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Original Article

Effect of *Vernonia cinerea* (L.) Less. lozenges as a smoking cessation aid in patients with non-communicable diseases

[Efecto de las pastillas de *Vernonia cinerea* (L.) Less. como ayuda para dejar de fumar en pacientes con enfermedades no transmisibles]

Krittin Bunditanukul[1], Chanchai Sittipunt[2], Arintaya Phrommintikul[3], Nattaphon Chokemaitree[4], Phantipa Sakthong[1*]

[1]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Phaya Thai Road, Pathumwan, Bangkok, 10330, Thailand.
[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine Chulalongkorn University, Rama 4 Road, Pathumwan, Bangkok, 10330, Thailand.
[3]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, 110 Intawaroros Road, Sriphoom, Muang Chiang Mai, 50200, Thailand.
[4]Department of Psychiatry and Neurology, Phramongkutklao Hospital, Ratchawithi Road, Thung Phaya Thai, Ratchathewi, Bangkok, 10400, Thailand.
*E-mail: phantipa.s@pharm.chula.ac.th

Abstract

Context: Smoking is the leading cause of premature death or severe disability. *Vernonia cinerea (VC)* is an herb that is used in traditional Thai medicines for quitting smoke and is inexpensive.

Aims: To assess the efficacy and safety of *VC* lozenges for smoking cessation compared with a placebo in non-communicable diseases (NCD) patients.

Methods: This study was a multicenter randomized, paralleled, double-blind, controlled trial (Clinicaltrial.gov Identifier: NCT06268002). Five hospitals and two community pharmacies in Thailand participated between September 2017 and December 2021. The inclusion criteria were smokers aged at least 18 years and smoking at least 10 cigarettes per day for at least one month who had the desire to quit smoking and had established NCD. All eligible patients were randomly assigned to receive either *VC* lozenges or a placebo. The primary outcome was a lower continuous abstinence rate (CAR) after four weeks.

Results: Ninety-three smokers with NCD were enrolled. After four weeks, there were more CAR events in the *VC* lozenges group than in the control group (6 vs. 1; odds ratio [OR] 10.74, 95% confidence interval [CI] 0.82-140.28) but with no statistically significant differences (p=0.083). When compared to the baseline, the number of cigarettes smoked per day and exhaled carbon monoxide levels decreased significantly in patients who received *VC* lozenges. No serious adverse events or abnormal laboratory data were reported during the use of *VC* lozenges.

Conclusions: In smokers with NCD, the CAR rate at four weeks in the *VC* lozenges group was not different from the placebo group. NCD patients who received *VC* lozenges were well tolerated, and no serious side effects were found.

Keywords: Non-communicable diseases; smoking cessation; *Vernonia*.

Resumen

Contexto: Fumar es la principal causa de muerte prematura o discapacidad grave. La *Vernonia cinerea* (*VC*) es una hierba que se utiliza en la medicina tradicional tailandesa para dejar de fumar y es económica..

Objetivos: Evaluar la eficacia y seguridad de las pastillas de *VC* para dejar de fumar en comparación con un placebo en pacientes con enfermedades no transmisibles (ENT).

Métodos: Este estudio fue un ensayo controlado, aleatorizado, paralelo, doble ciego y multicéntrico (Identificador Clinicaltrial.gov: NCT06268002). Participaron cinco hospitales y dos farmacias comunitarias de Tailandia entre septiembre de 2017 y diciembre de 2021. Los criterios de inclusión fueron fumadores de al menos 18 años de edad que fumaran al menos 10 cigarrillos al día durante al menos un mes, que tuvieran el deseo de dejar de fumar y tuvieran una ENT establecida. Todos los pacientes elegibles fueron asignados aleatoriamente para recibir pastillas de *VC* o un placebo. El resultado primario fue una tasa de abstinencia continua (CAR) más baja después de cuatro semanas.

Resultados: Se inscribieron noventa y tres fumadores con ENT. Después de cuatro semanas, hubo más eventos de CAR en el grupo de pastillas de *VC* que en el grupo control (6 vs. 1; odds ratio [OR] 10,74, intervalo de confianza del 95% [IC] 0,82-140,28) pero sin diferencias estadísticamente significativas (p=0,083). En comparación con el valor inicial, el número de cigarrillos fumados por día y los niveles de monóxido de carbono exhalado disminuyeron significativamente en los pacientes que recibieron pastillas de *VC*. No se informaron eventos adversos graves ni datos de laboratorio anormales durante el uso de pastillas de *VC*.

Conclusiones: En fumadores con ENT, la tasa de CAR a las cuatro semanas en el grupo de pastillas de *VC* no fue diferente del grupo placebo. Los pacientes con ENT que recibieron pastillas de *VC* fueron bien tolerados y no se encontraron efectos secundarios graves.

Palabras Clave: enfermedades no transmisibles; dejar de fumar; *Vernonia*.

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AUTHOR INFO
ORCID: 0000-0003-4835-0897 (KB) 0000-0002-9092-7912 (NC)
0000-0002-9906-4615 (CS) 0000-0001-7044-0923 (PS)
0000-0003-3986-1951 (AP)

Abbreviations: CAR: Continuous abstinence rate; CBC: Complete blood cell count; CI: Confidence interval; CO: Carbon monoxide; COPD: Chronic obstructive pulmonary disease; FBS: Fasting blood sugar; FTND: Fagerstrom test for nicotine dependence; HR: Hazard ratio; NCD: Non-communicable diseases; OR: Odds ratio; PAR: 7-day point prevalence abstinence rate; *VC*: *Vernonia cinerea*; WHO: World Health Organization.

INTRODUCTION

Smoking is a leading cause of disability and premature death. Cigarette smoke causes many diseases, both acute and chronic, such as heart disease, stroke, chronic obstructive pulmonary disease (COPD), and cancer. Smoking is a major factor in death and disease that can be prevented (CDC, 2021; WHO, 2023). The World Health Organization (WHO) reported that 8 million people die as a result of smoking cigarettes every year, with 1.3 million people dying from second-hand smoke. Eighty percent of the world's 1.3 billion smokers live in low- or middle-income countries (WHO, 2023). The WHO estimated that in 2010 in Thailand, 27% of the population over the age of 15 (about 14 million people) were smokers (WHO, 2019). According to the National Statistical Office of Thailand, in 2017, there were 10.7 million smokers in Thailand aged 15 years and over, accounting for 19.1% (National Statistical Office, 2018).

A pooled analysis of 16 Asian population-based cohort studies indicated that the hazard ratio [HR] (95% confidence interval [CI]) for current smokers increased to 1.55 (1.44–1.68) for all-cause death, 1.49 (1.36–1.64) for cardiovascular death, and 4.34 (3.59–5.25) for cancer-related death compared to non-smokers (Yang et al., 2022). Smoking cessation was linked to a 34% reduction in lung cancer mortalities and an 11% drop in all-cause mortality in former smokers who stopped smoking less than five years ago, compared to current smokers (Yang et al., 2022).

Vernonia cinerea (L.) Less. *(VC)* is a synonym of *Cyanthillium cinereum* (L.) H.Rob., family *Asteraceae*. This herb is used in numerous traditional Thai medicines and also for the cessation of smoking. Thailand's National List of Essential Herbal Drugs placed *VC* whole plant extract under the indication for smoking cessation. One benefit of applying *VC* to stop smoking is the low price because the cost of smoking cessation drugs is another barrier preventing smokers from seeking therapy and using the medication directed by guidelines. The exact mechanism of *VC* for smoking cessation remains unclear. In the past, nitrate compounds in *VC* that caused tongue numbness were believed to reduce the taste of cigarettes when smoking (Ketsuwan et al., 2017). Several studies have investigated the impact of *VC* on smoking cessation. *VC* and its active compounds (apigenin, chrysoeriol, luteolin, quercetin, and four hirsutinolide-type sesquiterpene lactones) block dopamine's metabolism by inhibiting the MAOI or cytochrome P450 enzyme (Pouyfung et al., 2017; Prasopthum et al., 2015), while *VC* leaves contain nicotine (Ketsuwan et al., 2017). Many studies suggested that *VC* might be employed as an alternative smoking cessation method (Chaikoolvatana et al., 2017; Chaisawad and Makanuntachote, 1996; Leelarungrayub et al., 2010; Lertsinudom et al., 2021; Tripopskul and Sittipunt, 2016; Wongwiwatthananukit et al., 2009). A meta-analysis from five studies, which included 347 smokers, found that when compared to the placebo group, the *VC* product showed a greater cessation rate at eight weeks (risk ratio [RR] 1.69 for continuous abstinence rate and 1.51 for 7-day point prevalence abstinence rate) (Puttarak et al., 2018).

Most previous studies investigated the effect of *VC* on smoking cessation in healthy volunteers, but some patients, especially chronic non-communicable disease (NCD) patients, may still actively smoke. Cigarette smoke can alter many bodily functions and exacerbate chronic diseases by triggering the production of free radicals and the inflammatory process (Kopp, 2022). Therefore, this study assessed the efficacy and safety of *VC* lozenges for smoking cessation compared with a placebo in NCD patients.

MATERIAL AND METHODS

Study design

This multicenter randomized, paralleled, double-blind, controlled trial was conducted at five hospitals and two community pharmacies in Thailand (Clinicaltrial.gov Identifier: NCT06268002). The research was approved by the Review Committee of the Faculty of Pharmaceutical Science Chulalongkorn University on August 30, 2017 (approval number 8/2560). The Review Board at each participating institution approved the trial, which was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. All the patients provided written informed consent. This research was supported by the 100th Anniversary Chulalongkorn University Fund for Doctoral Scholarship and the 90th Anniversary Chulalongkorn Fund (Ratchadaphiseksomphot Endowment Fund), which had no role in this study.

Trial population

The trial population consisted of patients who were 18 years or over, smoked at least 10 cigarettes

per day for at least one month, had the desire to quit smoking, and had an established NCD, including hypertension, diabetes, dyslipidemia, cardiovascular diseases, cerebrovascular diseases, stable asthma (defined as no asthmatic exacerbation for the preceding four weeks necessitating oral prednisolone or increased use of inhaled corticosteroid, the use of rescue treatment no more than three times a week, and with no clinical indication for change in treatment medication), COPD stage A-C according to GOLD guidelines and stage 3 chronic kidney disease based on KDIGO guidelines. Key exclusion criteria were renal dysfunction (eGFR < 30 mL/mins/1.73 m^2), liver dysfunction (Child-Pugh score C), hyperkalemia (serum potassium ≥ 5 mEq/L), documented active depression or psychosis, active cancer, history of an acute coronary syndrome in the previous four weeks, known cases of pregnancy or lactation, used other tobacco products or other addictive substances except for alcohol, and used other smoking cessation drugs.

Randomization and Intervention

During the screening and baseline visit (week 0), medical history, vital signs, and laboratory data were obtained, including complete blood cell count (CBC), fasting blood glucose (FBG), liver enzyme, renal function test, and serum electrolytes. A smoking history, demographic data, and the Fagerstrom Test for Nicotine Dependence (FTND) score were also recorded.

Smokers who met the inclusion criteria at the study site were randomly assigned in a 1:1 ratio to receive *VC* lozenges, one tablet three times daily for 12 consecutive weeks or matching placebo lozenges according to a computer-generated random list prepared by the Medical Research Network of the Consortium of the Thai Medical Schools, which was not involved in the enrolment process, with block sizes of 4. Randomization was stratified by level of nicotine addiction (FTND ≤ 5 or > 5). The subjects were blinded to treatment assignments. Both groups received similar advice to stop smoking from the healthcare professional according to Thailand's smoking cessation guidelines. The patient's diary was used to measure treatment adherence. Patients were considered to have good adherence if they took at least 80% of the lozenges.

The *VC* lozenges and matching placebo lozenges used in this study were manufactured and donated by Greater Pharma Co., Ltd, a manufacturer and distributor of *VC* lozenges for smoking cessation in Thailand, and approved by the Thai FDA. The company did not play any other role in this study. Each *VC* lozenge was standardized to be equivalent to 2 grams of *VC* tea. One lozenge contained 450 milligrams of *VC* whole extract, not less than 5 milligrams of nitrate, and not less than 15 milligrams of total phenolic compounds as the recommended dosage in the Thai National List of Herbs for reducing cigarette cravings (Herbal Products Division, 2023).

Outcomes

The primary study outcome was the continuous abstinence rate (CAR) four weeks after the scheduled stop smoking date, defined by self-reported smoking cessation plus an exhaled CO level (Smokerlyzer®) less than 10 ppm. Participants were considered to fail to stop smoking if they stopped participating or were lost during the follow-up. Secondary outcomes were CAR at 12 weeks, the 7-day point prevalence abstinence rate (PAR) at 4 and 12 weeks, the number of cigarettes smoked per day in the *VC* lozenges group compared to the baseline, and the change in exhaled carbon monoxide (CO) levels from the baseline in the intervention group.

The safety endpoints were the incidence of all observed or self-reported serious adverse events and any adverse events through 12 weeks of intervention.

Statistical analysis

The sample size was calculated by setting the power at 80% and the alpha value at 0.05 for a two-tailed test based on the meta-analysis result of *VC* for smoking cessation (Puttarak et al., 2018). Results suggested that 110 samples were required in each group. To allow for 20% of the participants to withdraw during the study, 130 samples were needed in each group.

For the demographic data, categorical variables were summarized as frequencies and percentages, with continuous variables presented as medians and interquartile ranges (IQR). The baseline characteristics were compared using the χ^2 test or Fisher's exact test for categorical variables as appropriate, while the independent t-test or Wilcoxon rank sum test was used for continuous data. A logistic regression was also used to compare the CAR and PAR between the two groups at each time point. CAR and PAR analyses were based on an intention-to-treat approach. Repeated-measurement ANOVA was used to compare the number of cigarettes smoked per day and exhaled CO levels at the baseline and 12 weeks. Frequencies and percentages were used to summarize the adverse events, and the χ^2 test or Fisher's exact test was performed to compare the proportion of participants in each group who encountered those particular events. For the primary endpoint and all subsequent endpoints, a p-value of less than 0.05 was

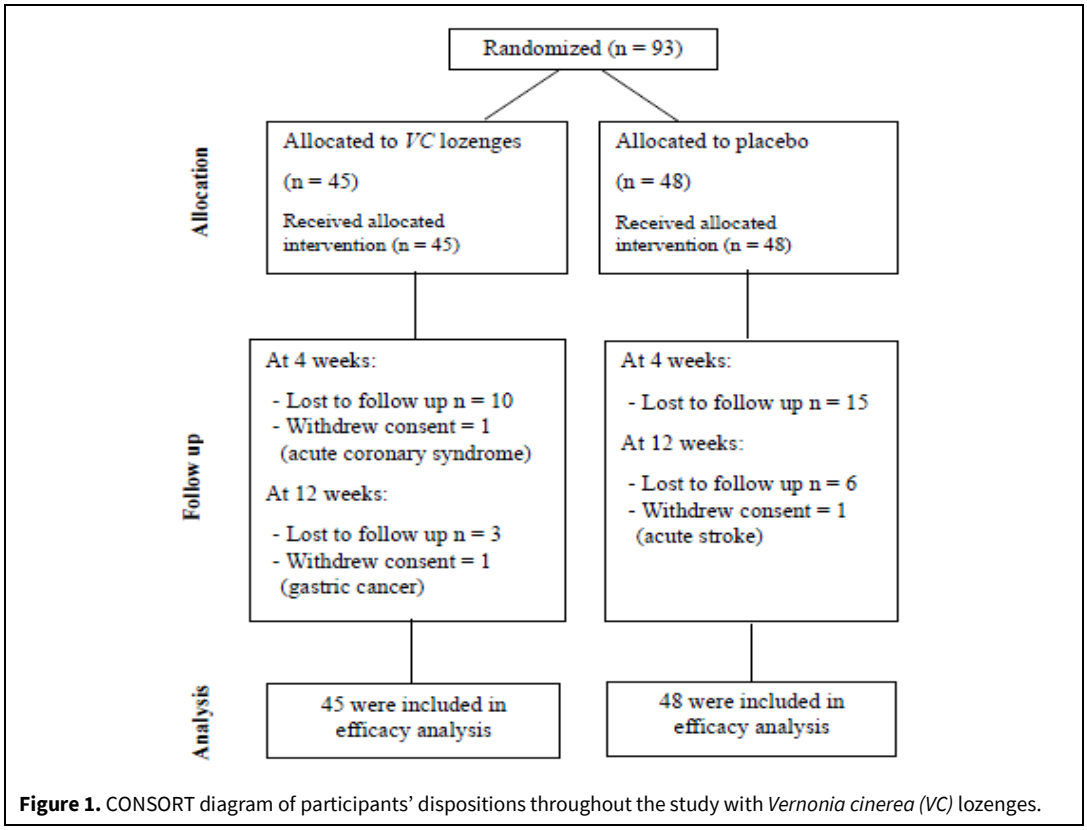

Figure 1. CONSORT diagram of participants' dispositions throughout the study with *Vernonia cinerea (VC)* lozenges.

considered to indicate a significant difference between the two groups. All statistical analyses performed using SPSS software version 28.

RESULTS

Participants and baseline characteristics

Initially, the recruitment of 260 participants was planned. However, the 2019 COVID-19 pandemic had a significant effect on patient enrollment and follow-up, and the *VC* lozenges and placebo expired in February 2022. Thus, only 93 NCD (*VC* group = 45 and placebo = 48) patients were enrolled from September 2017 to December 2021. Loss of follow-up was the main cause of discontinuation in both groups. At four weeks, 11 patients (23%) lost follow-up in the intervention group, with 15 (31%) in the control group. At 12 weeks, 6 (18%) and 7 (21%) participants lost follow-up in the intervention and control groups, respectively. Fig. 1 illustrates a trial flow chart. By the twelfth week, the average compliance rate of the *VC* group was 70.29%, while the compliance rate in the placebo group was 75.81%.

There were no statistically significant differences in the baseline characteristics and smoking history of the two study groups, with the number of cigarettes smoked per day significantly higher in the placebo group (p=0.048). The average age was 52.96 ± 12.40 and 52.02 ± 13.67 years for the *VC* group and the placebo group, respectively. Most participants were male (87%) in both groups (Table 1). The ages at which the subjects started smoking in the *VC* group and the placebo group were 18.89 ± 7.37 and 18.67 ± 6.95 years, respectively. The duration of smoking was 33.42 ± 14.61 years in the *VC* group and 33.48 ± 15.07 years in the control group. The level of nicotine addiction, assessed using the FTND test, was 4.53 ± 1.96 points in the study group and 5.23 ± 1.98 points in the control group. In the intervention group, the exhaled CO level was 13.40 ± 5.11 ppm, while in the control group, it was 15.94 ± 7.10 ppm.

CAR outcomes

After four weeks, there were more CAR events in the *VC* lozenges group than in the control group (6 vs. 1; odds ratio [OR] 10.74, [95% CI 0.82-140.28]) but there was no significant statistical difference (p=0.083) (Table 2). At the end of week 12, 1 patient (4%) in the control group and 4 patients (14%) in the *VC* group had managed to stop smoking (OR 6.39, 95% CI 0.46-88.52) with no statistical significance (p=0.167).

PAR outcomes

In week 4, there was no significant difference in the PAR event between the *VC* group and the control group. (6% vs. 6%, OR 0.92, 95% CI 0.11-7.92). By the end of week 12, 5 patients in the control group and 4 patients in the *VC* group achieved the PAR criteria (OR 0.74, 95% CI 0.17-3.19) (Table 2).

Number of cigarettes smoked per day

At the end of 12 weeks, participants in both groups smoked a reduced number of cigarettes per day compared to the baseline. However, there was no statistical difference between the change in the number of cigarettes smoked per day between the intervention and control groups (p=0.846) (Table 3). The number of cigarettes smoked per day between the groups at four weeks was statistically significant (p=0.029) as 8.56 ± 6.85 in the intervention group and 12.40 ± 9.56 in the placebo group, while at 12 weeks, the two groups showed no statistical difference (p=0.060). When comparing the daily cigarette use in the *VC* group after 12 weeks, the baseline daily cigarette consumption significantly decreased (p<0.001).

Exhaled CO level

After 12 weeks, compared to the baseline, participants in both groups recorded lower exhaled CO levels, but there was no statistically significant difference between the groups (p=0.179) (Table 3). There was no statistically significant change in the exhaled CO level between the groups at 4 and 12 weeks. By the end of the investigation, the exhaled CO level decreased from 13.40 ± 5.11 ppm at the baseline to 8.89 ± 5.91 ppm in the *VC* group (p<0.001).

Safety outcomes

No serious adverse events or abnormal laboratory data were reported during the use of the *VC* lozenges (Table 4). Adverse events that caused subjects to withdraw before the end of the study included one case of myocardial infarction and gastrointestinal cancer in the study group and one case of stroke in the control group. These serious adverse events were not related to the study drug.

Table 1. Demographic and clinical characteristics of the participants.

Characteristics	*VC* group (n = 45)	Placebo group (n = 48)	p-value
Age, year (median, [IQR])	56 (45-60)	54.5 (43.5-63)	0.957
Sex			0.905
Male (%)	39 (86.67)	42 (87.5)	
Female (%)	6 (13.33)	6 (12.5)	
Body mass index (kg/m^2) (median, [IQR])	24.84 (20.94-27.24)	24.83 (23.07-26.67)	0.617
The income per month, baht; (median, [IQR])	20000 (10500-28980)	20000 (11916-30000)	0.658
History of alcohol drinking			0.936
No (%)	24 (53.33)	26 (54.17)	
Age of start smoking (median, [IQR])	18 (15-20)	18 (15-20)	0.731
No. of years smoked (median, [IQR])	39 (24-40)	34 (22-45.4)	0.675
No. of cigarettes/day, (median, [IQR])	10 (10-20)	15 (10-20)	0.048
10-15 cigarettes/day (%)	31 (68.89)	26 (54.17)	
History of stopping attempts (%)	27 (60)	24 (50)	0.333
FTND (median, [IQR])	5 (3-6)	5 (4-6.5)	0.147
0-3 points (%)	17 (37.78)	10 (20.83)	
4-5 points (%)	13 (28.89)	19 (39.58)	
≥ 6 points (%)	15 (33.33)	19 (39.58)	
Exhaled CO level, ppm (median, [IQR])	12 (10-15)	14 (10-18)	0.110
Hypertension (%)	28 (62.22)	26 (54.17)	0.431
Diabetes (%)	16 (35.56)	12 (25)	0.267
Dyslipidemia (%)	14 (31.11)	18 (37.5)	0.517
Cardiovascular disease (%)	5 (11.11)	3 (6.25)	0.477
Asthma (%)	1 (2.22)	1 (2.08)	1.000
COPD (%)	3 (6.67)	5 (10.42)	0.715

VC: *Vernonia cinerea*; IQR: Interquartile range; FTND: Fagerstrom test for nicotine dependence; COPD: Chronic obstructive pulmonary disease.

Table 2. Continuous abstinence rate and point prevalence abstinence rates at 4 and 12 weeks.

Outcomes	*VC* group (n = 45) Number of events	Placebo group (n = 48) Number of events	Odd ratio (95% CI)*	p-value**
CAR at 4 weeks	6	1	10.74 (0.82-140.28)	0.070
CAR at 12 weeks	4	1	6.39 (0.46-88.52)	0.167
PAR at 4 weeks	2	2	0.92 (0.11-7.92)	0.937
PAR at 12 weeks	4	5	0.74 (0.17-3.19)	0.685

* Adjusted for the number of cigarettes smoked per day, and FTND score (≤3, 4-5, and >6). **Logistic regression. *VC: Vernonia cinerea;* CAR: Continuous abstinence rate ; PAR: 7-day point prevalence abstinence rate; CI: Confidence interval.

Table 3. Number of cigarettes smoked per day and change in exhaled carbon monoxide (CO) level from the start of the study in the intervention group.

Outcomes	Baseline	Week 4	Week 12	p-value
Mean number of cigarettes smoked per day				0.846*
VC group (n = 45)	14.07 ± 6.12	8.56 ± 6.85	8.64 ± 6.88	<0.001**
Placebo group (n = 48)	17.79 ± 9.16	12.40 ± 9.56	12.06 ± 10.00	<0.001**
p-value***		0.029	0.060	
Mean exhaled CO level (ppm)				0.881*
VC group (n = 45)	13.40 ± 5.11	8.80 ± 5.82	8.89 ± 5.91	<0.001**
Placebo group (n = 48)	15.94 ± 7.10	11.27 ± 7.38	11.15 ± 8.09	<0.001**
p-value***		0.078	0.130	

*p-value of the mean difference between the *Vernonia cinerea (VC)* group and placebo through 12 weeks by repeated measurement ANOVA. **p-value of the mean difference from baseline through 12 weeks by repeated measurement ANOVA. ***p-value between each week.

Table 4. Incidence of adverse events in the *Vernonia cinerea (VC)* group and the placebo group through 12 weeks of treatment.

Adverse drug reactions	*VC* group (n = 45)	Placebo group (n = 48)	P-value
Tongue numbness (%)	21 (46.67)	14 (29.17)	0.195
Dry mouth (%)	12 (26.67)	11 (22.92)	0.863
Anorexia (%)	9 (20)	7 (14.58)	0.794
Dizziness (%)	7 (15.56)	5 (10.42)	0.562
Dry throat (%)	0 (0)	4 (8.33)	1.000
Headache (%)	4 (8.89)	3 (6.25)	1.000
Insomnia (%)	2 (4.44)	2 (4.17)	1.000
Nausea (%)	2 (4.44)	2 (4.17)	1.000
Somnolence (%)	1 (2.22)	0 (0)	1.000
Stomachache (%)	0 (0)	1 (2.08)	1.000
Myalgia (%)	0 (0)	1 (2.08)	1.000
Palpitation (%)	1 (2.22)	0 (0)	1.000

The most common adverse events in the study group were tongue numbness (46.67%), dry mouth (26.67%), and anorexia (20%). No statistically significant differences in adverse events between the study and control groups were found. At one month, tongue numbness (44.12%) was the most frequent

adverse effect in the *VC* group, higher than in the placebo group with statistical significance (p=0.01).

When comparing laboratory data at the baseline through twelve weeks between the intervention and control groups, all the laboratory examinations showed no statistically significant differences.

DISCUSSION

Vernonia cinerea, a traditional Thai herb, has been recognized as an alternative treatment for smoking cessation in Thailand. This research study was conducted to determine whether *VC* lozenges were an effective and safe option for stopping smoking for smokers in Thailand who had NCD. After four weeks, among 93 smokers with NCD, *VC* lozenges showed a trend for higher CAR (OR 10.74; 95% CI 0.82-140.28) in this randomized, placebo-controlled study, with no harmful side effects.

The exact mechanism for stopping smoking by *VC* remains unknown, but neurotransmitter metabolism regulation may be involved (Pouyfung et al., 2017; Prasopthum et al., 2015). Previous studies have reported conflicting results about the effect of *VC* products on smoking cessation (Chaikoolvatana et al., 2017; Chaisawad and Makanuntachote, 1996; Leelarungrayub et al., 2010; Lertsinudom et al., 2021; Tripopskul and Sittipunt, 2016; Wongwiwatthananukit et al., 2009). Based on a meta-analysis (Puttarak et al., 2018), the *VC* products increased CAR by 1.54 and 2.18 times at weeks four and 12, respectively, when compared to the placebo. In terms of comparing the effect of *VC* products with active comparators on smoking cessation, only one study compared *VC* 2 grams with nortriptyline and the CAR (primary outcome), daily cigarette use, exhaled CO level, and relapse rate. Results demonstrated that the effectiveness of *VC* was not inferior to nortriptyline (Tuenthosarn et al., 2023). In our study, the *VC* lozenges did not have a significant effect on CAR in NCD patients, possibly primarily due to a lack of participants. At both four and 12 weeks, no significant difference was recorded in PAR between *VC* lozenges and the placebo. Studies by Chaikoolvatana et al. (2017), Chaisawad and Makanuntachote (1996), Leelarungrayub et al. (2010), Lertsinudom et al. (2021), Tripopskul and Sittipunt (2016); and Wongwiwatthananukit et al. (2009) indicated similar results, with *VC* products showing greater smoking cessation rates than the placebo.

NCD patients who received *VC* lozenges smoked fewer cigarettes per day compared to the baseline after the 12-week intervention period. However, the number of daily cigarettes was obtained from interviews and patient reports without objective data confirmation. After 12 weeks, the exhaled carbon monoxide levels in the *VC* group were lower than the baseline. These positive results supported the effect of *VC* products as an alternative for smoking cessation.

The WHO and the United States Medical Office declared in 2000 that smoking was one form of chronic disease and recommended that smoking should have standard practice recommendations for quitting (Fiore, 2000). Only 7% of smokers who received counseling alone without medication successfully quit, while for those who received both counseling and medication, the rate of success was 30% (Fiore, 2000; Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel). The medication regimen for smoking cessation requires at least one to three months, and the cost of the drugs is another obstacle for patients. Therefore, *VC* showed promise as an attractive, cheap alternative therapy for stopping smoking.

Most previous studies that examined the use of *VC* products to assist in stopping smoking were performed on healthy smokers, raising concern when these methods were applied to smokers who had underlying medical conditions, particularly NCD. A study in the Songjiang and Fengxian districts of Shanghai found that every one in five smokers had an NCD (Wang et al., 2022). Research conducted in Japan revealed that only 20% of patients with TIAs or asthma were able to stop smoking within one year after diagnosis, and only 40% of patients diagnosed with lung cancer or acute myocardial infarction were able to stop smoking (Taniguchi et al., 2023). In our study, NCD patients assigned to receive *VC* lozenges and those assigned to receive a placebo had comparable incidences of major adverse events. At four weeks, more patients in the *VC* lozenges group than in the placebo group experienced tongue numbness. A well-known side effect of *VC* products is tongue numbness caused by high concentrations of nitrate compounds in *VC* (Ketsuwan et al., 2017). However, at 12 weeks, there was no difference in this unfavorable effect between the two groups, consistent with no difference in tongue numbness between the *VC* tea and control groups (Wongwiwatthananukit et al., 2009). This effect may be described by patients who tolerate this adverse effect over time.

The advantage of this study was double-blind for NCD patients instead of healthy subjects to provide more data for *VC* products on smokers who had NCD. *VC* lozenges with a standardized amount of essential substances in each lozenge were used, and the treatment period was extended from four weeks to 12 weeks. The major limitation of this trial was enrolling only 93 smokers with NCD. This number was less than originally planned. Based on the odds

ratio, the *VC* lozenges might show positive outcomes if we enrolled enough participants. The loss of follow-up rate was higher than estimated because, during the COVID-19 outbreak, some patients were reluctant to visit the hospital or community pharmacy. The NCD patients in our study were stable outpatients, and they should be cautious when used with unstable patients.

CONCLUSION

This study shows that in smokers with NCD, the CAR rate at four weeks in the *VC* lozenges group was not different from that of the placebo group. NCD patients who received *VC* lozenges were well tolerated, and no serious side effects were found.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Bunditanukul K	Sittipunt C	Phrommintikul A	Chokemaitree N	Sakthong P
Concepts or ideas	x	x			x
Design	x				x
Definition of intellectual content	x				x
Literature search	x				
Clinical trial	x		x	x	
Experimental studies	x				
Data acquisition	x		x	x	
Data analysis	x				x
Statistical analysis	x				x
Manuscript preparation	x				
Manuscript editing		x	x	x	x
Manuscript review	x	x	x	x	x

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