

Efficacy of a Traditional Iranian Almond-Based Formulation (*Prunus dulcis* Laoq) in Treatment-Resistant Chronic Cough: A Randomized Double-Blind Placebo-Controlled Trial

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ABSTRACT

Chronic cough often persists despite standard treatments, highlighting the need for alternative therapies. *Prunus dulcis* Laoq, a traditional Iranian herbal formulation, has historically been used for respiratory relief. This study evaluated its efficacy in managing treatment-resistant chronic cough. A randomized, double-blind, placebo-controlled trial was conducted with 100 participants. Patients received either *Prunus dulcis* Laoq or a placebo for 14 days. Symptom progression was assessed using a validated cough severity questionnaire. Data were analyzed using repeated measures ANOVA and mixed-effects models. The Laoq group showed a significant reduction in cough severity compared to placebo ($F = 9.48$, $p = 0.03$). Improvements were consistent across demographic subgroups. No adverse effects were reported, supporting the formulation's safety. *Prunus dulcis* Laoq demonstrated clinical efficacy in reducing symptoms of treatment-resistant chronic cough and may serve as a safe complementary therapy. Further studies are recommended to assess its long-term effects and potential broader applications.

Keywords: Iranian traditional medicine, Herbal therapy, Chronic cough, Randomized controlled trial, Complementary medicine

INTRODUCTION

Cough is a vital reflex that protects the respiratory system by clearing the airways of secretions, irritants, foreign particles, and microorganisms. It is one of the most common symptoms of respiratory conditions, often serving as an early indicator of underlying health issues [1-2]. While commonly associated with infections, cough can also result from allergies, lung cancer, or environmental triggers, highlighting its broad diagnostic significance [3]. Understanding its causes and variations helps healthcare providers diagnose and manage respiratory and systemic conditions more effectively [4].

Chronic cough, defined as a persistent cough lasting more than eight weeks, can significantly impact a person's health and well-being. It often accompanies other symptoms such as wheezing, shortness of breath, chest pain, and throat irritation. Conditions like asthma, Chronic Obstructive Pulmonary Disease (COPD), Gastroesophageal Reflux Disease (GERD), and postnasal drip are common causes, while environmental factors such as air pollution and smoking can also contribute [5]. Beyond physical discomfort, chronic cough can interfere with sleep, strain muscles, cause fatigue, and even lead to incontinence. Additionally, its persistence may affect mental health, increasing the risk of anxiety, depression, and social isolation [6]. Thus, identifying its root cause is essential for effective treatment and management. Given these challenges, traditional medicine has gained attention as a complementary approach. Traditional medicine involves the use of medicinal plants, minerals, and natural substances to treat and prevent diseases, a practice deeply rooted in many cultures worldwide. Herbal medicine, a subset of traditional medicine, relies on plant-based formulations known for their therapeutic benefits [7-8-9]. In recent years, herbal treatments have become increasingly popular due to their natural origins, lower risk of side effects, and holistic approach to well-being. Additionally, their accessibility and affordability make them a viable healthcare option for many individuals [10-11].

Among the numerous traditional remedies for cough, several natural ingredients have been recognized for their effectiveness. The World Health Organization (WHO) endorses medicinal substances such as honey [12-13], ginger [14], licorice root [15], thyme [16-17], and almonds [18] for cough relief. Combining these remedies with modern treatments offers an opportunity to improve patient outcomes, particularly for conditions like chronic cough [19].

One such traditional preparation is Laoq, an herbal formulation described in Iranian traditional medicine for respiratory conditions. Designed to pass gently through the throat, Laoq maximizes its medicinal effects [20]. This edible remedy falls between a solid and liquid state, with a viscosity similar to honey. It shares characteristics with Linctus, a thick medicinal liquid, and Lozenge, a dissolvable medicinal confection [21].

This study aims to investigate the therapeutic potential of *Prunus dulcis* Laoq, a traditional Iranian almond-based formulation, as a complementary treatment for chronic cough. The primary objective is to determine its effectiveness in reducing cough frequency and severity in patients with treatment-resistant chronic cough, offering a potential alternative for individuals who have not responded to conventional therapies.

Study Design and Participants

This study was a randomized, double-blind clinical trial (IRCT20210315050707 N1), designed to assess the efficacy of *Prunus dulcis* Laoq as a complementary treatment for chronic cough. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMEDREC.1400.176).

Patients eligible for this study met the following criteria: diagnosis of chronic cough persisting for more than eight weeks, confirmed by pulmonologists at Imam Reza Hospital, Tabriz University of Medical Sciences. Treatment-resistant chronic cough, defined as persistent cough symptoms despite standard pharmacological treatments, including bronchodilators, corticosteroids, proton pump inhibitors (PPIs), and antihistamines. Age ≥ 14 years to ensure accurate symptom assessment and compliance with treatment protocols. No active respiratory infections or acute exacerbations at the time of enrollment. Willingness to adhere to study protocols, including using the assigned formulation and participating in follow-up evaluations. Participants were excluded if they met any of the following conditions: presence of underlying conditions affecting cough response or treatment efficacy, including: uncontrolled diabetes (HbA1c $> 8\%$), hypertension (SBP > 160 mmHg or DBP > 100 mmHg), renal failure (eGFR < 30 mL/min/1.73 m²), history of adverse reactions to herbal formulations, particularly *Prunus dulcis* or other ingredients used in the Laoq formulation., current use of immunosuppressive drugs that could interfere with study outcomes, pregnancy or lactation, due to potential pharmacological interactions, recent history of smoking or exposure to environmental toxins that could confound cough severity assessments, inability to comply with study requirements, including follow-up visits and prescribed treatment regimen.

Participants were randomly assigned into two study arms using block randomization (block size = 4). To ensure eligibility, all participants underwent preliminary health assessments, including: Medical history review, physical examination, and blood sugar measurement (to exclude uncontrolled diabetes), blood pressure assessment (to exclude hypertension). These screening evaluations confirmed adherence to the study's inclusion and exclusion criteria, ensuring participant safety and reliable outcomes.

Intervention and Blinding

Participants were divided into two treatment groups: the Experimental Group (Received Laoq formulation) and the Control Group (Received placebo). To maintain blinding, random assignment was performed, and group allocations were concealed from both participants and researchers throughout the study.

Almond Laoq Formulation and Administration

The Laoq formulation was meticulously prepared under the supervision of Tabriz University of Medical Sciences at the Traditional Medicine Health Center of Baharan. This herbal-based remedy contained natural ingredients known for their potential respiratory benefits, including: almond kernels (*Prunus dulcis*), Gum Arabic, Starch, Catechu, Sweet almond extract, Raw pumpkin seeds, Sugar, and rose water (used as the base material for consistency and absorption).

Quality Control and Safety Measures

To ensure purity and safety, the formulation underwent rigorous microbiological testing in a controlled laboratory environment: Cultured on Sabouraud dextrose agar (SDA) and blood agar (BA) to detect potential microbial and fungal contamination. Upon confirmation of purity, 5-gram sachets were prepared for distribution.

Intervention and Participant Instructions

Participants were instructed to dissolve the sachet contents in their mouth three times daily for 14 days. Avoid drinking water, tea, or coffee for 30 minutes post-use to ensure maximum absorption and therapeutic effectiveness.

Placebo Group Protocol

The placebo formulation was designed to mimic the Laoq formulation in appearance, taste, texture, and viscosity, ensuring complete blinding. However, it lacked active medicinal ingredients, serving as a control to evaluate the true effectiveness of Laoq. Participants in the placebo group followed the same dosage and usage instructions as the treatment group. Research staff maintained neutral communication during follow-ups to avoid influencing patient perceptions.

Daily Follow-Up and Monitoring Procedures

To ensure treatment adherence, track symptom progression, and maintain study integrity, all participants (both treatment and placebo groups) underwent daily follow-up calls. The follow-up protocol included daily symptom evaluation calls.

Checklist-Based Monitoring

A predefined checklist was used to track: cough frequency and severity changes. Presence of side effects such as throat irritation, gastrointestinal discomfort, or allergic reactions. Overall health and well-being throughout the study. In cases of adverse reactions, participants were guided on appropriate action, and adjustments were documented.

Compliance Verification and Reminders

Participants were regularly reminded of proper usage, including sachet dissolution technique and post-use restrictions (avoiding liquids for 30 minutes). Any missed doses or inconsistencies were recorded for further analysis.

Blinded Follow-Up for the Placebo Group

Placebo recipients were unaware of their group assignment, ensuring psychological neutrality. Researchers avoided leading questions that might indicate a participant was receiving the placebo. Any reported symptom improvements in the placebo group were noted for potential placebo effect analysis.

A researcher-developed questionnaire was designed and validated to assess cough symptoms and treatment response in patients with chronic cough. This instrument consisted of 25 items that were scored to evaluate treatment effectiveness (Table 1 supplement: Cough Assessment Questionnaire). Participants were asked to rate the severity of their headaches using a structured five-point scale ranging from 0 to 4. A score of 0 indicated the complete absence of headache, while a score of 4 represented the highest level of intensity experienced. Patients selected the most appropriate value corresponding to their perceived headache severity.

Validity and Reliability

A panel of eight specialists, including pulmonologists, traditional medicine practitioners, herbal medicine experts, medical historians, and epidemiologists, assessed the questionnaire. These aspects were qualitatively evaluated to confirm the questionnaire's relevance and comprehensiveness in capturing key symptoms and treatment outcomes. Internal consistency was tested using Cronbach's alpha, yielding a strong reliability coefficient ($\alpha = 0.876$), indicating high internal coherence among questionnaire items. Since external consistency could not be tested and the questionnaire was not repeatable, a checklist based on its core items was employed for continuous monitoring. Patients were followed up weekly via phone calls to document symptom progression, and reminders regarding proper usage of the formulation were provided during these interactions. To further confirm the accuracy of the checklist in assessing treatment response, a subset of 40 cases was randomly selected and compared with direct clinical evaluation by a pulmonologist. The checklist demonstrated 100% sensitivity and 100% specificity, reinforcing its diagnostic precision and reliability in symptom tracking.

Sample Size and Statistical Analysis

A total of 100 participants were recruited for this study, with 50 individuals in each group: Experimental Group ($n = 50$) – received the Laoq formulation. Placebo Group ($n = 50$) – Received an inactive placebo identical in appearance and taste.

The sample size was determined based on a 95% confidence level and 80% statistical power, ensuring adequate representation to detect treatment effects. Consideration was given to potential dropouts, and necessary adjustments were made to maintain statistical robustness. Descriptive statistics were used to calculate mean $\pm$ standard deviation (SD) and median values. Reliability analysis was conducted using Cronbach's alpha. Repeated measures analysis (Simple and Multiple) and Friedman tests were applied to evaluate treatment effectiveness. Data were analyzed using SPSS 24 software (SPSS Inc., Chicago). This study employed the Intention-to-Treat approach to ensure all participants were analyzed in their originally assigned groups, regardless of adherence to the intervention. This technique maintains the integrity of randomization and minimizes bias in outcome evaluation.

RESULTS

A total of 100 patients were enrolled in the study (50 in the intervention group, 50 in the placebo group), with final retention rates of 45 in the intervention group and 48 in the placebo group, as shown in figure 1. The baseline demographic characteristics presented in Table 1 confirm no statistically significant differences between groups in age ($p = 0.196$), gender distribution ($p = 0.366$), education level, smoking habits, marital status, or water pipe usage (all $p > 0.05$), ensuring comparable starting conditions.

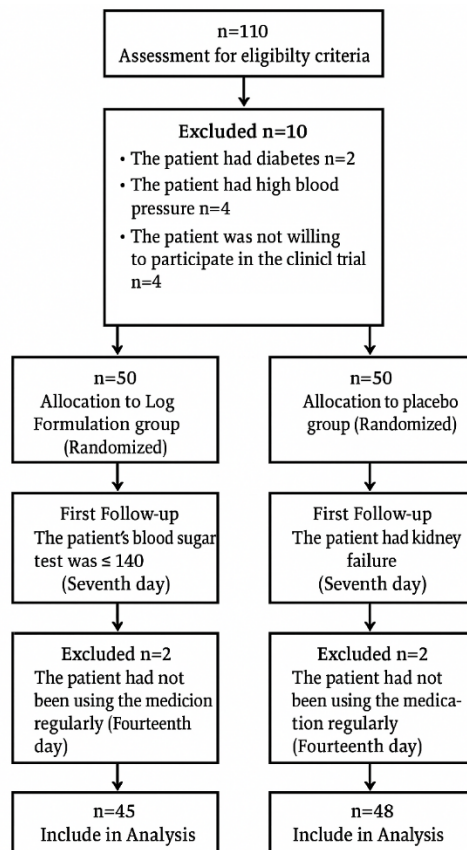


Fig. 1 Flowchart of study inclusion, allocation, and follow-up.

Table 1 Comparison of some demographical and clinical characteristics of patients (frequency (%) and means (SD)) in two groups)

		Intention to treat population			Final population			
Characteristic, Variable		Laog Group;n(%) (n=46)	Formulation Placebo (%) (n=48)	Group;n	P-Value	Laog Group;n (%) (n=45)	Formulation Placebo Group;n (%) (n=48)	p-value
Gender	Male	22 (47.8)	19 (39.6)		0.420	22 (48.9)	19 (36.9)	0.366
	Female	24 (52.2)	29 (60.4)			23 (51.1)	29 (60.4)	
Marital Status	Single	16 (34.8)	30 (65.2)		0.63	15 (33.3)	19 (39.6)	0.391
	married	19 (39.6)	29 (60.4)			30 (66.7)	29 (60.4)	
Smoking	No	21 (45.7)	25 (54.3)		0.409	20 (44.4)	26 (54.2)	0.349
	Yes	26 (54.2)	22 (45.6)			25 (55.6)	22 (45.8)	
Water pipe	No	27 (64.3)	15 (35.7)		0.654	27 (65.9)	14 (34.1)	0.771
	Yes	33 (68.8)	15 (31.3)			33 (68.8)	15 (31.3)	
allergies	No	26 (57.8)	19 (42.2)		0.726	26 (59.1)	26 (54.2)	0.634
	Yes	26 (54.2)	22 (45.6)			18 (40.9)	22 (45.8)	
Job Status	Jobless	2 (4.3)	18 (0.0)		0.260	1 (2.2)	0 (0.0)	0.377
	Household	18 (39.1)	14 (29.2)			18 (40)	14 (29.2)	
	Student	11 (23.9)	16 (33.3)			11 (24.4)	16 (33.3)	
	Staff	5 (10.9)	10 (20.8)			5 (11.1)	10 (20.8)	
	Worker	10 (21.7)	8 (16.7)			10 (22.2)	8 (16.7)	
Education Status	Elementary	13 (28.3)	7 (14.6)		0.367	13 (28.9)	7 (14.6)	0.386
	Middle	7 (15.2)	6 (12.5)			6 (13.3)	6 (12.5)	
	Diploma	9 (19.6)	12 (25)			9 (20)	12 (25)	
	College	17 (37)	23 (47.9)			17 (37.8)	23 (47.9)	
BMI	18.5-24.9	21 (45.7)	15 (31.3)		0.151	20 (44.4)	15 (31.3)	0.189
	>25	25 (54.3)	33 (68.6)			25 (55.6)	33 (68.6)	
Age;Y		44.76 (20.09)	39.73 (20.39)		0.232	45.2 (20.09)	39.79 (20.39)	0.196

Symptom Progression and Treatment Efficacy

The effectiveness of *Prunus dulcis* Laoq in managing chronic cough was assessed through a repeated measures analysis, capturing symptom score at three time points: baseline (Day 0), midpoint (Day 7), end of Treatment (Day 14). A linear decline in cough scores was observed in the intervention group, indicating sustained symptom improvement over time (F Greenhouse-Geisser = 32.74, $p < 0.001$). In contrast, no consistent trend was detected in the placebo group, highlighting the efficacy of the Laoq formulation. A direct between-group

(intervention and placebo groups) comparison confirmed statistically significant differences in cough score reductions ($F = 9.48$, $p = 0.03$), reinforcing treatment impact (Fig. 2).

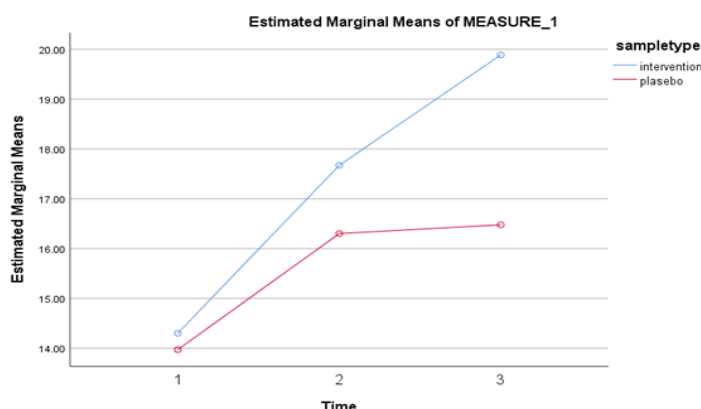


Fig. 2 Comparisons of scores in three -time point (beginning of treatment, at the end of 1 week and the end of the treatment period) in intervention group and placebo group.

Analysis with Additional Variables

A mixed repeated-measures analysis was conducted to assess additional variables. In the presence of the gender variable, a significant linear trend in cough scores was observed (Greenhouse-Geisser $F = 32.93$, $p < 0.0001$). The difference between intervention and control groups remained significant ($F = 8.79$, $p = 0.004$), while no significant differences in cough scores were found between males and females ($F = 1.20$, $p = 0.275$).

When age was considered, a significant linear trend in cough scores was observed (Greenhouse-Geisser $F = 8.037$, $p < 0.0001$). The difference between intervention and control groups remained significant ($F = 4.23$, $p = 0.045$), but no significant correlation was found between age and cough scores ($F = 1.26$, $p = 0.149$).

In the presence of education level, a significant linear trend was found in cough scores (Greenhouse-Geisser $F = 24.71$, $p < 0.0001$). The difference between intervention and control groups remained statistically significant ($F = 10.69$, $p = 0.002$), although no significant differences in cough scores were observed across education levels ($F = 1.98$, $p = 0.124$).

When marital status was included, a significant linear trend in cough scores was identified (Greenhouse-Geisser $F = 32.99$, $p < 0.0001$). The difference between intervention and control groups remained significant ($F = 9.98$, $p = 0.002$), while marital status itself did not show a significant effect on cough scores ($F = 1.51$, $p = 0.223$).

After adjusting for BMI, the effectiveness of treatment remained statistically significant across time points (Greenhouse-Geisser $F = 65.0$, $p < 0.001$; between-group effect $F = 8.32$, $p = 0.005$). BMI didn't show a significant effect on cough scores ($F = 1.70$, $p = 0.141$).

Sensitivity and Specificity Validation

To further evaluate the accuracy of symptom assessment, 40 randomly selected cases were compared between checklist evaluations and pulmonologist examinations. The checklist exhibited 100% sensitivity and 100% specificity, indicating its diagnostic precision in monitoring patient progress.

Severity of Cough

Figure 3 illustrates a bar chart comparing cough severity between the intervention and control groups at three time points. The intervention group initially had a higher median severity (4) than the control group (3). Over time, the intervention group experienced a notable reduction, decreasing to 2 at time point 2 and 1 at time point 3, while the control group's severity remained stable around 3. The intervention group demonstrated a significant decline in cough severity across the observed periods, while the control group's severity remained relatively unchanged.

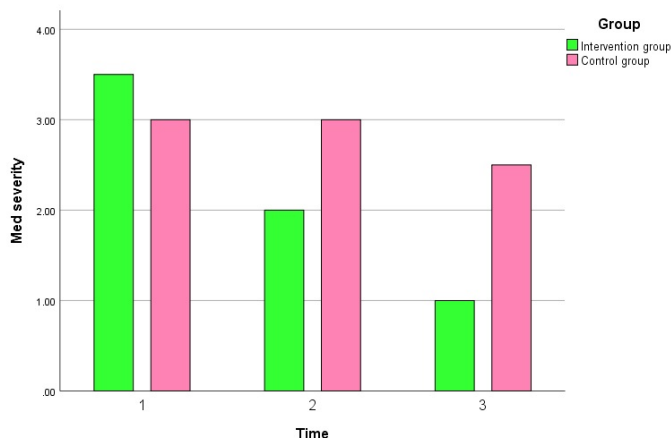


Fig. 3 Comparisons of severity of cough between intervention group and placebo group based on rank 0 and 4.

DISCUSSION

Chronic cough, defined as a persistent cough lasting more than eight weeks, significantly impacts patients' quality of life, leading to social isolation, psychological distress, and sleep disturbances. Many affected individuals continue to experience symptoms despite treatment of underlying conditions such as gastroesophageal reflux disease (GERD), asthma, and rhinitis, emphasizing the pressing need for novel and complementary therapeutic approaches [22].

The findings of this randomized controlled trial demonstrate that the *Prunus dulcis* Laoq formulation was effective in reducing cough symptoms in patients with treatment-resistant chronic cough. The linear trend in cough scores across the three assessment periods indicates a significant and progressive improvement in symptoms following the use of the Laoq formulation. Moreover, the statistically significant difference between the intervention and control groups highlights the notable impact of the intervention on recovery, an effect that persisted after adjusting for potential confounding variables such as gender, age, and BMI, thereby reinforcing the robustness of our primary outcome.

The observed therapeutic effect of *Prunus dulcis* Laoq can be attributed to the synergistic action of its natural constituents, which align with both traditional use and modern pharmacological insights. Almonds (*Prunus dulcis*) are rich in fatty oils, vitamins, and minerals, which are known for their demulcent and emollient properties. These properties likely form a protective coating over the irritated oropharyngeal and esophageal mucosa, reducing sensory nerve activation and the urge to cough [18, 24]. Furthermore, other components of the formulation, such as Gum Arabic, possess mucilaginous qualities that can soothe the throat, while Catechu has been traditionally used for its astringent and anti-inflammatory effects. We hypothesize that the formulation acts through a multi-target mechanism: 1) providing a physical barrier to protect mucosal surfaces, 2) reducing local inflammation in the upper and lower airways, and 3) potentially modulating the neural pathways involved in the cough reflex arc, which is often hypersensitive in patients with chronic cough [5].

Our results are consistent with and build upon a growing body of evidence supporting the use of natural products in respiratory care. Prior studies provide supporting evidence for the therapeutic potential of almond-based formulations. For instance, Anoushirvan *et al.* (2020) demonstrated that a herbal composition containing almond gum powder significantly improved symptoms in patients with refractory asthma [21]. This aligns with our findings, suggesting a shared therapeutic pathway for different chronic respiratory conditions characterized by airway irritation and inflammation.

Furthermore, the broader scientific literature offers mechanistic support for our findings. A network pharmacology study by Cai, S. Y *et al.* (2021) identified multiple active ingredients in almonds that could interact with targets involved in inflammatory pathways, supporting the notion of a multi-component, multi-target effect [23]. Additionally, the traditional use of almonds in Greek and Unani medicine for respiratory ailments, as reviewed by Siddiqui and Begum (2023), provides a long historical context for its efficacy, which our study now substantiates with clinical evidence [24]. Studies on other herbal polysaccharides and extracts, such as those by Nosalova *et al.* [25] and Jin *et al.* [26] and Hosseinkhani *et al.* [27], further confirm that natural compounds can effectively suppress cough reflex and modulate immune responses, highlighting the scientific plausibility of our intervention.

It is important to acknowledge the potential role of the placebo effect in any symptomatic treatment for cough, a highly subjective sensation. While our placebo group showed minimal improvement, the significant between-group difference confirms that the effect of Laoq extends beyond a non-specific placebo response. The meticulous design of our placebo to match the active formulation in taste, texture, and appearance was crucial in isolating the specific therapeutic effect of the active ingredients.

The positive outcomes of this trial suggest that *Prunus dulcis* Laoq can be integrated as a safe and effective complementary therapy alongside conventional treatments for patients who have not found adequate relief. Its natural origin and lack of adverse effects make it a particularly attractive option for long-term management, potentially reducing the reliance on pharmacologic agents that may carry more significant side effects. Future research could explore its efficacy in other conditions characterized by airway irritation, such as subacute cough or cough in post-infectious syndromes.

The main strengths of this study include its rigorous randomized, double-blind, placebo-controlled design, the use of a validated outcome instrument, and diligent daily follow-up ensuring high adherence and safety monitoring. The high sensitivity and specificity of our monitoring checklist further validate the reliability of the symptom data collected.

However, several limitations must be considered when interpreting these results. As noted, the study is limited by its relatively small sample size and short duration, which restricts the generalizability of the findings and precludes any assessment of long-term efficacy and safety. The reliance on a subjective patient-reported outcome, while validated, is a limitation; future studies would be strengthened by the inclusion of objective measures such as cough frequency monitoring (e.g., with Leicester Cough Monitors) or quality-of-life questionnaires.

Conclusion

This study demonstrates the effectiveness of the *Prunus dulcis* Laoq formulation in reducing chronic cough symptoms, with a significant linear decline in cough scores observed in the intervention group over the treatment period. The statistically significant difference between the intervention and placebo groups reinforces the therapeutic impact of the formulation.

Further analyses confirm that treatment efficacy persists even after adjusting for confounding variables, ensuring the reliability of the findings. Notably, no significant differences in treatment response were observed across gender, age, education level, or marital status. However, BMI showed a significant association with cough score trends, suggesting that individual physiological factors may influence treatment outcomes. These findings justify further investigation through larger, longer-term trials that incorporate objective outcome measures and seek to unravel the underlying molecular mechanisms of its action.

Consent for Publication

Not applicable. No individual person's data or images are presented in this manuscript in a form that requires consent for publication.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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Authors' Contributions

MS and LS contributed to the conception and design of the study. YR, FR, YK, LN, and ZS contributed to data collection and study implementation. MS and LS contributed to data analysis and interpretation. All authors contributed to drafting and critically revising the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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