EFFICACY OF *VERNONIA CINEREA* FOR SMOKING CESSATION

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ABSTRACT: The aim of this study was to compare the efficacy and safety of *Vernonia cinerea* Less. (Compositae) (VC) with placebo. A 24 week, randomized, single-blind, placebo-controlled, parallel trial was conducted at outpatient smoking cessation clinic at Thanyarak Institute, Pathumthani, Thailand. A 3-gram of crushed dried whole plant of VC was prepared in infusion tea bag. Sixty-four subjects were equally randomized to receive a 14-day VC tea taken three times daily or placebo. Primary outcomes were continuous abstinence rate (CAR) and the 7-day point prevalence abstinence rate (PAR) which were confirmed by urine cotinine. Adverse events and laboratory data were assessed at baseline and at clinic visits. Results showed that the 12-week CARs were 28.1% with VC versus 12.5% with placebo (p = 0.12). CARs through 24 weeks post-treatment were 18.8% with VC and 9.4% with placebo (p = 0.28). The 7-day PARs at week 12 were 43.8% with VC versus 21.9% with placebo (p = 0.06) and at week 24, 34.4% with VC versus 15.6% with placebo (p = 0.08). VC was well tolerated with no serious adverse events. As expected, the daily cost of VC ($0.30) was lower than that of daily bupropion ($2.42) and nicotine replacement therapy (gum and patch) ($2.72 - $3.65). 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. Our results show promise and suggest that VC may be of potential alternative treatment with cost savings for smoking cessation. Larger scale trials are needed to verify the efficacy of VC.

Keywords: smoking cessation, *Vernonia cinerea* Less, effectiveness, safety, tobacco dependence, placebo-controlled trial

INTRODUCTION: Tobacco smoking is recognized as contributing to a number of acute and chronic disease processes[1]. It is the leading preventable cause of morbidity and mortality, with enormous economic costs for the individual smoker and for society in general[1,2]. This habit globally kills more than 5 million people annually[2] and will rise to over 8 million deaths per year in 2030[2]. Yet, despite numerous attempts to enlighten people about the dangers of smoking, many begin and continue to smoke. Smokers who try to quit using willpower have about 5-7% long-term success[3]. If they use behavioral counseling and/or pharmacotherapy, the long-term quit rates are approximately double or even trebling the rates of successful quitting relative to placebo, which is generally less than 30%[3-5]. Despite the benefits of pharmacotherapy, its major disadvantage is high cost, which may affect patient affordability, resulting in underutilization of this therapy[5]. Some medications are also associated with unwanted side effects such as weight gain, nausea, dry mouth and sedation[4-6]. Long-term abstinence remains difficult and is associated with a high rate of relapse[3-6]. Thus, there is clearly a need to search for alternative or new treatment for smoking cessation to meet the diverse needs of smokers.

VC has been documented and widely used as a Thai traditional medicine and in other countries for relieving cigarette craving, asthma, cough, fever, malaria, arthritis and urinary calculi[7-11]. It is a perennial herbaceous plant distributed in the tropical regions which are commonly found in South-East Asia and Hawaii[7,8,11,12]. A one-group design study has been conducted to determine the effectiveness of an infusion tea bag of VC in 62 healthy smokers[13]. A 4-gram tea bag which contained the whole dried crushed plant of VC 2.86 grams was prepared. Patients were instructed to take a 15-day VC tea taken three times daily with follow-up of smoking status

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through 4 months. At the end of 4 months, 43 patients (69.6%) were continuous abstinence from smoking and 19 patients (30.6%) failed to quit. Reasons for abstinence include tongue numbness, decreased appetite, decreased cigarette craving, dislike the taste and smell of cigarette smoke, and decreased coughing. However, there are some limitations in this study, such as no comparison group, lack of randomization, self-report smoking status without biochemical verification, lack of safety and adherence data, and short-term follow-up. To our knowledge, this study was the first trial designed to evaluate the efficacy and safety of VC for smoking cessation compared with placebo in healthy smokers.

MATERIALS AND METHODS:

Design

A randomized, single-blind, placebo-controlled, parallel trial was conducted between November 2006 to August 2007 at the outpatient smoking cessation clinic, Thanyarak Institute, Pathumthani, Thailand. The study protocol was approved by the Human Subjects Research Committee of Faculty of Pharmaceutical Science, Chulalongkorn University with the consent of the Director of Thanyarak Institute.

Participants

Smokers were at least 18 years of age, smoked $\geq$ 5 cigarettes/day in the past 6 months, motivated to quit smoking in the preparation or action stages of Transtheoretical Model[3,6], signed an informed consent form, and had no period of abstinence > 3 months in the past year. Subjects were excluded if they had a history of diseases including cardiovascular, cerebrovascular, gastrointestinal, endocrine, cancer, pulmonary disease, significant hepatic and renal impairment, neurologic and psychiatric disorder and those with clinically significant laboratory abnormalities. Other exclusion criteria were pregnancy or lactation, history of alcohol or drug abuse in the past year, previous use of smoking cessation products within a month (e.g., nicotine replacement, bupropion, nortriptyline, clonidine), and use of other forms of tobacco products other than cigarettes. If the subjects experienced an intolerable or serious adverse event such as arrhythmias, gastrointestinal bleeding, showed hypersensitivity to VC during the treatment period, they would be asked to withdraw from the study.

Interventions

A screening visit was conducted 2 weeks prior to the baseline visit (week 0). During the screening visit, we obtained a medical history, physical examination, chest x-ray, 12-lead electrocardiogram, vital signs (blood pressure, heart rate, body weight), laboratory data including complete blood cell count (CBC), fasting blood glucose (FBG), liver enzyme levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), renal function test (blood urea nitrogen [BUN], creatinine (Cr). A smoking history, demographic data, and the Fagerström Test for Nicotine Dependence (FTND)[14]score were also obtained. During baseline visit, we obtained baseline characteristics on subjects and enrolled subjects based on inclusion and exclusion criteria. All eligible subjects were randomly assigned to VC or placebo using block randomization (i.e., block size = 4). Subjects were blinded to treatment assignments. Adherence to treatment was assessed by counting leftover tea bags and interviewing subjects at clinic visit during the treatment period. Patients were instructed to leave any missed doses in the box and were examined by the investigators at the end of the 2-week treatment period. Good adherence to follow-up was defined as patients take the tea bag at least 90% of the total tea bags.

The whole plant of VC was prepared at Rangsit University, Pathumtani, Thailand by washing, air drying, and incubating in hot air oven set at 50-70 degree celsius. Subsequently, the plant were crushed and sieved to a smaller size and packed in a 3-gram of infusion tea bag. The aqueous soluble extract of the crushed dried whole plant of VC was standardized for the content of luteolin by thin layer chromatography. Subjects in VC group received a 3-gram of VC tea bag. They were instructed to use 14 days of treatment with VC tea taken three times daily by pouring 150 mL boiling water over tea bag, stirring well, covering cup for 15-20 minutes before drinking. Placebo group receive a 3-gram of *Morus alba* Linn. (MA)

infusion tea bag and received instruction to use similar to those in the VC group. The reasons to use MA were that the tea provides the same color similar to VC tea and there is no smoking cessation effect. Subjects were asked to completely stop smoking on their target quit date which was scheduled for day 8 after their baseline visit. Both groups were given standardized, individual brief 10-minute counseling based on the US Agency for Healthcare Research and Quality Guidelines[5] by a clinical pharmacist at each clinic visit. The follow-up period was 24 weeks with 5 clinic visits (weeks 2, 4, 8, 12, and 16) and 1 telephone contact (week 24).

Measures

The primary outcomes were self-report of continuous abstinence rate (CAR) and the 7-day point prevalence abstinence rate (PAR) which were confirmed by the measurement of urine cotinine. CAR was defined as no cigarette smoking, not even a puff since target quit date. PAR was defined as no cigarette smoking, not even a puff for the previous 7 days. Subjects who discontinued the study or who were lost to follow-up were classified as smokers for the remainder of the study. The urine cotinine confirmed self-report of CAR and PAR for 5 clinic visits was measured qualitatively by using GC 5890/ MS5972 Injector HP6890 series, USA. Vital signs were measured at all clinic visits and laboratory data were measure at the screening visit, week 2, and week 12. All observed or self-reported adverse events during the treatment period were documented in case report forms at week 1 using telephone contact and at the end of week 2 and followed up until they resolved or to the end of study.

Analyses

Based on the previous study[13], an estimated sample of 54 subjects was calculated to detect a difference of 35% abstinence rate between the VC and placebo groups[13] at an α significance level of 0.05 and a power of 80%. The statistical analyses were performed on an intention-to-treat basis. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 15.0. Both descriptive and inferential statistics were determined for outcome variables. Baseline characteristics were compared using the χ^2 test or Fisher's exact test or independent *t*-test, as appropriate. The odds ratio and the difference of CAR and PAR variables between the 2 groups was compared using the χ^2 test. Adverse events were summarized using frequencies and percentages and χ^2 test or Fisher's exact test was used for each type of adverse events to compare the percentage of subjects who experienced an event between the 2 groups.

RESULTS: Of the 75 subjects screened, 64 were eligible, randomized to receive VC or placebo (32 subjects in each group), and included in the analysis. Of the 64 subjects, 42.2% (27/64) completed the study. The 24-week completion rates were 47% (15/32) for VC and 38% (12/32) for placebo. The reasons for discontinuation in both 2 groups were loss to follow-up (53.1%) and refusal to participate further (4.7%). We treated those lost to follow-up and refusal (20.3%) as smokers. Adherence of 100% for the subjects who completed the 2-week treatment period was demonstrated by counting leftover tea bags at the end of week 2 clinic visit.

There were no statistically significant differences in the baseline characteristics and smoking history between those receiving VC versus placebo except gender, which percentage of male was significantly higher in the VC group (Table 1). Overall, the majority of subjects were male, 100% in the VC group and 78.1% in the placebo group. Subjects were aged 18 to 65 years and the mean ages were 40.1 and 41.7 years for VC and placebo groups, respectively. Subjects had smoked for 4 to 50 years with the overall means of 23.6 years and smoked a mean of 19.1 cigarettes/day over the past 6 months. The overall mean score on the FTND was 5.31 out of a possible total of 10.

The urine cotinine-confirmed CARs were not significantly higher for VC compared with placebo at all clinic visits (weeks 4, 8, 12, and 16) and at week 24 (Figure 1). The odds ratios, which were the likelihood of subjects treated with VC abstinence compared with placebo, tended to be

at doubling or nearly trebling a subject's odds at quitting smoking from week 8 through week 24. The 7-day PARs (Figure 2) were higher for VC than for placebo at all assessment points, but the differences in abstinence rate between the 2 groups were not significantly different. The odds ratios of the PAR at week 8, 12, 16, 24 demonstrated that about twice as many subjects in VC were abstinent in the previous 7 days than in the placebo.

No significant difference in the average change of blood pressure and heart rate was observed between the 2 groups at all clinic visits. Blood pressure and heart rate in each group at all clinic visits were not significantly different from baseline visit. There were no significantly different changes in CBC, FBG, AST, ALT, BUN, and Cr in each group at week 2 and week 12 from baseline visit. All laboratory data were also no significant difference between VC and placebo groups at baseline visit, week 2, and week12. Table 2 shows the percentages of subjects who reported adverse events during the treatment period. There were no significant differences in adverse events between the groups except percentage of subjects who disliked the taste and smell of cigarette smoke, which was significantly higher in VC group. No serious adverse event was reported during the treatment period. There were no significant differences in the mean body weight between VC and placebo groups at baseline visit, weeks 2, 4, and 12 (all $p>0.05$). The mean (SD) weight change from baseline visit to week 12 was 2.30 (0.19) kg for subjects who received VC versus

Table 1 Baseline Subject Characteristics

Characteristics	*Vernonia cinerea* (N = 32)	Placebo (N = 32)	p value[a]
Gender, N (%)			
Male	32 (100.0)	25 (78.1)	0.005[b]
Female	0 (0.0)	7 (21.9)	
Age, y mean ± SD (range)	40.13±11.86 (18-65)	41.72±11.29 (18-64)	0.584[c]
Weight, kg (mean ± SD)	67.39 ± 15.00	65.47 ± 12.22	0.576[c]
Body mass index, kg/m² (mean ± SD)	24.35 ± 5.30	23.88 ± 3.85	0.685[c]
Blood pressure, mm Hg (mean ± SD)			
systolic	121.72 ± 16.28	128.90 ± 19.92	0.112[c]
diastolic	71.47 ± 11.44	76.31 ± 11.12	0.091[c]
No. of years smoked			
mean ± SD (range)	23.44 ± 11. 79 (4-50)	23.81 ± 9.52 (5-44)	0.889[c]
No. of cigarettes/day in past 6 months			
mean ± SD (range)	19.88 ± 10.57 (8-60)	18.83 ± 10.31(10-60)	0.568[c]
No. of previous quit attempts			
mean ± SD (range)	2.31 ± 1.33 (1-5)	2.50 ± 1.69 (1-5)	0.623[c]
Fagerström Test for Nicotine Dependence score			
(mean ± SD)	5.22 ± 2.56	5.41 ± 1.86	0.725[c]

[a] statistical significance set at $\alpha \leq 0.05$.
[b] χ^2 test used to compare the number of patients between the 2 groups.
[c] Independent *t*-test used to compare the mean between the 2 groups.
[d] Score range from 0 to 10, with higher score representing a higher degree of nicotine dependence.

Table 2 Adverse Events Occurring of VC-treated Subjects Compared with Placebo

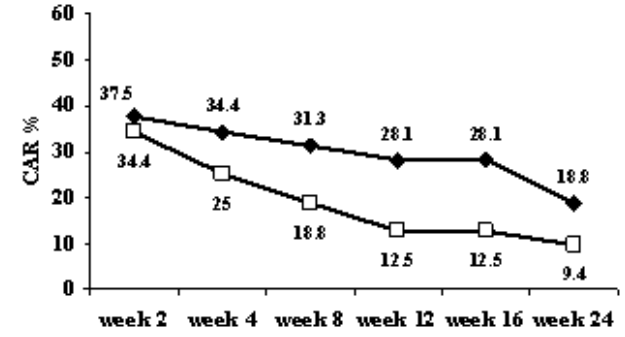
Adverse Events	VC Group (N = 32)	Placebo Group (N = 32)	p value[a,b]
Tongue numbness	15 (46.9)	14 (43.8)	0.802
Upper abdominal pain	7 (21.9)	6 (18.8)	0.756
Nausea	9 (28.1)	9 (28.1)	1.000
Headache	13 (40.6)	12 (37.5)	0.798
Palpitation	5 (15.6)	7 (21.9)	0.522
Drowsiness	19 (59.4)	20 (62.5)	0.798
Craving reduction	21 (65.6)	16 (50.0)	0.206
Dislike the taste and smell of cigarette smoke	20 (62.5)	12 (37.5)	0.046

[a] statistical significance set at $\alpha \leq 0.05$
[b] χ^2 test used to compare the number of patients between the 2 groups

1.54 (0.25) for placebo subjects. The daily cost of VC ($0.30) was lower than that of daily bupropion ($2.42) and nicotine replacement therapy (gum and patch) ($2.72 - $3.65).

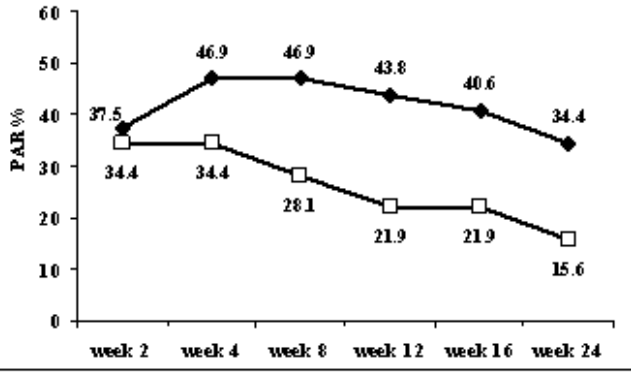
DISCUSSION: This study is the first, randomized, placebo-controlled trial to evaluate the efficacy VC compared with placebo in healthy smokers. VC group tended to produce higher CAR and PAR than placebo group at all follow-up periods. The smokers' odds at quitting smoking for VC were about 2.0-3.0 times that for placebo from week 8 to week 24. This is consistent with results of most current pharmacotherapies for smoking cessation[5]. However, our findings did not reach statistical significance due probably to the relatively small number of participants to detect the effect of at least 9.4 – 22.0% difference in CAR or PAR between the VC and placebo groups. Large scales trials with longer duration of treatment and follow-up are needed to verify the efficacy of VC versus placebo. One limitation of our study is that the inclusion criterion was limited to the relatively motivated healthy smokers, excluding smokers with concurrent medical illnesses. This may probably limit the generalizability of the results to the majority of smokers in a typical primary care population.

Few female smokers were enrolled in the study and there is a significant difference in gender between VC and placebo group. One might argue that gender may affect the abstinence rate, but several smoking cessation trials have indicated that the abstinence rates were not significantly different between male and female[15,16]. We observed no serious adverse events and abnormal laboratory data across two groups. The dropout rate was higher in the placebo than VC. This provides reassurance the tolerability of VC. Craving reduction and dislike the taste and smell of cigarette smoke were higher in VC compared with placebo. From this result, we hypothesize VC may decrease the reinforcing effect of cigarette



	week 2	week 4	week 8	week 12	week 16	week 24
p-value	0.794	0.412	0.248	0.120	0.120	0.281
Odds ratio	1.15	1.57	1.97	2.74	2.74	2.23
(95%CI)	(0.41-3.18)	(0.53-4.64)	(0.62-6.30)	(0.74-10.1)	(0.74-10.1)	(0.51-9.83)

Figure 1 Continuous abstinence rates (CAR) in *Vernonia cinerea* group compared with placebo



	week 2	week 4	week 8	week 12	week 16	week 24
p-value	0.794	0.309	0.121	0.062	0.106	0.083
Odds ratio	1.15	1.68	2.26	2.78	2.44	2.29
(95%CI)	(0.41-3.18)	(0.62-4.61)	(0.80-6.36)	(0.93-8.27)	(0.82-7.31)	(0.85-9.40)

Figure 2 7-Day point prevalence abstinence rates (PAR) in *Vernonia cinerea* group compared with placebo

smoking. A translational opportunity for research to discover the active compounds of VC as potential use for smoking cessation, evaluate its mechanism of action and potential as therapeutic agents, develop alternative dosage formulations of VC to enhance the convenience and adherence, and replicate clinical trials with larger sample size, optimal duration of treatment and longer follow-up period are warranted. Lack of affordability or health insurance to cover for smoking cessation pharmacotherapy can reduce smoker adherence, which may result in failure to quit smoking. VC produces a saving in the cost spent compared with other currently approved pharmacotherapy for smoking cessation. This could greatly lower the substantial costs of health care for smokers who desire to quit smoking.

CONCLUSION: Our preliminary study shows promise and VC could be an alternative therapeutic target with low cost for the treatment of tobacco dependence. VC was generally well tolerated. Unpleasant taste and smell of cigarette smoke and craving reduction were the most common report for VC. While our CAR and PAR results did not reach statistical significance due to the relatively small number of subjects, we hope that VC may be of potential use for smoking cessation and stimulate interest in future smoking cessation research.

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