 10.70	0.168	141.17 ± 13.11	136.79 ± 11.84	0.188
RBC ($x10^{12}$/L)	4.84 ± 0.57	4.64 ± 0.48	0.146	4.79 ± 0.48	4.59 ± 0.43	0.097
Hematocrit (%)	0.43 ± 0.04	0.42 ± 0.03	0.231	0.42 ± 0.04	0.41 ± 0.03	0.177
MCV (fL)	89.00 ± 4.91	90.47 ± 4.87	0.25	88.63 ± 5.13	90.10 ± 5.07	0.273
MCH (pg)	29.70 ± 2.00	29.90 ± 2.24	0.717	29.57 ± 2.00	29.90 ± 2.32	0.56
Platelets ($x10^9$/L)	286.10 ± 67.34	262.80 ± 43.13	0.116	281.33 ± 67.23	263.66 ± 51.39	0.262
WBC ($x10^9$/L)	7.73 ± 2.00	6.75 ± 1.91	0.057	7.77 ± 1.85	6.39 ± 1.27	0.002
Neutrophils ($x10^9$/L)	4.37 ± 1.51	3.74 ± 1.58	0.122	4.40 ± 1.49	3.40 ± 1.01	0.004
Lymphocytes ($x10^9$/L)	2.37 ± 0.75	2.12 ± 0.54	0.145	2.37 ± 0.77	2.12 ± 0.53	0.155
Monocytes ($x10^9$/L)	0.59 ± 0.14	0.60 ± 0.22	0.888	0.60 ± 0.13	0.56 ± 0.17	0.305
Eosinophils ($x10^9$/L)	0.33 ± 0.23	0.25 ± 0.20	0.136	0.34 ± 0.24	0.27 ± 0.24	0.308
Basophils ($x10^9$/L)	0.07 ± 0.04	0.06 ± 0.03	0.227	0.06 ± 0.04	0.06 ± 0.03	0.281
Sodium (mmol/L)	139.90 ± 1.77	140.07 ± 2.05	0.737	139.97 ± 1.96	140.52 ± 1.75	0.259
Potassium (mmol/L)	4.28 ± 0.32	4.14 ± 0.24	0.061	4.14 ± 0.26	4.18 ± 0.34	0.65
Chloride (mmol/L)	104.63 ± 2.30	104.23 ± 1.72	0.448	103.87 ± 2.37	104.66 ± 2.22	0.194
Bicarbonate (mmol/L)	25.67 ± 2.20	26.27 ± 2.07	0.281	25.97 ± 2.82	25.59 ± 3.72	0.659
Glucose (mmol/L)	5.09 ± 1.00	5.35 ± 1.69	0.471	5.17 ± 1.49	5.50 ± 1.42	0.388
Urea (mmol/L)	5.03 ± 0.76	5.36 ± 1.59	0.303	5.30 ± 1.14	5.32 ± 1.27	0.931
Creatinine (umol/L)	69.63 ± 11.79	68.77 ± 14.74	0.802	71.10 ± 10.91	69.24 ± 11.89	0.534
eGFR (mL/min)	87.23 ± 5.94	88.20 ± 4.44	0.478	87.97 ± 4.21	88.69 ± 3.66	0.485
Uric acid (mmol/L)	0.33 ± 0.09	0.32 ± 0.10	0.677	0.34 ± 0.09	0.32 ± 0.08	0.316
Total bilirubin (mmol/L)	9.03 ± 2.93	10.50 ± 5.17	0.181	9.47 ± 3.47	10.03 ± 4.93	0.61
ALP (U/L)	72.90 ± 18.88	69.43 ± 25.30	0.55	72.70 ± 16.02	67.86 ± 24.39	0.37
GGT (U/L)	33.63 ± 23.81	29.97 ± 19.73	0.519	33.97 ± 24.38	29.55 ± 16.91	0.424
ALT (U/L)	35.00 ± 21.11	28.40 ± 13.83	0.157	34.43 ± 21.75	30.00 ± 16.22	0.38
AST (U/L)	30.03 ± 10.02	26.67 ± 9.66	0.19	29.73 ± 9.59	27.21 ± 11.65	0.366
Lactate dehydrogenase (U/L)	187.00 ± 32.64	179.17 ± 31.94	0.351	184.63 ± 29.96	182.72 ± 33.71	0.819
Calcium (mmol/L)	2.33 ± 0.11	2.37 ± 0.10	0.193	2.35 ± 0.08	2.36 ± 0.13	0.761
Phosphate (mmol/L)	1.05 ± 0.16	0.98 ± 0.24	0.209	1.03 ± 0.19	1.01 ± 0.14	0.696
Total protein (g/L)	71.97 ± 3.36	70.23 ± 4.21	0.083	71.07 ± 3.54	69.38 ± 4.90	0.134
Albumin (g/L)	42.27 ± 2.16	41.83 ± 2.87	0.511	42.03 ± 2.39	41.48 ± 3.12	0.449
Globulin (g/L)	29.70 ± 2.76	28.40 ± 2.54	0.062	29.00 ± 2.36	28.00 ± 2.75	0.139
Cholesterol (mmol/L)	5.26 ± 0.88	5.12 ± 0.90	0.552	5.18 ± 1.08	5.10 ± 0.81	0.728
Triglyceride (mmol/L)	1.48 ± 0.89	1.33 ± 0.86	0.508	1.52 ± 1.12	1.50 ± 0.92	0.92

N = 30 in each group. Data is represented as mean ± SD. Data is represented as mean ± SD. Data was analysed by Unpaired 't' test for each parameter. RBC, red blood cell; MCV, mean cell volume; MCH, mean cell hemoglobin; WBC, white blood cell; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

spray of a polyphenol-rich standardized cinnamon bark extract (IND02) significantly improved quality of life and reduced the severity of nasal and non-nasal symptoms associated with SAR without serious adverse events. The positive clinical effect in nasal, eye and night-time symptoms was observed within 24 h of application and was accompanied by improvements in work productivity and general activity by the end of treatment.

These results are in line with the previous clinical study with a four-week treatment period.[26] However, the present study demonstrated that the beneficial effects were observed after short-term treatment of a seven day timeframe. Furthermore, the study also demonstrated that the therapy as a sole treatment, was effective in the management of allergies induced by allergens across the various classes of environmental allergies, as anti-histamines were excluded in the pre-treatment and treatment phases of the study.

The results of the present study are also supported by earlier reports of cinnamon bark extract on SAR symptoms and the underlying pathophysiology. The combination product, an orally administered tablet, containing 150 mg each of cinnamon bark extract, *Malpighia glabra* and *Bidens pilosa*, significantly reduced nasal symptom scores during the eight hours following a nasal allergen challenge and marginally inhibited the release of prostaglandin D2 into nasal lavage fluid.[27] Cinnamon bark extract is also reported to act on cytokines and interleukins which play a role in nasal inflammation.[28] Polyphenols extracted from *C. zeylanicum* was found to reduce the symptoms associated with SAR *in vivo*.[15]

Resveratrol, a stilbenoid polyphenol, along with a positive control (budesonide) and placebo group, when administered as nasal sprays,

was shown to decrease clinical symptoms as well as reduce IgE, interleukin-4, tumour-necrosing factor-α, and eosinophil levels.[29] Furthermore, the results obtained from a RCT study of an orally-dosed apple extract (52% procyanidins, 8% flavonionds, 9% catechins) for dust mite allergy which showed improvement in swelling of the nasal turbinate as well as providing clinical relief,[30] supports the benefits of polyphenol-rich extracts for managing symptoms of SAR. Interestingly, polyphenols derived from apple prevent degranulation by promoting the stability of granulocytes while concurrently inhibiting histamine release along with dose-dependent inhibitory effect on the activity of hyaluronidase, an enzyme associated with inflammation which is also released by degranulation, thereby suppressing inflammation.[12]

The collective research suggests polyphenol-rich extracts may provide a uniquely different mechanism of action to current anti-histamines medications, and modulate the onset of allergic inflammation by acting directly on immune cells.[12,29–31] It has also been reported that polyphenols such as flavones, flavone-3-ols, catechins, anthocyanidins, flavanones, procyanidins and resveratrol can suppress antigen-specific IgE antibody formation.[6] Quercetin, a flavonoid that has been shown to stabilise mast cells and inhibit histamine release via basophils, also decrease leukotriene synthesis and reduce the release of histamine and other mediators.[10,31–33] Most recently, type-A procyanidins polyphenols from *C. zeylanicum* were shown to inhibit induced mast cell degranulation and reduce the levels of histamine, β-beta-hexasominidase and Interleukin-4.[34]

In conclusion, the polyphenol-rich standardized cinnamon bark extract nasal spray was found to not only decrease the severity of the symptoms of SAR, but also reduce general activity impairment along with a corresponding improvement in quality of life and work productivity.

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Declaration of Competing Interest

None.

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