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Phyllencit Mixture, a Combination of Medicinal Herbs, as an Antitussive Agent for Acute Cough Treatment: A Pilot Pre-Post Clinical Study

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ABSTRACT

PhyllenCit, a herbal anti-cough mixture, has been traditionally used in Traditional Thai Medicine hospital, Prince of Songkla University, for the treatment of oral diseases, as well as cough. However, the efficacy of the recipe has not been validated. Therefore, this current study aimed to clinically prove the efficacy of the PhyllenCit mixture in suppressing cough and improving quality of life (QOL) in patients with acute cough. PhyllenCit mixture used for this study was prepared by a traditional Thai doctor at a Traditional Thai Medicine hospital. This study was a single-centre, open blind, pre-post clinical trial. Patients were recruited for the experiment according to the inclusion and exclusion criteria. The assessment of cough level, cough severity index, and a score of QOL was performed before starting the treatment. Patients with acute cough were advised to take the mixture (5 mL) orally for three days. At the end of the study, all the parameters were assessed. The frequency of cough and any adverse effects observed throughout the treatment period (day 1 to day 3) were also recorded by patients. The study revealed that after three days of the intervention, levels of cough symptoms and total severity of cough were significantly extenuated (p<0.05), which was associated with changes in throat characteristics and tonsil size. Similarly, significant improvement of QOL in the patients was observed with no adverse effects. This work scientifically proved that PhyllenCit mixture could be used as an antitussive agent in cases of acute cough.

***Keywords*:** PhyllenCit mixture; anti-cough activity; Quality of life; Acute cough.

Introduction

Cough is a common symptom that can occur in patients of all ages. It is an essential protective reflex mechanism that can help the body clear foreign particles out of the airway. Cough can be classified into three types: acute, subacute, and chronic cough, depending on the duration. Acute cough, coughing that last less than three weeks, is the most common type, usually due to upper respiratory tract infections.[1] It highly impacts morbidity, loss of personality and also causes difficulties in performing daily activities, worsening a patient's quality of life.[2] Though it seems to be a common health problem, it can lead to several serious complications such as urinary incontinence, arterial hypotension, and gastroesophageal reflux diseases.[1] Currently, treatment of cough in western medicine commonly uses antitussive drugs to reduce the cough reflex effectively. However, the drugs are associated with multiple side effects, including sedation, nausea, and hallucinations.[1,3] Therefore, it is necessary to search for an alternative treatment for cough.

In traditional Thai medicine, herbs are always used as a recipe: a combination of medicinal plants to treat several diseases. Many herbs have shown promising potential in relieving cough and its associated symptoms.[4] PhyllenCit is a herbal anti-cough mixture comprising several beneficial medicinal plants as mentioned in Table 1. A traditional Thai doctor has used it to treat oral diseases, throat irritation, and cough at a Traditional Thai medicine hospital, Prince of Songkla University. The different plants in the mixture include *Phyllanthus* emblica,[5] *Citrus aurantiifolia*[6], *Zingiber* officinale,[7] and *Glycyrrhiza* glabra,[8] have been scientifically proved to alleviate cough and other related symptoms. Scientific reports of the anti-cough potency of individual plants in the mixture abound in the literature. However, the combination of these plants as an anti-cough mixture has not been indicated yet. Therefore, the current study has aimed to clinically prove the efficiency and safety of the PhyllenCit mixture in reducing cough and improving quality of life (QOL) in patients with acute cough.

Materials and Methods

Preparation of PhyllenCit mixture

Herbal components, the common name, the plant part, and the ratio of each plant in the PhyllenCit mixture are shown in Table 1. All the plant materials were bought from a famous Thai herbal shop and identified by our staff botanist. Specimens of these plants with Voucher numbers (PHM001-PHM012) were deposited at the Faculty of Traditional Thai Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand. The plant samples were collected in December 2019. For pharmaceutical preparation, each dry medicinal plant in the ratio shown in Table 1 was mixed and then boiled with sterile distilled water (3 L) for 30 minutes. The mixture solution was filtered, and the marc was re-extracted by boiling with 3 L of sterile distilled water for another 30 min and filtered. The filtrates were mixed and then left at

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room temperature for 24 h. Finally, Lime was added to the mixture. The total mixture solution was filtered, and 100 mL was transferred into a sterile bottle for clinical use.

Table 1: Herbal component, the common name, plant part, and the ratio of each herb in PhyllenCit mixture

Plants (Family)	Common name	Pant part	Ratio (%)
Phyllanthus emblica Linn. (Euphorbiaceae)	Indian gooseberry	Fruit	32.25
Citrus aurantiifolia (Christm.&Panz.) Swing. (Rutaceae)	Lime	Fruit	32.25
Solanum indicum L. (Solanaceae)	Brinjal	Fruit	3.23
Solanum trilobatum L. (Solanaceae)	-	Fruit	3.23
*Piperretro fractum*Vahl (Piperaceae)	Long pepper	Flower	3.23
Piper sarmentosum Roxb. (Piperaceae)	Wild betal leaf bush	Flower	3.23
Zingiber officinale Rosc. (Zingiberaceae)	Ginger	Rhizome	3.23
Syzygium aromaticum(Linn.) Merr. &Perry. (Myrtaceae)	Clove	Flower	3.23
Allium sativum Linn. (Alliaceae)	Garlic	Rhizome	3.23
Allium ascalonicum L. (Alliaceae)	Shallot	Bulbs	3.23
Glycyrrhizaglabra L. (Leguminosae)	Licorice	Wood	3.23
Cinnamomum verum(Lauraceae)	Cinnamon	Bark	3.23
Sodium chloride	Salt	-	3.20

Stability testing
Stability testing was carried out on the mixture using two different methods, as previously reported.[9] Firstly, the stability of the mixture was determined by the freeze-thaw stability test according to the previous report with slight changes. Briefly, the sample was kept under two different temperatures at 4ºC for 24 h and at 30 ºC for another 24 h, three cycles. Moreover, short-term stability testing was also performed by placing the sample at a temperature of 30 ºC for 30 days. At the end of the experimental period(s), the samples were tested and observed for changes in appearance (colour, precipitation) and pH values.

Study design
This study was a single-centre, open blind, pre-post clinical trial aimed to study the efficacy of herbal anti-cough mixture in patients suffering from acute cough. The design was performed according to a previous study with some modifications.[3] This study recruited patients from Traditional Thai Medicine hospital, Faculty of Traditional Thai Medicine, Prince of Songkla University between November 2019 and February 2020. The ethical committee of the Faculty of Traditional Thai Medicine, Prince of Songkla University, Thailand, approved the clinical protocol (EC.62/TTM.01-019) for this study.

Patients
Patients who fulfilled all the approval inclusion criteria and none of the exclusion criteria were included in this study.[3] Inclusion criteria were patients aged 18-60 years who visit the Traditional Thai medicine hospital, Prince of Songkla University, with acute dry cough and throat irritation less than three weeks without any underlying severe diseases explained in exclusion criteria. All patients who were willing and able to sign informed consent were also included in the study. Patients with one or more of the following conditions: (1) Patients with underlying diseases including liver diseases, kidney diseases, pneumonia, bronchitis, pertussis, chronic obstructive pulmonary disease, asthma, and tuberculosis; (2) Patients who have a fever (body temperature >38ºC); (3) Patients who have previous medical treatment for cough and antibiotics; and (4) pregnant, breastfeeding, or planning a pregnancy, and who are allergic to the ingredient of a herbal anti-cough mixture, were excluded from the study. A sample size of 14 patients was calculated according to the following formula.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \sigma^2}{(\mu - \mu_0)^2}$$

Reference value ($\mu 0$) = 1.6
Mean (μ) = 1
Standard deviation (σ) = 0.8
Alpha (α) = 0.05; Beta (β) = 0.2

Intervention and Trial procedure
PhyllenCit mixture (0.025 %, w/v) was prepared as previously described above. Eligible patients were recruited and treated for three days. On the first visit, patients were assessed for baseline medical information, including medical history, cough level, cough severity index, clinical signs and symptoms, vital signs, throat irritation, tonsil size, and a score of QOL by a traditional Thai doctor. Quality of life was evaluated using the Leicester Cough Questionnaire (LCQ). All patients received a bottle of the herbal anti-cough mixture (100 mL) and were advised to orally take the mixture (5 mL) every time they cough for three days. At the end of the study, all the assessments were done by the same traditional Thai doctor. Also, the frequency of cough during the first day until the third day was recorded by patients. The development of any adverse effects that occurred to patients was carefully observed throughout the trial. Treatment and assessment were performed under a licensed traditional Thai doctor. All data were statistically analyzed to compare between pre-and post-treatment.[3]

Efficacy endpoints
The primary endpoints of this study were changes in cough level, cough severity index, and cough frequency between pre-and post-treatment. Secondary endpoints were composed of improvement of cough-related QOL and the adverse effect of the mixture during the treatment period.[3]

Statistical analysis
The statistical data analysis was carried out to evaluate the efficacy of the PhyllenCit mixture as an anti-cough agent using the Statistical Package for the Social Sciences software (SPSS 20) for Windows. Paired-samples T-test and 2-related samples tests were used to compare different changes from before and after treatment. Results were presented as mean ± SD or percentage. A difference was considered statistically significant when the *p*-value was less than 0.05.

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Results and Discussion

Stability testing

Table 2 shows the physical appearances and pH values of the PhyllenCit mixture after freeze-thaw and short-term stability testing. After three rounds of the freeze-thaw cycle (3-cycle freeze-thaw), slight changes in colour, odour, taste, and pH values were observed. The observed differences were within the acceptable range according to the guideline of the Thailand FDA. Short-term stability was also performed to investigate possible changes in the mixture at room temperature for 30 days. Results show no differences in colour, odour, and pH values of the herbal mixture. However, there were precipitates and slight modifications in the taste of the mix. Notwithstanding, the stability testing showed that the PhyllenCit mixture was stable.

Demographic characteristics of patients in the study

Figure 1 shows the CONSORT chart of patients in the study. Of the 18 patients screened, four patients were excluded from the study because they did not meet the criteria and refused to participate. Therefore, only 14 patients were engaged and analyzed in the study. Table 3 represents the baseline characteristics of participants in the study. 92.86% of the participants were female, with a mean age of 21.93 years old. Five patients had congenital disorders including, allergic rhinitis (40%), gastritis (20%), and allergy (20%). In the past year, they experienced ill-health associated with respiratory tract diseases such as common cold (66.67%), laryngitis (25%), and bronchitis (8.33%), but were cured before the study. Four of them have a history of food and drug allergy. Three patients lived close to the suspected allergens. Some patients had a history of alcohol drinking (50%), coffee drinking (35.71%), and smoking (50 7.14%). Some of the participants in this had cough for about six days before the commencement of treatment. At the baseline, all patients had normal vital signs (Table 4).

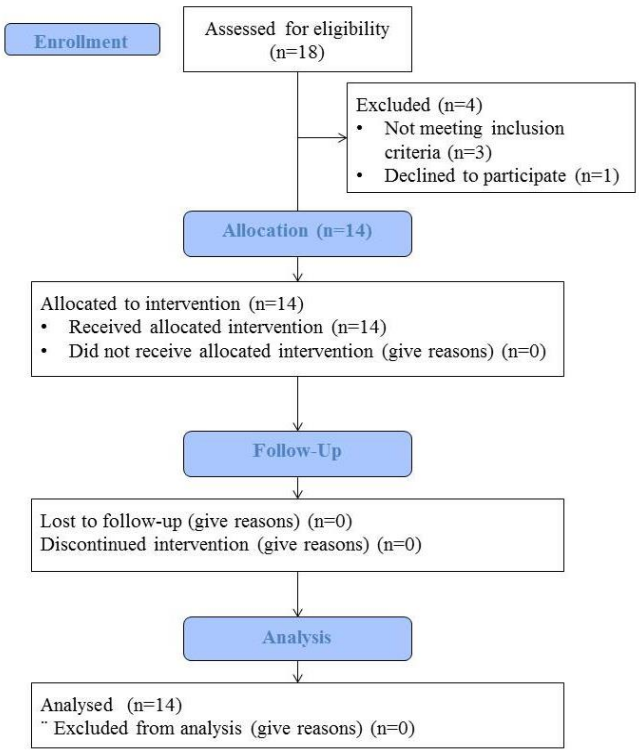

Figure 1: CONSORT flow chart of patients enrolled in the study

Table 2: Physicochemical changes in appearances and pH values of PhyllenCit mixture after freeze-thaw and short-term stability testing

Stability tests	Temperature	Parameters				
		Color	Odor	Taste	Participation	pH
Freeze-Thaw stability						
Round 1	4ºC	Light brown	NC[a]	NC	NC	2.30
	30 ºC	Light brown	SC[b]	NC	SC	2.29
Round 2	4ºC	Light brown	MC[c]	SC	SC	2.27
	30 ºC	Light brown	MC	MC	SC	2.21
Round 3	4ºC	Dark brown	MC	MC	SC	2.22
	30 ºC	Dark brown	MC	MC	SC	2.14
Short term stability						
Day 0	30 ºC	Light brown	NC	NC	NC	2.53
Day 30	30 ºC	Light brown	NC	SC	SC	2.52

[a]NC :No change, [b] SC: Slight change, [c] MC: Moderate change

Acute cough, coughing less than 3 weeks, is a common health problem that plays a vital role in protecting the body from foreign particles. A previous report demonstrated that almost all patients who suffered from cough and its associated symptoms for 18 days or longer, depending on their health status, will heal without any treatment.[10] Cough co-morbidities include common cold, allergic rhinitis, environmental irritant rhinitis, and upper respiratory tract infections.[1] It is unexpectedly initiated when the sensory cough-inducing receptors in a respiratory tract are stimulated by a variety of irritants, including dust, smoke, allergens, pollen, as well as environmental pollution, leading to throat irritation.[1] Demographic characteristic revealed that around 21% (3/14) of patients had underlying disease related to allergy, and some are currently living in allergy-inducing places. Before the start of treatment, patients that suffered from a cough for six days had a severity level of 16.50. Interestingly, treatment with the PhyllenCit mixture significantly relieved cough level, cough severity, and cough frequency.

Clinical efficacy of the herbal anti-cough mixture on cough

Table 5 shows changes in symptoms related to cough level, cough severity index, and quality of life (QOF) before and after three days of treatment with the PhyllenCit mixture. After three days of the intervention, the symptoms associated with cough significantly improved from 17.07 (day 0) to 10.43 (day 3).

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Table 3: Baseline characteristics of the participants (n = 14)

Characteristics	Participants; N (%)
Sex; Female	13 (92.86)
Career; Student	14 (100.00)
Congenital Disease	5 (35.71)
Allergic rhinitis	2 (40.00)
Gastritis	1 (20.00)
Allergy	1 (20.00)
Thalassemia	1 (20.00)
Past illness related to the respiratory tract (Within the past 1 year)	12 (85.71)
Cold	8 (66.67)
Laryngitis	3 (25.00)
Bronchitis	1 (8.33)
Food allergy history	2 (14.28)
Basil	1 (50.00)
Shrimp	1 (50.00)
Drug allergy history	2 (14.29**)**
Naproxen	1 (50.00)
Minocycline	1 (50.00)
A residence that has stimuli	3 (21.43)
Alcohol drinking	7 (50)
Coffee drinking	5 (35.71)
Smoking history	1 (7.14)

Table 4: Baseline cough onset and a routine physical examination of participants (n = 14)

Parameters	mean ± SD
Age(years)	21.93 ± 1.07
Weight (kg)	55.16 ± 12.57
Height (cm)	160.86 ± 8.54
Cough onset before the treatment(Days)	5.86 ± 2.80
Temp (º C)	36.66 ± 0.49
Pulse (bpm)	85.71 ± 11.15
Respiratory rate (bpm)	17.57 ± 1.65
Systolic (mmHg)	106.79 ± 13.18
Diastolic (mmHg)	68.86 ± 7.73

There was no significant difference in the nasal symptoms between day 0 and day 3. Interestingly, cough symptoms, including cough frequently, cough more than 4-6 times per day, day cough, and night cough, decreased after the treatment ($p < 0.05$). This decrease was related to the total severity of the cough that was significantly extenuated ($p = 0.001$) after the treatment. Moreover, levels of throat irritation were also significantly relieved ($p = 0.005$) related to changes in throat characteristics and tonsil size (Table 6). After three days of treatment, most patients had no redness (78.57%) on the throat, and the tonsil size was normal (78.57%). Patients also assessed the frequency of cough in a day during the treatment. The results found that patients had a cough about 32 times on the first day of the treatment. By the second day, it was attenuated to 19 times a day, and it consecutively decreased until the third day (8.93 times in a day) of the treatment (Figure 2). PhyllenCit mixture is a herbal anti-cough recipe comprising 12 beneficial medicinal plants, including *Phyllanthus emblica*, *Citrus aurantiifolia*, *Solanum indicum*, *Solanum trilobatum*, *Piperretro fractum*, *Piper sarmentosum*, *Zingiber officinale*, *Syzygium aromaticum*, *Allium sativum*, *Allium ascalonicum*, *Glycyrrhiza glabra*, and *Cinnamomum verum*.

Table 5: Comparison of cough parameters between day 0 and day 3 after PhyllenCit mixture treatment

Factors	Duration of treatment (mean ± SD)		*p*-value
	0	3	
Symptoms[a]	17.07 ± 4.73	10.43 ± 4.29	0.002
Frequent cough	1.93 ± 0.62	1.47 ± 0.47	0.001
Cough ≥4-6 times/days	2.43 ± 0.85	1.71 ± 0.91	0.015
Day cough	2.14 ± 0.86	1.07 ± 0.47	0.004
Night cough	2.50 ± 0.76	1.36 ± 1.01	0.004
Consecutive cough in the last 3 weeks	2.07 ± 0.83	0.93 ± 1.00	0.003
Nasal congestion	2.57 ± 1.09	2.36 ± 1.28	0.317
Stuffy nose	0.57 ± 0.94	0.21 ± 0.43	0.160
Running nose	0.71 ± 0.91	0.29 ± 0.61	0.058
Sore throat	0.64 ± 0.93	0.36 ± 0.63	0.234
Throat irritation	1.36 ± 0.93	0.57 ± 0.76	0.005
Cough severity index[a]	16.50 ± 5.13	6.36 ± 4.27	0.001
LCQ[b]	82.07 ± 9.84	109.21 ± 11.11	0.001

[a]Higher values indicate more symptoms
[b]Higher values indicate better quality of life

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Table 6: Throat characteristic and tonsil size on day 0 and day 3 after PhyllenCit mixture treatment

Characteristics	Duration of treatment in days; N (%)	
	0	3
Throat		
No redness	4 (28.57)	11 (78.57)
Slightly red	8 (57.14)	3 (21.43)
Red	2 (14.29)	0 (0.00)
Very red	0 (0.00)	0 (0.00)
Tonsil size scoring		
Grade 0	4 (28.57)	11 (78.57)
Grade 1	6 (42.86)	2 (14.29)
Grade 2	4 (28.57)	1 (7.14)
Grade 3	0 (0.00)	0 (0.00)
Grade 4	0 (0.00)	0 (0.00)

It was reported that *P.emblica* or *Emblica officinalis* possessed profound antitussive activity by reducing the number of cough efforts, cough frequency, and cough intensity in cats via the mechanisms of anti-inflammation anti-oxidation, and mucus secretion.[11]
Also, *G.glabra*, *Z.officinale*, and *S.trilobatum* have been reported to significantly inhibit cough reflex *in vivo* study.[6-8,12] The combination of *G.glabra* and *Z. official* exhibited mucoactive activity in mice.[7] Infections are complicated conditions that can stimulate cough, throat inflammation, sore throat, throat irritation, and tonsil enlargement.[13,14] Interestingly, this study exhibited that throat irritation and tonsil enlargement was improved after treatment with PhyllenCit mixture, which may be due to the biological properties of each medicinal plant in the mix. Studies have shown that most of the medicinal plants in the PhyllenCit recipe possess antitussive activity. They have also been reported to inhibit infections due to Gram-positive and Gram-negative bacteria, especially those implicated in throat infection bacteria.[15-19] Other studies also report their *in vitro* and *in vivo* anti-inflammatory potentials [20-26], which may be responsible for alleviating throat inflammation and tonsil enlargement.

Clinical efficacy of the herbal anti-cough mixture on quality of life
As mentioned above, cough can affect the patient's life quality in all physical, psychological, and social dimensions.

Table 7: Comparison of quality of life between day 0 and day 3 after PhyllenCit mixture treatment using Leicester Cough Questionnaire

Symptoms	Duration of treatment in days (mean ± SD)		*p*-value
	0	3	
Q1 chest or stomach	6.71 ± 0.61	6.93 ± 0.27	0.180
Q2 sputum	4.43 ± 1.70	5.64 ± 1.39	0.004
Q3 tired	4.50 ± 1.51	6.36 ± 1.15	0.002
Q4 felt in control	3.43 ± 1.60	5.43 ± 1.28	0.001
Q5 felt embarrassed	5.14 ± 1.75	5.79 ± 1.12	0.179
Q6 feel anxious	4.86 ± 1.10	6.07 ± 0.92	0.010
Q7 interfered with daily activities	4.07 ± 0.83	5.71 ± 1.33	0.003
Q8 interfered with life enjoyment	4.64 ± 1.01	5.86 ± 1.17	0.004
Q9 paints or fumes	4.21 ± 2.01	5.43 ± 1.09	0.007
Q10 sleep	3.71 ± 1.98	5.43 ± 1.40	0.004
Q11 coughing bouts	3.29 ± 1.68	5.21 ± 1.37	0.002
Q12 feel frustrated	3.00 ± 1.04	5.71 ± 1.07	0.002
Q13 feel fed up	4.00 ± 1.84	5.64 ± 1.01	0.009
Q14 hoarse voice	4.43 ± 1.34	5.86 ± 0.95	0.000
Q15 energy	4.64 ± 1.50	4.93 ± 2.20	0.458
Q16 worry	5.00 ± 1.84	6.14 ± 1.41	0.007
Q17 concerned with other people	5.36 ± 1.28	5.71 ± 1.27	0.150
Q18 conversation	4.07 ± 1.07	5.57 ± 1.22	0.000
Q19 annoyed friends	3.98 ± 1.44	5.86 ± 0.95	0.002
Physical Domain	4.49	5.72	0.012
Psychological Domain	4.30	5.81	0.001
Social Domain	4.37	5.71	0.068

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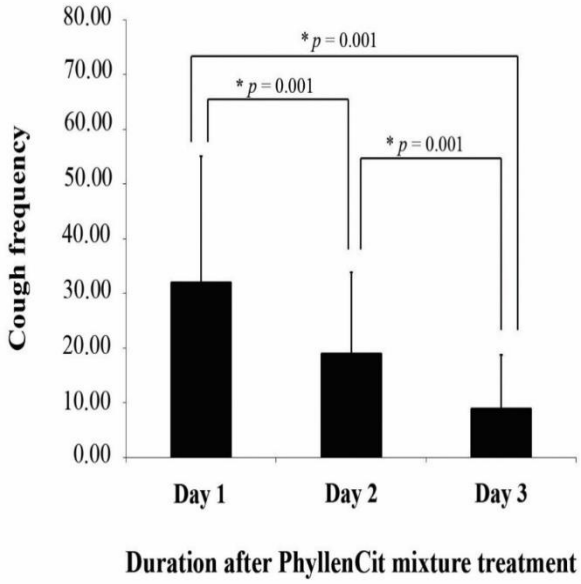

Figure 2: The frequency of cough in a day during the treatment (n = 14)

Therefore, this work also focused on evaluating the quality of life in the patients after treatment with PhyllenCit mixture using Leicesters Cough Questionnaire. On the screening visit, the LCQ score was 82.07 ± 9.84, which improved to a higher score of 109.21 ± 11.11 after treatment for three days (p=0.001). This suggests that treatment with PhyllenCit mixture improved QOL on both physical and psychological domains (p<0.05). Moreover, there were no significant changes in the social environment of QOL (Table 7). No adverse effects of the mixture were observed in this study.
Previously, the total QOL score using LCQ in patients associated with cough was poor in all physical, psychological, and social domains related to our current study.[27] Noticeably, the PhyllenCit mixture intimately improved the score of total LCQ in both the physical and psychological domains.

Conclusion

The study is the first scientific clinical report investigating PhyllenCit mixture's efficiency as a cough-reducing agent. The study revealed that cough level, cough severity index, cough frequency, and signs and symptoms related to cough were significantly diminished after three days of treatment with PhyllenCit mixture. The QOL amongst participants was greatly improved. This study clinically proved that PhyllenCit mixture could be used as an alternative therapeutic approach for treating acute cough without any adverse effects. However, it is also important to further investigate its activity in chronic or other productive coughs.

Conflict of interest

The authors declare no conflict of interests.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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