DEVELOPMENT AND EVALUATION OF THE EFFECTIVENESS OF *VERNONIA CINEREA* (VC) COOKIES FOR SMOKING CESSATION

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ABSTRACT:

Background: *Vernonia cinerea* (VC) has been known as a herbal medicine for a long time. Recently, it was used for smoking cessation. The study investigated the effectiveness of VC cookies in smoking cessation, side effects and satisfaction with this product.

Methods: The study was designed as a quasi-experimental study. VC cookies were developed. A total of 63 subjects (high school students) were selected and all were current smokers. Each subject was selected into the VC or non-VC (Control) group. The study (VC) group received 5 VC pieces a day, whereas the control (non VC) group received 5 plain cookies per day for six months. All data were collected via a questionnaire paper. The descriptive and analytical analyses including Chi-square (χ^2) test and Mann-Whitney–test, and adjusted odds ratio and 95% confidence interval were used.

Results: The percentages of quitters in the study (VC) group were significantly higher than those in the control (non VC) group throughout 6 month periods (*VC; 81.8, 97, 81.8%, Non-VC; 3.3, 6.7, 13.3%, p* <.001, .001, and <.001, consecutively). Additionally, average carbon-monoxide (CO) levels of the VC group from *1*-month to *6*-month periods were significantly lower compared to the non VC group (p <.001). Common side effects of VC found, including; dry mouth and throat, high blood pressure.

Conclusion: *Vernonia cinerea* (VC) has been shown the high percentages of sustained abstinence rates with the decrease of CO levels compared to non VC group. Some minor side effects and positive feedback regarding VC cookies were also reported. Further investigations of the efficacy and safety of VC products should be conducted.

Keywords: *Vernonia cinerea* (VC) cookies; Smoking cessation; Side effects of smoking

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INTRODUCTION

Cigarettes can cause lung diseases including tuberculosis (TB), coronary heart disease, and linked to a variety of other conditions and disorders, including slow healing of wound, infertility and peptic ulcer disease [1-3]. According to a previous study, it was revealed there were significant associations between early age at initiation of smoking, duration of smoking, and smoking exposure and the occurrence of tuberculosis [4]. Moreover, Smoking had a strong relation with other risk behaviors such as drug use, alcoholic consumption. In Asia, Thailand is one of the critical

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regions for tobacco consumption. The Thai National Statistics Office reported that the prevalence of smoking among adolescents aged 15 to 18 had increased from 4.29 percent in 2004 to 4.45 percent in 2006[5]. This evidence has been confirmed by the Global Adult Tobacco Survey (GATS) finding that showed that 25.4 percent of all daily smokers or occasional smokers were in the 15-24 age group, indicating that young adults are the largest at-risk group. Noticeably, despite the dangers of cigarette smoking, many still continue to smoke. However, for those who wanted to quit might try different methods including, willpower, counseling, and pharmacotherapy [6]. They might experience some disadvantages including, various responds, high cost, and some side effects which affect patient affordability, unpleasant outcome, resulting in underutilization of these cessation strategies [7-9]. Thus, there is certainly a need to search for alternative or new treatment for smoking cessation to reach the diverse needs of smokers.

In Thailand, the plant of the genus *Vernonia cinerea* (VC) (Compositae) is widely distributed in most tropical and subtropical countries, and has long been used in traditional medicine to treat various types of diseases. This herb has been used to treat a number of disorders including inflammation, malaria, fever, worms, pain, diuresis, cancer, abortion, and various gastro-intestinal disorders [10]. Interestingly, this herb has been widely used to quit smoking in Thailand and other countries [11-15]. Regarding the smoking cessation effect, the mechanism of smoking cessation is the chemical substances inside VC called 'nitrate salt', potassium nitrates which induce tongue numbness, and cause less favor of cigarette smell and taste. Therefore, a smoker does not enjoy smoking cigarette and consequently cut off number of cigarettes [16]. This medicinal herb is also official in Herbal List of National List of Essential Medicine 2011 for smoking cessation, remedy dose of 2 g in 120 - 200 ml boiling water, after meal, for 3-4 times daily [17]. It was found that the potassium nitrate obtained from the stems and roots of VC [17]. Nitrate salt is claimed to act as smoking tasteless and facilitating smokers to give-up smoking. The cessation products of VC have been investigated recently including, VC coffee, capsules, and tea bags [13, 18-20]. The overall results of each product were favorable despite some limitations occurred including, only adult groups, lack of randomization, and short term follow up [18, 19, 21, 22].

Regarding the cessation indicators, quit rates, carbon-monoxide (CO) levels, and smoking behavior changing are all crucial values to predict whether a smokers could quit smoking successfully. Generally, a study required at least one indicator to assess the quit success. Regarding CO gas, a cigarette normally produces CO gas during the burning process, gets into and remains in the lungs after smoking. At present, CO measurement is one of the precise indicators to investigate the quit success. As the endogenous carboxyhemoglobin level in man is estimated between 0.1 and 1.0 percent. CO dissociates very slowly due to the tight binding of CO to haemoglobin, having a half-time of 3–4 hours. Consequently, CO reduces the total amount of oxygen available by direct replacement of oxygen with CO [23]. The smoking of tobacco, particularly as cigarettes, results in increased CO levels. As a result, it has been estimated that cigarette smokers may be exposed to a CO concentration of 460–575 mg·m-3 (400–500 ppm) for the approximate 6 min needed to smoke cigarette [24, 25].

The amount of CO gas left in the lungs depended upon the duration of cigarette smoking (the longer duration, the higher levels). As a result, when using CO levels, a smoker needs to blow their breath into a CO meter which digitally calculated CO which left in their lungs. Normally, the cutting points of standard CO levels related to the severity of nicotine addiction were not officially addressed. We followed a guideline of Thai Health Professional Alliance Against Tobacco. In this study, CO levels and history data were implemented to be as the indicator for quit success, because the CO meter is available for each smoking cessation clinic enrolled into 'Pharsai Clinic Network, Thailand'.

As the young smokers in Thailand are the high risk majority that need to be sorted out. Also, currently the available VC products might not be suitable for them. Therefore, a research group of Pharsai Clinic, Ubon Ratchathani University has developed an innovation for quit smoking called '*Vernonia cinerea* (VC) cookies' which help young smokers gradually quit smoking with pleasant tastes of cookies without any serious side effects. The study aims to investigate the effectiveness of VC cookies related to smoking cessation via carbon-monoxide (CO) levels. Additionally, levels of nicotine withdrawals were important to see whether the subjects could tolerate and get through the rough time during the study period. Withdrawal levels

were rated from 1 to 10 depended on how much the subject felt on craving. Furthermore, the measurement of safety related VC cookies is important to consider whether the innovation could be possibly developed as 'a real product'.

MATERIALS AND METHODS

Design

The study was a quasi-experimental study. The study was conducted between August 2015 and March 2016 (8 months).

Participants

The subjects were junior high school students with a history of cigarette smoking in the past month (at least 1 roll/day). They need to be qualified via inclusion criteria including, 1) no history of cardiovascular, renal, liver, and mental diseases, 2) non-pregnancy, 3) no history of cessation therapy prior to the study, and 4) good communication. The consent agreements were signed prior to the study. If the subjects experienced with any serious side effects including arrhythmias, gastrointestinal bleeding, showed hypersensitivity to VC during the treatment period, they would be asked to withdraw from the study. Totally there were 63 subjects enrolled into the study. A teacher had already divided subjects into two groups. Later the investigators randomly selected each group to be either a study (33) or a control (30) group via a simple random sampling technique. A smoking history form was filled out three different times including; first visit, 3-month visit, and 6-month visit.

Prior to the study, all subjects were requested to sign the consent forms in which all personal information were confidential. This study was conducted under the approval by the Mahidol University Institutional Review Board (MU-IRB) (COA. No 2014/011.401).

Vernonia cinerea cookies development

Dried VC was boiled with water at 80^{o}C for 45 minutes to extract the essential crude from VC. The extract solution was frozen with 'freeze drying technique' until received VC powder. Since a smoker normally needs 6 g of VC powder per day to stop smoking [12]. Therefore each piece of cookies made was contained 1.2 g of VC powder. As a result, the subject was required to eat 5 pieces of VC cookies per day (6 g) to reach cessation effect. There were 2 favors of VC cookies, vanilla and chocolate and they were developed and tested via the subjects to assure the taste was favorable. The VC cookies were freshly prepared for the subjects every 2 weeks throughout 6 months as required for smoking cessation. Both groups received cookies from the investigators. Each day, the VC group took five pieces of VC cookies before class, on the weekend they were given 10 pieces of VC cookies. This process was similar to those in the non-VC group. Only the investigators knew which cookies contained either VC or non-VC.

Steps of *Vernonia cinerea* cookies evaluation

Questionnaire

The investigators followed a guideline of Thai Health Professional Alliance Against Tobacco for questionnaire items. It contained the following information related to smoking history: 1) Demographic data including, gender, age, education background, income, medical history, marital status, and alcohol consumption, 2) Smoking history including, types of cigarettes, smoking duration, and number of rolls (per day), carbon-monoxide (CO) levels, 3) Cessation strategies including, types of treatment (VC or non-VC cookies), counseling duration , and withdrawal symptoms. Regarding the satisfaction of the subjects related to VC cookies, Likerts' scale rating was implemented and scored into different scales from *Very much* (5) to *Very little* (1) based on an individual questionnaire item. The reliability of VC satisfactory question items was assessed with 30 participants to measure the Cronbach's Alpha Coefficient of the question items (α). The mean value of α was 0.789 (standard $\alpha \geq 0.7$). The VC group informed some common side effects of VC via the questionnaire items.

Outcomes

The primary outcomes included continuous abstinence rates (CAR) at *1*-, *3*-, and *6*-month periods between study (VC) and control (non-VC) groups. Secondly, CO levels between groups at the same different periods were measured via CO meter. In addition, the comparisons of CO levels between groups from one to six-month periods were evaluated (CO 1-3 ppm → *Normal*; 4-6 ppm → *Low*; 7-8 ppm → *Moderate*; and above 8 ppm → *High*). Thirdly, the occurrence of any side effects including, dry mouth and throat, high blood pressure, nausea and vomiting, headache, and anxiety which could be observed via the interview. Finally, the relationship between CAR and VC was investigated

Conducting the study trials

VC and plain (non-VC) cookies were produced

Table 1 Demographic data (m =63)

Demographic information	VC group (n=33)		Non-VC group (n=30)		*p*-value
	f	%	f	%	
Gender(s)					
Males	31	93.9	30	100.0	0.493[a]
Females	2	6.1	0	0.0	
Age (years)					
Mean (S.D.)	13.6 (0.7)		13.4 (0.9)		0.331[b]
Median (IQR)	14 (1)		13 (1)		
Alcohol consumption					
Never	30	90.9	20	66.7	
Sometimes	1	3.0	1	3.3	0.024 [a]
Regular	2	6.1	9	30.0	
Smoking history					
Yes	25	75.8	30	100.0	
No	-	-	-	-	0.005 [a]
Ex-smoker(s)	8	24.2	0	-	
Types of cigarettes					
Factory	33	100.0	27	90.0	
Roll your own (RYO)	-	-	1	3.3	0.102 [a]
Both	-	-	1	3.3	
Miscellaneous	-	-	1	3.3	
Duration of smoking (months)					
Mean (SD)	13.5 (13.0)		4.7 (2.9)		0.001[b]
Median (IQR)	12 (13)		4 (5)		
Numbers of cigarettes (rolls/day)					
Mean (SD)	2.6 (3.6)		3.8 (2.4)		0.001[b]
Median (IQR)	1 (2)		3 (3)		

Note: [a] tested via Fisher exact test, [b] tested via Mann-Whitney test

every 2 weeks and given to the subject everyday after a first morning class. The subjects were given the information about this trial objectives and steps by a counselor. The questionnaire was given out to the subjects. Subjects in study group were required to take five pieces of VC cookies per day, whereas those in control group only took plain cookies with the same instruction. All subjects were blinded whether they received VC or plain cookies. In case, the subjects experienced some withdrawal symptoms, they were told to cope those symptoms via the withdrawal management protocol given at the first place. However, if the symptoms were serious, it was strongly recommended to seek a counselor. After taking cookies, all subjects were appointed to see the counselor for following up every month for six months. The subjects were allowed to quit the study at any time. Finally, all data were collected and analyzed later.

Statistical analyses

For demographic information, smoking history, common side effects, and nicotine withdrawal were measured via descriptive statistics including, frequencies, percentages, standard deviation (SD). Regarding the nominal and ratio variables, Chi-square (χ^2) test and Mann-Whitney –test were utilized to assess the group differences. For CO levels between groups, and average scores of nicotine withdrawals, mixed effects linear regression was used. Continuous abstinence rates (CAR) at *1*-, *3*-, and *6*-month periods between groups were analyzed via Chi-square (χ^2) test with significance at level 0.05. Finally, the investigation of the relationship between VC and cessation behavior was performed via multiple logistic regression by controlling some factors including, alcohol consumption, smoking duration, number of cigarette roll per day, and counselors. The results were revealed with adjusted odds ratio and 95% confidence interval.

RESULTS

Demographic data

Totally, there were 63 subjects in the study, 33 in study (VC) and 30 in control (Non-VC) groups. The majority were males with an average age between 13 and 14, and no history of alcohol consumption. Above seventy-five percent of subjects were current smokers who regularly

Table 2 Frequency, percentage of CAR between groups (*1-, 3-, and 6- months*)

Cessation behaviors	*1*-month		*p*-value	*3*-month		*p*-value	*6*-month		*p*-value
	VC	Non-VC		VC	Non-VC		VC	Non-VC	
Quit	27(81.8)	1(3.3)		32(97.0)	2(6.7)		27(81.8)	4(13.3)	
No quit	6(18.2)	29(96.7)	<0.001	1(3.0)	28(93.3)	<0.001	2(6.1)	24(80.0)	<0.001
Relapse	-	-		-	-		4(12.1)	2(6.7)	

Note: tested via Chi-square (χ^2) test

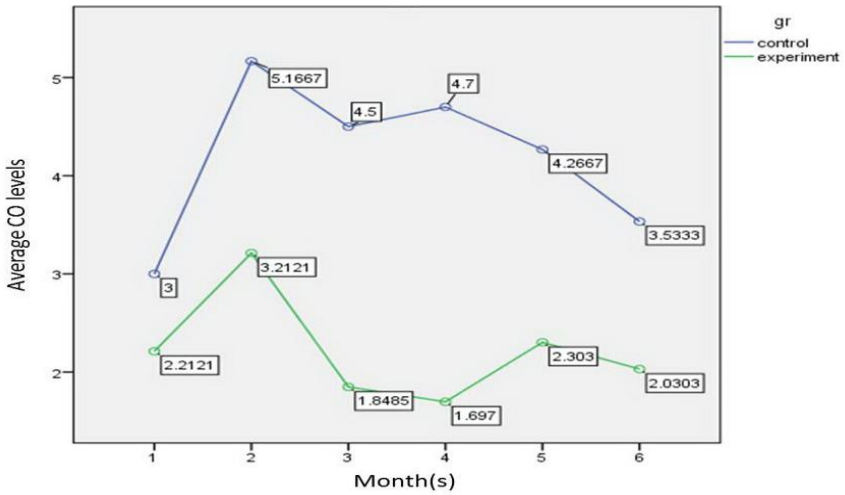

Figure 1 Average CO level between groups from 1- to 6- month periods

Note: CO level: 0-3 ppm Low nicotine addiction; 4-5 ppm Intermediate nicotine addiction; 6 ppm High nicotine addiction

Table 3 Comparison of CO levels between groups (*1-* to *6-* month periods)

Duration	Meandiff	95% CI diff	*p-value*	Meandiff$_{adj.}$	95% CI diff	*p-value*
1-month	ref			ref		
2-month	1.95	0.98, 2.92	<0.001	1.87	0.92, 2.83	<0.001
3-month	2.65	1.68, 3.62	<0.001	2.57	1.61, 3.53	<0.001
4-month	3.00	2.03, 3.98	<0.001	2.92	1.94, 3.90	<0.001
5-month	1.96	0.98, 2.94	<0.001	1.88	0.88, 2.89	<0.001
6-month	1.50	0.52, 2.49	0.003	1.42	0.30, 2.46	0.007

Note: Meandiff$_{adj}$: the differences of CO levels between groups when controlling some confounding variables

smoked 3 to 4 rolls of cigarettes per day with duration of smoking between five and fourteen months (Table 1).

Continuous abstinence rate (CAR)

The CAR at 1-, 3-, and 6-month periods of VC groups were 81.8, 97, and 81.8 % respectively. When compared CAR between groups from 1-, 3-, and 6- month periods, it was revealed the percentages of quitters in study (VC) group were significantly higher than those in control (non VC) group throughout 6 month periods (p <.001, .001, and <.001, consecutively) (Table 2). Noticeably, there were four subjects in VC group who still smoked regardless of taking VC cookies.

Average CO levels

Figure 1 showed average CO levels between groups from *1*-to *6*- month periods. It revealed CO levels in VC group were overall lower than those in non VC group. The ranges of CO levels of VC and non VC groups were 1.69 to 3.21, and 3 to 5.16 consecutively. As we know the smoking of tobacco, particularly as cigarettes, results in increased CO levels. Thus, it implied smokers taking VC cookies tended to cut down cigarettes more than those in a non VC group.

The results revealed average CO levels of VC group from *1*-month to *6*-month periods were significantly different compared to non VC group (p <.001). On *2*-month, CO level of VC group was

Table 4 Comparison of nicotine withdrawal levels between groups from *1*- to *6*- month periods

Duration	Meandiff	95% CI diff	*p-value*	$Meandiff_{adj.}$	95% CI diff	*p-value*
1-month	ref			ref		
2-month	0.85	0.51, 1.18	<0.001	0.91	0.55, 1.27	<0.001
3-month	1.37	1.01, 1.72	<0.001	1.44	1.06, 1.81	<0.001
4-month	0.65	0.28, 1.02	0.001	0.71	0.32, 1.10	<0.001
5-month	0.49	0.10, 0.89	0.015	0.56	0.14, 0.98	0.008
6-month	0.47	0.04, 0.90	0.031	0.54	0.09, 0.98	0.018

Note: $Meandiff_{adj}$: the differences of nicotine withdrawal levels between groups when controlling some confounding variables

Table 5 Comparison of VC cookies satisfaction between groups (1- and 6- month period)

Questionnaire items	*1*-month	*6*-month	Meandiff (S.D.)	*p*-value
You like the taste of VC cookies	4.00(0.98)	3.57(0.63)	0.43(1.33)	0.105^{w}
You think it is convenient to take VC cookies with you	3.67(0.48)	3.57(0.68)	0.1(0.88)	0.452^{w}
You think you will use VC cookies next time	3.57(1.28)	3.43(0.86)	0.13(1.28)	0.573^{t}
You think VC cookies help you to decrease your smoking	3.40(1.30)	2.97(1.00)	0.43(1.41)	0.149^{w}
You think VC cookies help you to quit smoking	3.07(1.26)	3.20(0.89)	-0.13(1.38)	0.601^{t}
You concern about side effects of VC such as dry throat and mouth	2.63(1.43)	2.23(0.97)	0.40(2.08)	0.169^{w}
You concern about side effects of VC such as dry throat and mouth	2.83(1.28)	2.23(0.98)	0.62(1.61)	0.031^{w*}

*Note: T = paired t-test, w= Wilcoxon sign rank test * significance at level 0.05*

decreased by 1.95 ppm, 2.65 ppm on *3*-month, 3.00 ppm on *4*-month , 1.96 ppm on *5*-month, and 1.50 ppm on *6*-month periods, compared to non VC group. When some confounding variables were controlled including, alcohol consumption, duration of smoking, number of cigarettes, the similar results were shown as $Meandiff_{adj}$. The differences of CO levels between groups were decreased by 1.87 in *2*-month, 2.57 in *3*-month, 2.92 in *4*-month, 1.88 in *5*-month, and 1.42 ppm in *6*- month periods (Table 3). Interestingly, it might be implied that during *3*- and *4*-month periods, the subjects tended to quit more successfully compared to the others.

Nicotine withdrawal levels

It was reported there were some significantly differences of nicotine withdrawal levels between two groups ($p<.05$) when some confounding variables were controlled including, alcohol consumption, duration of smoking, number of cigarettes. $Meandiff_{adj}$ values between groups were dropped continuously throughout *6*-month periods (0.91 to 0.54), except on *3*-month (Table 4).

Common side effects of VC cookies

Frequencies (f) of VC side effects were counted during *1*- , *3*-, and *6*-month periods. The most common side effects of VC found in study group were dry mouth and throat, especially in *1*-month period (f= 26, 7, and 3), followed by insomnia (f= 5, 0, 2), and headache (f= 3, 0, 0) respectively. However, those symptoms were relieved when the time passed. Regarding dry mouth and throat, the subjects informed to drink plenty of water to relieve the symptom.

VC cookies satisfaction

Once the subjects completed the study, they were asked to be interviewed regarding having the VC cookies. The subjects were satisfied with VC cookies taste, product carrying, and continuation of VC cookies (> 60 %). Nevertheless, subjects still concerned about some common side effects of VC including, dry throat and mouth, and high blood pressure. When compared between *1*- and *6*- month periods, the subjects were less favorable about common side effects of VC, particularly high blood pressure. The score of satisfaction on this topic was significantly dropped by 0.62 points (p = .031). Nevertheless, they were overall satisfied with taste, product carrying, smoking cessation effect, and continuation of VC cookies with no statistical differences (Table 5).

The relationship between VC and cessation behavior

Interestingly, there was a significant relationship between VC cookies and cessation behavior. VC subjects had a chance to quit smoking more than non VC subjects 20.38 times (95% CI: 1.65, 251.60) when controlled some confounding variables including, alcohol consumption, duration

Table 6 Relationship between VC and cessation behavior

Groups	Number of quitters (%)	OR_{Crude}	95%CI	OR^{a}_{Adj}	95%CI
Non VC	4(13.33)	1		1	
VC	27(81.80)	28.17**	7.11, 111.62	20.38*	1.65, 251.60

[a] *Adjusted Odds ratio* * *significance at level 0.05* ** *significance at level 0.001*

of smoking, number of cigarettes, and types of counselors (Table 6).

DISCUSSION

In Asian countries including Thailand, *Vernonia cinerea* (VC) is commonly known a medicinal plant [26]. This herb has been used to treat a number of disorders including inflammation, malaria, fever, worms, pain, diuresis, cancer, abortion, and various gastro-intestinal disorders [27]. Interestingly, has been documented and widely used as a Thai traditional medicine and in other countries for relieving cigarette craving [16, 28, 29]. In Thailand, VC was initially studied for smoking cessation effects in 1994 by a pharmacist researcher [30]. Thus, this first investigation has gained some public attention regarding effects of VC related to smoking cessation. Later many trials have widely been investigated its pharmacological effects including, ameliorative potential for neuropathic pain and smoking cessation [13, 31-33].

The CAR results were favorable satisfied by the end of the study. As a number of quitters in VC groups were higher than those in non VC group (Table 2). Noticeably, as the purpose of the study was to investigate whether VC could possibly help subjects stop smoking. Therefore, only four smokers in VC group who continued to smoke (Table 2) would not interfere the overall favorable results of VC smoking cessation effect. The similar findings were reported in some previous studies [12, 34, 35]. For example, one study evaluated the effects of *Vernonia cinerea* (VC) supplementation and exercise on oxidative stress biomarkers, beta-endorphin release, and the rate of cigarette smoking. The results founds most participants had lower levels of CO after the intervention. The smoking rate for light cigarette decreased [34]. The VC mouthwash formula was another VC-product developed by Thai-researchers [36]. It contained similar nitrate salts which caused tongue numbness and eventually quit smoking. Interestingly, an innovation of VC was found in a southern area of Thailand called 'VC coffee'. It added the value to coffee for Krabi's agricultural promoting, and response to ministry of health's policy in smoking cessation for health enhancement. The findings showed the volunteer smokers were less addicted, evaluated by Fagerstrom test (FTND), the score 6.35±1.14 was less to 5.10±1.97 and 3.35±2.32 after 1 and 2 months in sequent of coffee consumption with 95% confident [20]. Another trial produced the similar results was a 24 week, randomized, single-blind, placebo-controlled, parallel trial. Primary outcomes were continuous abstinence rate (CAR) and the 7 day point prevalence abstinence rate (PAR). Results showed that CARs and PARs tended to be greater than in VC compared with the placebo over 24-week follow-up period, but this difference was not statistically significant [12]. Our results suggest that VC may be of potential alternative treatment with cost savings for smoking cessation. The findings also showed the maximum differences of CO levels between groups during *3*- and *4*- month periods by 2.57 and 2.92 ppm (Table 3). Additionally, VC subjects had more chance to quit cigarettes compared to those in non VC (20.38 times) (Table 6). Thus, it was implied VC could be able to decrease cigarette smoking via its mechanism of actions.

Exhaled carbon-monoxide is a readily available, simple and affordable marker that can be assessed using a noninvasive technique that produces immediate and reliable results [37]. The subject only holds their breath for 20 seconds, then blows into a CO monitor. Readings of CO levels more than 10 ppm indicated that smoking has probably taken place in the preceding 12–24 hours. The results of an initial test may sound alarming to many smokers, but within just a couple of days of stopping, CO levels drop right down to normal, it will be very encouraging for smokers to see the difference after working their way through the first few days without cigarettes. Thus, CO monitoring could be a motivational tool [38]. From these explanations, all participants in the study were instructed the correct techniques of using CO meter during the visits. For each visit, they were asked to write down the CO level each time for self-monitoring alongside with some advice to help a smoker get through a tough time.

What remains controversial is the actual level of

CO that indicates a patient continues to smoke. To date, no reliable cut-off point has been set that differentiates between smokers and non-smokers [39]. In this study, the authors followed a guideline of Thai Health Professional Alliance Against Tobacco indicated CO cut-off point as in 'measurement' section. Another limitation is CO levels fall overnight and so morning readings may give misleadingly low results. It is suggested to collect afternoon CO levels to avoid.

Regarding side effects, most available medications could cause insomnia, dry mouth, nausea, drowsiness, and tongue numbness which normally occurred with VC products [30]. We observed no serious adverse events across two groups except dry mouth and throat. Another evidence of VC safety came with a short review which evaluate and systematically review the medicinal properties of the plant *Vernonia cinerea* and serious side effects. The findings indicated the plant has some potential pharmacological effects used for further studies and treatment purposes in living individuals instead of the drugs used which may have various side effects. Additionally, the whole plant is said to have minimal side effects [40]. Additionally, there has recently been a meta-analysis which investigated clinical studies of the efficacy and safety of medications used in tobacco dependence. The main results of Cochrane Collaboration with meta-analysis compared the effectiveness of medications used for tobacco dependences with placebo, revealed *Vernonia cinerea* (VC) showed efficacy in small clinical studies (quit rate 40-62.7 percent within 2 months follow-up period) and minor side effects including, nausea vomiting, dry mouth [33].

For the satisfaction of taking VC cookies, the findings were overall favorable, except for common side effects. Recently, *Venonia cinerea* products including, coffee, tea, capsules, and cookies have been developed and utilized for smoking cessation due to their ease, convenience, taste, and efficacy[41-43]. Nevertheless, some common side effects were addressed including, dry mouth and throat, high potassium level, high blood pressure. As a result, the information related to indication, precaution, and patient education of VC products are essentially required [44].

Overall, *Vernonia cinerea* (VC) cookies could be implemented into national policy related to tobacco control in Thailand, especially for young smokers. As its advantages including low cost, well effective, and minor side effects are investigated, this alternative might be able to be an alternative for a smoker seeking to quit smoking. More adequate data related to the efficacy and safety is required. The advocacy from the government and anti-tobacco network in Thailand is essential to support the research funding and manpower. As a result, more available choices for smoking cessation will be provided for the seekers.

Finally, it is important to address some noticeable limitations. First, the sampling method might not have been suitable. All participants were non-randomly selected by a teacher into two groups. Then each group was randomly selected to be either a study (VC) or a control (non-VC) group. Most likely, the participants in the study group tended to have longer duration of smoking and more alcohol consumptions compared to those in the control group. Therefore, the basic characteristics of both groups were different and might have lead to the uncertainty of the outcomes. To minimize the limitation, a randomized-controlled trial (RCT) with single blind should be conducted for the further study. Secondly, there were two female smokers in the VC group (Table1). A previous finding found that men and women differ in their smoking behaviors. For instance, women smoke fewer cigarettes per day, tend to use cigarettes with lower nicotine content, and do not inhale as deeply as men [45]. As a result, the smoking cessation strategies between genders could be different. Moreover, there are some evidences indicated the gender is a factor affecting success in quitting smoking [46, 47]. Thus, the genders could minimize the creditability of the study results. Fortunately, the overall outcomes analyses with or without female smokers were not different. However, the investigators should carefully consider on this issue for the future work.

CONCLUSION

Vernonia cinerea (VC) has been proved to be an alternative for smoking cessation. Some crucial indicators including, CAR, CO levels, side effects were measured and the findings were revealed the subjects responded to VC cookies favorably, except some minor side effects including dry mouth, headache. Further investigations regarding long term efficacy and side effects are needed. Also, vital signs and blood chemistry are required for safety. The investigation of multi-center trails needs to be conducted. Finally, this innovation should be further

commercially supported by the government to be 'One Tambon One Product' (OTOP) which helps villagers to establish their own incomes.

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Conflict of interest

There is no conflict of interest related to the trial. It was funded by the National Alliance for Tobacco Free Thailand for academic and research purposes only. This innovation is currently in the process of Petty Patent filing from Department of Intellectual Property (DIP), Thailand.

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