J Herbmed Pharmacol. 2022; 11(2): 143-153.

http://www.herbmedpharmacol.com doi: 10.34172/jhp.2022.19

Journal of Herbmed Pharmacology

Efficacy of *Vernonia cinerea* (L) Less for smoking cessation: An updated meta-analysis of randomized controlled trials

Wiraphol Phimarn[1*], Rotjanawat Sakhancord[1], Kritsanee Saramunee[1], Bunleu Sungthong[2]

[1]Social Pharmacy Research Unit, Faculty of Pharmacy, Mahasarakham University, Kantharawichai, Maha Sarakham, Thailand, 44150
[2]Pharmaceutical Chemistry and Natural Products Research Unit, Faculty of Pharmacy, Mahasarakham University, Kantharawichai, Maha Sarakham, Thailand, 44150

ARTICLE INFO

Article Type:
Review

Article History:
Received: 11 October 2021
Accepted: 22 December 2021

Keywords:
Vernonia cinerea
Alternative treatment
Smoking dependency
Withdraw
Systematic review and meta-analysis

ABSTRACT

Vernonia cinerea (VC) has been used for smoking cessation. A previous meta-analysis (MA) reported the efficacy of VC in smoking cessation. However, there have been updated randomized controlled trials (RCTs) on the efficacy of VC for smoking cessation, and the previous MA lacked pooled adverse events (AEs) related to VC. The objective of this study was to systematically review and perform an updated MA on the efficacy of VC for smoking cessation continuous abstinence rate (CAR), prevalence abstinence (PAR), and AE. The research articles were retrieved via electronic databases including PubMed, Science Direct, Web of Science, Thai-Journal Citation Index Center (TCI), and ThaiLis. Ten RCTs published prior to 2019 were included in this study. The number of participants in the studies ranged from 35 to 172, and the follow-up duration for the primary outcomes was 2-12 weeks. Our updated MA found that VC could significantly improve CAR2 (RR=1.54; 95% CI = 1.06, 2.23), CAR4 (RR=1.65; 95% CI = 1.25, 2.17), CAR 8 (RR=1.85; 95% CI = 1.25, 2.75), CAR12 (RR=2.56; 95% CI = 1.66, 3.95), and CAR16 (RR=2.21; 95% CI = 1.03, 4.73). Moreover, VC improved PAR2 (RR=1.47; 95% CI = 1.06, 2.04), PAR4 (RR=1.35; 95% CI = 1.02, 1.79), PAR8 (RR=1.60; 95% CI = 1.11, 2.31), and PAR12 (RR=1.70; 95% CI = 1.25, 2.30). There was no significant difference in the AE between the two groups. The study substantiates claims that VC products are effective in assisting with smoking cessation.

Implication for health policy/practice/research/medical education:
This meta-analysis demonstrated that *Vernonia cinerea* product is an alternative treatment for smoking cessation.

Please cite this paper as: Phimarn W, Sakhancord R, Saramunee K, Sungthong B. Efficacy of *Vernonia cinerea* (L) Less for smoking cessation: An updated meta-analysis of randomized controlled trials. J Herbmed Pharmacol. 2022;11(2):143-153. doi: 10.34172/jhp.2022.19.

Introduction

Smoking presents many problems for global public health. According to a previous report, smoking is the most important but preventable cause of morbidity and mortality (1). In 2017, there were 1.1 billion people frequently smoking across 195 countries (2). Smoking is one of the most important risk factors for many diseases, such as cardiovascular diseases, respiratory diseases, and cancer (3-5). Previous studies have indicated that smokers have a lower quality of life than non-smokers (6). Therefore, health authorities around the world would like to control the problem by reducing the number of new smokers and helping current smokers to give up the habit (7).

Vernonia cinerea (VC) has been used to relieve cough, fever, stomachache, flatulence, and dysuria (8). VC relieves withdrawal symptoms because it contains nicotine. Additionally, VC contributes to smoking cessation by numbing the tongue, an effect arising from its high nitrate content. It also makes the cigarette smell unpleasant and perturbs the sense of taste (9,10).

Previous randomized controlled trials (RCTs) point to prevalence abstinence (PAR) and continuous abstinence rate (CAR) as effective measures of evaluating the efficacy of VC on smoking cessation (9,11,12). The systematic review and meta-analysis (MA) published in 2018 included five RCTs of VC in various dosage forms compared to placebos (capsules, lozenges, and juice) in 347 participants (13). In a previous review, the primary outcomes were CAR and PAR, which were directly compared using standard

***Corresponding author**: Wiraphol Phimarn,
Email: wiraphol.p@msu.ac.th

pairwise MA. In 2018 a systematic review with six RCTs on VC efficacy on smoking cessation has been published. However, there have been updated RCTs on the efficacy of VC for smoking cessation, and the previous MA lacked pooled adverse events (AEs) related to VC. Therefore, this systematic review and MA was conducted to update the estimation of treatment efficacy for all dosage forms available for smoking cessation and to compare the adverse side effects of all treatments.

Methods

Search strategy

This systematic review and MA was conducted according to the Cochrane Collaboration Framework guideline (14), and reporting follows the PRISMA statement (15). A literature search was performed to retrieve RCTs on the effects of VC on smoking cessation. The studies were identified from the following sources: PubMed, Science Direct, Web of Science, Thai-Journal Citation Index Center (TCI), ThaiLis, and the references of selected articles.

The search terms were constructed based on patients and interventions; they were "*Vernonia cinerea*" or "*Cyanthillium cinereum*", and "smoking" and "smoking cessation". The final search was performed on 31st August 2021.

The identified studies were selected for inclusion based on the information from the title and abstract, individual RCTs or cluster RCTs in smokers, studies examining the clinical effects of VC on smoking cessation, and studies comparing any dosage forms of VC and comparators. The exclusion criteria aimed at excluding studies with no reported outcomes of interest. The titles and abstracts were independently screened by WP and RS. Disagreements were resolved using the BS, if necessary.

Data extraction

Data extraction was performed by two authors (WP and RS) using the data extraction forms in accordance with the CONSORT statement for reporting herbal medicinal interventions (16). Data extraction included study characteristics, patient characteristics, details of treatment, details of outcomes, and data for pooling. The primary outcomes of interest were CAR and PAR at weeks 2, 4, 8, 16, and 24. The secondary outcomes were AEs, which were reported as a number/percentage of individuals experiencing AEs after receiving treatment.

Quality assessment and risk of bias assessment

The quality of the included studies was assessed using the Jadad scale (17). Scores had a possible range from zero to five; a cutoff of two was used to identify studies between high and low quality. Studies with a score of 2 points or less were classified as low quality, while those with a score of 3 or more were classified as high quality.

The risk of bias of the included studies was assessed using seven domains and their respective criteria, as described in the Cochrane Collaboration's tool for assessing the risk of bias. The Cochrane risk of bias was evaluated based on the number of criteria sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other sources of bias (18).

Statistical analysis

The primary outcomes were CAR and PAR. The secondary outcomes included AEs. If the recruited study reported the risk of abstinence as percent abstinence, then the results were converted to the number of participants exhibiting abstinence.

Pooled effects were calculated and stratified according to the outcome data. Summary statistics of dichotomous outcomes were expressed as a risk ratio (RR) with 95% confidence interval (CI), whereas summary statistics of continuous outcomes were expressed as mean with standard mean differences (SMD).

I^2 statistics were used to assess the heterogeneity between studies. In the absence of evidence for heterogeneity (P value of Q test more than 0.1 and I^2 statistic less than 50%, a random-effects model with the method of DerSimonian and Laird was used for all outcomes (19).

To ensure the robustness of the results, a sensitivity analysis was performed using fixed-effect models. In addition, we conducted subgroup analyses based on study design, VC dosage form, and VC extraction.

All analyses were performed using STATA version 14 (Stata Corp Statistic Software: Release 14. College Station, TX: StataCorp LLC) and RevMan version 5.2. Statistical significance was set at $P < 0.05$, except for the heterogeneity test wherein a P value < 0.1 was considered statistically significant.

Results

Study selection

A total of 172 articles were identified through database searching, including 81 from PubMed, 55 from Science Direct, 14 from Web of Science, 21 from the Thai database, and 1 from additional records identified through sources, as described in Figure 1.

By inspecting the title and abstract, 64 articles were screened out, leaving 14 articles for full-text review, after which, a further four articles were excluded. The reasons for exclusion in both the screening and full-text review steps, resulting in ten eligible studies, are shown in Figure 1.

Study characteristics

The characteristics of 10 eligible studies included 748 smokers, which were published between 2009 and 2019. All the studies were performed in Thailand. All were individual RCTs. The majority (7/10) were conducted in hospitals, while two trials were conducted in community

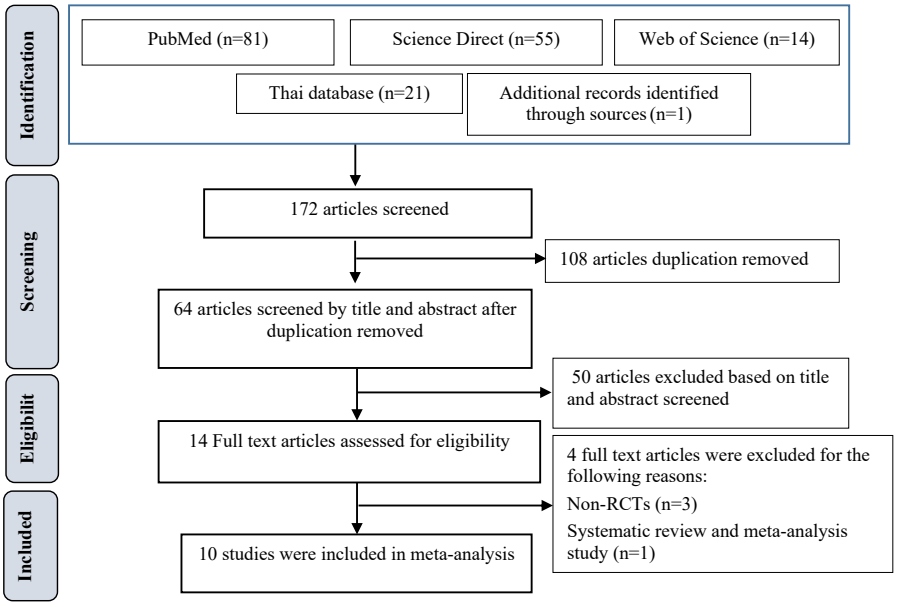

Figure 1. Flow diagram of studies selection.

pharmacies, and one study was performed in the course of home visits. All studies were conducted in a single center. Five studies were double-blind, RCTs.

The severity of nicotine dependence ranged from low to high. All studies assessed nicotine dependence by using the Fagerstrom test for nicotine dependence (FTND) score. FTND scores less than four and between four and six were defined as mild and moderate addiction, respectively (20). Most studies evaluated VC efficacy in smokers with moderate addiction. Only two studies (10,21) investigated the efficacy of VC in smokers with mild addiction.

Four trials have studied the efficacy of VC tea (9,21-23), two studies used VC lozenges (24,25), and two studies used VC pastilles (12,26), while two other studies evaluated VC capsules (11) and VC sprays (10). Only four studies have used VC extracts so far (10,12,24,26).

In terms of comparators, five studies described comparators as placebo capsules, lozenges pastilles, and sprays. Three studies used *M. alba* tea, while one study used *C. sinensis* tea as a control. All the tea used in the three studies had the same color and taste, but there were no smoking cessation effects. Two studies described the comparator as no placebo. The follow-up duration for the primary outcomes was 2-12 weeks. Most of the assessment outcomes were CAR and PAR, and only six trials reported adverse effects. The characteristics of the 10 eligible studies are presented in Table 1.

Quality of included studies

The results of the risk of biased assessment are shown in Figure 2. Only one study (21) was considered to have a high risk of bias in terms of random sequence generation and allocation concealment due to the lack of a statement regarding the process used for randomization or concealment. Moreover, in the blinding of participants and personnel domains, the risk of bias was high in two studies (22,25), which was described as a single-blinded RCT. By contrast, most studies were regarded as having a low risk of bias in incomplete outcome data, selective reporting, and other sources of bias. The Jadad score of most studies (6/10) ranged from 3/5 to 5/5. Only one study (25) scored only one point because this study was described as open-label or as evaluator-blind or did not describe the method to generate the sequence.

Primary outcomes

Efficacy of VC on CAR

RRs from 10 studies (9-12,21-26) involving 748 participants were pooled using fixed-effect model, yielding a statistically significant pooled RR on CAR at week 2 (RR = 1.54; 95% CI = 1.06, 2.23), week 4 (RR = 1.65; 95% CI = 1.25, 2.17), week 8 (RR = 1.85; 95% CI = 1.25, 2.75), week 12 (RR = 2.56; 95% CI = 1.66, 3.95), and week 16 (RR = 2.21; 95% CI = 1.03, 4.73). However, there was no significant pooled RR on CAR at week 24 (RR = 2.06; 95% CI = 0.82, 5.21). There was no significant heterogeneity in these outcomes (I^2<50.0%). The model was changed from a random effects model in the main analysis to a fixed effect model in the sensitivity analysis. The results for all the outcomes did not change (Table 2).

Efficacy of VC on PAR

MA showed that the VC-treated group showed a significant increase in PAR at week 2 (RR=1.47; 95% CI = 1.06, 2.04), week 4 (RR = 1.35; 95% CI = 1.02, 1.79), week 8 (RR = 1.60; 95% CI = 1.11, 2.31), and week 12 (RR = 1.70; 95% CI = 1.25, 2.30). However, the VC efficacy on PAR at weeks 16 and 24 demonstrated a non-significant pooled RR (95%

Table 1. Characteristics of studies included in the meta-analysis

Authors	Year	Study design	Setting	Duration of study	Age (years)	Cigarettes/day	FTND score	Smoking years	Intervention (n)	Control (n)	Outcomes	Jadad score
Leelarungrayup et al (22)	2008	RCT	Hospital	8 weeks	49.5±12.46	N/A	≥ 5	N/A	VC tea (30)	No (28)	CAR	2
Wongwiwatthananukit et al (9)	2009	RCT	Hospital	2 weeks	40.9±11.6	19.3610.45	5.3±2.25	23.6±10.65	VC tea (32)	MA tea (32)	CAR, PAR, AE	3
Punyaratabandhu et al (21)	2009	RCT	Hospital	4 weeks	34.8±9.95	11.67±6.9	3.05±2.6	N/A	VC tea (44)	CS tea (44)	CAR	2
Thripopskul et al (11)	2011	DRCT	Hospital	4 weeks	47.2±12.8	13.82±12.75	4.85±1.85	29.12±12.75	VC (dry powder 500 mg) capsule (35)	Placebo capsule (33)	CAR, PAR, AE	5
Kitpaiboontawee et al (24)	2012	DRCT	Hospital	4 weeks	40.6±13.2	13.58±13.4	4.25±1.95	22.4±13.4	VC (extract 185.49 mg) lozenges (33)	Placebo lozenges (34)	CAR, PAR, AE	5
Kuwivattanachai et al (23)	2017	DRCT	Hospital	2 weeks	48.67±12.56	11-20 (n=111) 21-30 (n=49) >30 (n=12)	5.76±2.33	31.77±13.15	VC tea (90)	MA tea (82)	CAR, PAR	4
Srisoi et al (26)	2018	DRCT	Community pharmacy	12 weeks	41.25±14.15	0-10 (n=81) 11-20 (n=25) 21-30 (n=4) >30 (n=1)	N/A	19.75±11.06	VC pastilles (extract 575.34 mg) (57)	Placebo pastilles (54)	CAR, PAR, AE	5
Thuksin (25)	2019	RCT	Home visit	12 weeks	36.3413.21	26.08±9.76	N/A	11.46±7.56	VC lozenges (31)	No (31)	CAR, PAR	1
Pitiporn et al (10)	2019	RCT	Hospital	6 weeks	31.24±6.09	<10 (n=25) 10-20 (n=9) >20 (n=1)	2.50±2.05	11.92±6.18	VC spray (extract) (18)	Placebo spray (17)	CAR, AE	2
Lertsinudom et al (12)	2019	DRCT	Community pharmacy	12 weeks	40.3±15.0	8.5±4.88	<4 (n=68) 4-6 (n=43)	20.0±9.75	VC pastilles (extract 575.34 mg) (57)	Placebo pastilles (54)	CAR, PAR, AE	5

Abbreviations: RCTs: randomized controlled trials; DRCT: double-blinded randomized controlled trials; FTND score: Fagerstrom test for nicotine dependence; N/A: not available; CAR: continuous abstinence rates; PAR: point abstinence rates; VC: *Vernonia cinerea*; CS: *Camellia sinensis*; MA: *Morus alba*; AE: adverse event.

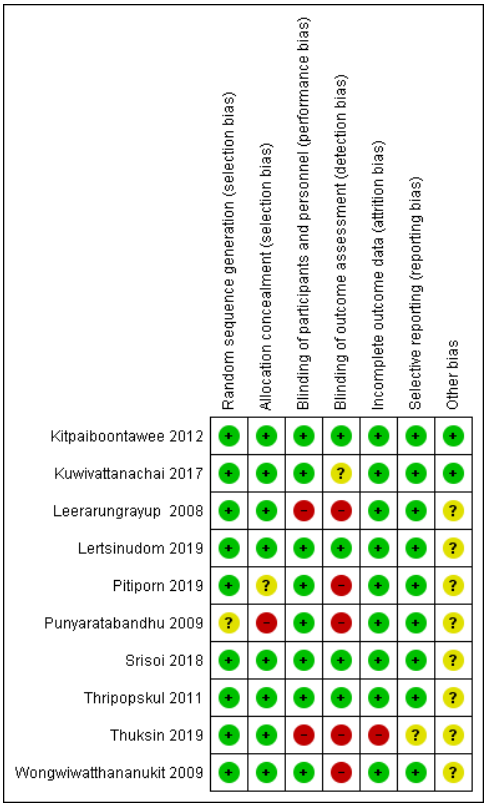

Figure 2. Risk of bias summary from individual studies: low risk (+), high risk (-), and unclear (?).

CI) of 1.66 (0.92, 2.99) and 1.44 (0.61, 3.42), respectively, with no evidence of heterogeneity. The sensitivity analysis was performed by changing from a random-effects model to a fixed-effect model. The results for all the outcomes did not change (Table 2).

Secondary outcomes

Adverse Events

Safety outcomes were reported in six of the ten studies involving 456 patients (9-12,24,26). The number of AEs was comparable between the two groups. There were no reports of serious AEs associated with VC after administration. Nevertheless, the pooled analysis showed that participants in the VC treated group were more likely to experience AEs including tongue numbness (RR = 1.20; 95% CI = 0.83, 1.72; *P* = 0.33), abdominal pain (RR = 1.01; 95% CI = 0.57, 1.79; *P* = 0.98), headache (RR = 1.08; 95% CI = 0.59, 2.00; p = 0.80), palpitation (RR = 1.00; 95% CI = 0.47, 2.11; p=0.99), drowsiness (RR=1.15; 95% CI = 0.80, 1.65; p=0.46), diarrhea (RR = 4.05; 95% CI = 0.98, 16.78; p=0.05), craving reduction (RR = 1.29; 95% CI = 0.90, 1.84; p=0.16), and aversion to the taste and smell of cigarette smoke (RR = 1.00; 95% CI = 0.70, 1.43; *P* = 0.98). However, there were no significant differences between the VC- and placebo-treated groups. More details and evidence of heterogeneity for all AEs are presented in Table 3.

Subgroup analysis

Subgroup analysis was conducted according to the study design, dosage form, and the form of VC that was used. This analysis suggested that the double-blind randomized controlled trial (DRCT) design improved CAR2, CAR4, CAR8, CAR12, PAR2, PAR8, and PAR12. Moreover, the VC capsule improved CAR2, while VC tea improved CAR4, CAR8, PAR8, and PAR12. The lozenge and pastille-treated group showed CAR12 improvement, while the VC extract group showed improved CAR4, CAR12, and PAR12 (Table 4).

Publication bias

Publication bias in the MA was assessed using a funnel plot (Figure 3). A summary estimate was observed in the plots, suggesting no considerable publication bias.

Discussion

This study constitutes a systematic review and MA to

Table 2. The main analysis outcomes and sensitivity analysis

Outcomes	Main analysis RR (95% CI; *P* value); I^2	Sensitivity analysis RR (95% CI; *P* value); I^2	References
CAR			
Week 2	1.54 (1.06, 2.23; 0.02); I^2 = 0.0%	1.60 (1.11, 2.32; 0.01); I^2 = 0.0%	9-11, 23, 24
Week 4	1.65 (1.25, 2.17; 0.0004); I^2 = 0.0%	1.65 (1.25, 2.18; 0.0004); I^2 = 0.0%	9, 11, 12, 21, 23, 24
Week 8	1.85 (1.25, 2.75; 0.002); I^2 = 9.0%	2.22 (1.54, 3.19; <0.0001); I^2 = 9.0%	9-11, 22-24
Week 12	2.56 (1.66, 3.95; <0.0001); I^2 = 12.0%	2.78 (1.88, 4.11; <0.0001); I^2 = 12.0%	9, 11, 12, 23-25
Week 16	2.21 (1.03, 4.73; 0.04); I^2 = 48.0%	2.21 (1.45, 3.67; 0.0004); I^2 = 48.0%	9, 22, 23
Week 24	2.06 (0.82, 5.21; 0.12); I^2 = 0.0%	2.06 (0.82, 5.21; 0.12); I^2 = 0.0%	9, 23
PAR			
Week 2	1.47 (1.06, 2.04; 0.02); I^2 = 0.0%	1.47 (1.06, 2.04; 0.02); I^2 = 0.0%	9, 11, 23, 24, 26
Week 4	1.35 (1.02, 1.79; 0.04); I^2 = 0.0%	1.43 (1.07, 1.90; 0.01); I^2 = 0.0%	9, 11, 12, 23-25
Week 8	1.60 (1.11, 2.31; 0.01); I^2 = 0.0%	1.65 (1.14, 2.39; 0.008); I^2 = 0.0%	9, 11, 23, 24
Week 12	1.70 (1.25, 2.30; 0.0007); I^2 = 0.0%	1.72 (1.26, 2.34; 0.0006); I^2 = 0.0%	9, 11, 12, 23, 24
Week 16	1.66 (0.92, 2.99; 0.09); I^2 = 0.0%	1.64 (0.91, 2.96; 0.10); I^2 = 0.0%	9, 23
Week 24	1.44 (0.61, 3.42; 0.41); I^2 = 37.0%	1.43 (0.73, 2.80; 0.29); I^2 = 37.0%	9, 23

Table 3. Adverse effects of Vernonia cinerea vs comparators

Adverse events (references)	Risk ratio	(95% CI); I^2	P^a	P^b
Tongue numbness (9-12, 24, 26)	1.20	(0.83, 1.72); 44.0%	0.33	0.10
Abdominal pain (9-12, 24, 26)	1.01	(0.57, 1.79); 0.0%	0.98	0.81
Nausea (9-12, 24, 26)	0.92	(0.57, 1.48); 0.0%	0.74	0.77
Headache (9)	1.08	(0.59, 2.00); N/A	0.80	N/A
Palpitation (9, 11, 24, 26)	1.00	(0.47, 2.11); 0.0%	0.99	0.90
Drowsiness (9, 11, 12, 24, 26)	1.15	(0.80, 1.65); 47.0%	0.46	0.10
Dizziness (10-12, 24, 26)	1.84	(0.94, 3.63); 0.0%	0.08	0.79
Diarrhea (11, 24)	4.05	(0.98, 16.78); 0.0%	0.05	0.34
Dry mouth (10-12, 24, 26)	0.67	(0.35, 1.30); 18.0%	0.24	0.30
Muscle pain (11, 26)	0.67	(0.11, 3.97); 28.0%	0.65	0.24
Craving reduction (9, 11, 12, 24, 26)	1.29	(0.90, 1.84); 0.0%	0.16	0.95
Aversion to the taste and smell of cigarette smoke (9, 11, 12, 24, 26)	1.00	(0.70, 1.43); 16.0%	0.98	0.31

Remark: *P*a: *P* value of effect size; *P*b: *P* value of heterogeneity; N/A: not applicable.

determine the efficacy and safety of VC for smoking cessation in mild-to-moderate smokers. Our MA indicated that VC could enhance clinical efficacy of smoking cessation with fewer adverse effects compared to placebo. Our findings demonstrated that VC treatment has the potential to improve CAR 2, 4, 8, 12, 16 and PAR 2, 4, 8, 12. This finding is in agreement with the previous SR and MA from Puttarak et al (13), who demonstrated that VC could improve CAR at weeks 8 and 12 and PAR at weeks 8 and 12. Moreover, there was no significant difference in all AEs between the VC-and placebo-treated groups. However, it was found that VC-treated groups could significantly improve CAR 2, 4, 16 and PAR 2, 4, 12. These outcomes were in contrast with those of the previous MA (13).

Our MA highlights several points that need to be addressed. First, this MA incorporated an update to five RCTs of VC assessment on smoking cessation published between 2017 and 2019. Furthermore, we performed a subgroup analysis and meta-regression to examine the impact of the variables on primary outcomes. Finally, AE pooling analysis was included in this MA.

The precise mechanism by which VC treatment improves smoking cessation remains unclear. A previous study reported that VC extract and its metabolites can reduce nicotine addiction by inhibiting monoamine oxygenase (27). All of the recruited studies involved oral VC administration. Aside from the obvious substitution of tobacco-smoke derived nicotine with nicotine from the VC, one possible mechanism of action was the local effect of tea, as sodium nitrate in the VC may cause tongue numbness, resulting in the reduction of cigarette craving (28). In addition, a pastille VC may be an effective dosage form for smoking cessation because it can be maintained and held in the patient's mouth, allowing for a longer duration of contact and effect. A longer duration may also be necessary for VC to exhibit any effect (12). Additionally, it may also affect the taste buds and olfactory receptors, which may further reduce craving. However, these effects were not found for the VC tea, lozenges, or pastilles. Thus, it is indicated that there are other modes of action at play, and the main route of absorption of nicotine and other substances is from the gastrointestinal tract into the bloodstream.

Teaktong et al (29) studied the effect of VC extract on dopamine 2 and NMDA receptors in nicotine-addicted animal studies. The results showed that VC increased dopamine 2 receptor activity while decreasing NMDA receptor activity. Previous studies have shown that smokers with nicotine addiction have decreased levels of D2 receptor activity (30) and increased levels of NMDA receptor activity (31). This finding may be implicated in the mechanism of action of VC in smoking cessation.

We confirmed the results of our MA by conducting a sensitivity analysis. By changing the model to the analysis of all outcomes, we found that the results remained unchanged. Therefore, our sensitivity analysis for all outcomes confirmed the robustness of our results pertaining to all outcomes.

The strength of our study is that it comprehensively summarizes the effects of VC on smoking cessation. There are three major strengths of our MA. The study was undertaken in a manner that is in accordance with a high standard of systematic review and MA and reported in alignment with PRISMA (15). This study represents an updated MA that included 10 RCTs, more than the previous study. We performed a pooled analysis of the AEs. However, there are factors that limit our MA. All recruited studies were conducted with mild to moderate nicotine addiction smokers, i.e., not including heavy smokers and

Table 4. Subgroup analysis of RCTs evaluating effects on clinical outcomes of *Vernonia cinerea*

Outcomes	No. of trials	RR	95% CI	I^2 (%)	p^a	p^b
CAR week 2						
Study design						
RCT	2	1.31	(0.76, 2.26)	0.0	0.33	0.37
DRCT	3	1.83	(1.12, 3.01)	0.0	0.02*	0.45
Dosage form						
Tea	2	1.21	(0.72, 2.04)	0.0	0.48	0.67
Capsules	1	3.46	(1.06, 11.30)	N/A	0.04*	N/A
Lozenges	1	1.70	(0.82, 3.51)	N/A	0.15	N/A
Sprays	1	1.89	(0.69, 5.14)	N/A	0.21	N/A
Extract						
Non extract	3	1.52	(0.95, 2.44)	31.0	0.08	0.24
VC extract	2	1.76	(0.98, 3.17)	0.0	0.06	0.87
CAR week 4						
Study design						
RCT	2	1.65	(1.10, 2.47)	0.0	0.01*	0.56
DRCT	5	1.61	(1.18, 2.21)	0.0	0.003*	0.84
Dosage form						
Tea	3	1.68	(1.15, 2.47)	0.0	0.007*	0.83
Capsules	1	1.89	(0.72, 4.94)	N/A	0.2	N/A
Lozenges	2	1.54	(0.98, 2.43)	0.0	0.06	0.41
Pastilles	1	1.55	(0.90, 2.66)	N/A	0.11	N/A
Extract						
Non extract	4	1.71	(1.20, 2.45)	0.0	0.003*	0.94
VC extract	3	1.54	(1.09, 2.19)	0.0	0.01*	0.61
CAR week 8						
Study design						
RCT	4	2.36	(1.48, 3.78)	48.0	0.0003*	0.13
DRCT	3	2.03	(1.13, 3.62)	0.0	0.02*	0.53
Dosage form						
Tea	4	2.47	(1.55, 3.93)	53.0	0.0001*	0.10
Capsules	1	2.36	(0.82, 6.79)	N/A	0.11	N/A
Lozenges	1	1.39	(0.60, 3.21)	N/A	0.45	N/A
Sprays	1	2.36	(0.53, 10.58)	N/A	0.26	N/A
Extract						
Non extract	5	2.45	(1.60, 3.75)	36.0	<0.0001*	0.18
VC extract	2	1.61	(0.77, 3.33)	0.0	0.20	0.54
CAR week 12						
Study design						
RCT	2	4.86	(2.32, 10.18)	66.0	<0.0001*	0.09
DRCT	4	2.08	(1.30, 3.34)	0.0	0.002*	0.99
Dosage form						
Tea	2	2.20	(0.95, 5.05)	0.0	0.06	0.95
Capsules	1	2.51	(0.73, 8.68)	N/A	0.14	N/A
Lozenges	2	1.98	(1.14, 3.44)	0.0	0.01*	0.61
Pastilles	1	2.01	(1.03, 3.92)	N/A	0.04*	N/A
Extract						
Non extract	3	2.29	(1.15, 4.57)	0.0	0.02*	0.98
VC extract	3	1.99	(1.30, 3.05)	0.0	0.001*	0.80
CAR week 16						
Study design						
RCT	2	2.40	(1.47, 3.94)	66.0	0.0005	0.05
DRCT	1	1.82	(0.47, 7.05)	N/A	0.38	N/A
CAR week 24						
Study design						
RCT	1	2.00	(0.55, 7.31)	N/A	0.29	N/A

Table 4. Continued

Outcomes	No. of trials	RR	95% CI	I^2 (%)	p^a	p^b
DRCT	1	2.13	(0.57, 7.95)	N/A	0.26	N/A
PAR week 2						
Study design						
RCT	1	1.09	(0.57, 2.10)	N/A	0.79	N/A
DRCT	4	1.59	(1.10, 2.32)	0.0	0.01*	0.99
Dosage form						
Tea	2	1.21	(0.72, 2.04)	0.0	0.48	0.67
Capsules	1	1.73	(0.72, 4.14)	N/A	0.22	N/A
Lozenges	2	1.65	(1.03, 2.65)	0.0	0.04*	0.91
Extract						
Non extract	3	1.34	(0.85, 2.09)	0.0	0.21	0.70
VC extract	2	1.65	(1.03, 2.65)	0.0	0.04*	0.91
PAR week 4						
Study design						
RCT	2	1.92	(1.07, 3.42)	68.0	0.03	0.08
DRCT	4	1.29	(0.93, 1.80)	0.0	0.12	0.98
Dosage form						
Tea	2	1.39	(0.83, 2.32)	0.0	0.21	0.93
Capsules	1	1.15	(0.55, 2.42)	N/A	0.71	N/A
Lozenges	2	1.42	(0.95, 2.12)	15.0	0.08	0.31
Extract						
Non extract	3	1.31	(0.86, 2.00)	0.0	0.21	0.92
VC extract	2	1.42	(0.95, 2.12)	15.0	0.08	0.31
PAR week 8						
Study design						
RCT	1	1.67	(0.86, 3.24)	N/A	0.13	N/A
DRCT	3	1.64	(1.05, 2.57)	0.0	0.03*	0.55
Dosage form						
Tea	2	1.86	(1.08, 3.20)	0.0	0.03*	0.67
Capsules	1	1.89	(0.80, 4.44)	N/A	0.15	N/A
Lozenges	1	1.24	(0.66, 2.31)	N/A	0.51	N/A
Extract						
Non extract	3	1.86	(1.18, 2.95)	0.0	0.008*	0.91
VC extract	1	1.24	(0.66, 2.31)	N/A	0.51	N/A
PAR week 12						
Study design						
RCT	1	2.00	(0.93, 4.29)	N/A	0.08	N/A
DRCT	4	1.671.67	(1.19, 2.34)	0.0	0.0007*	0.72
Dosage form						
Tea	2	1.84	(1.01, 3.35)	0.0	0.04*	0.77
Capsules	1	2.26	(0.89, 5.73)	N/A	0.08	N/A
Lozenges	1	2.26	(0.89, 5.73)	N/A	0.08	N/A
Pastilles	1	1.47	(0.91, 2.36)	N/A	0.12	N/A
Extract						
Non extract	3	1.96	(1.19, 3.24)	0.0	0.009*	0.90
VC extract	2	1.55	(1.06 2.29)	0.0	0.03*	0.70
PAR week 16						
Study design						
RCT	1	1.86	(0.85, 4.04)	N/A	0.12	N/A
DRCT	1	1.43	(0.58, 3.52)	N/A	0.43	N/A
PAR week 24						
Study design						
RCT	1	2.20	(0.86, 5.61)	N/A	0.1	N/A
DRCT	1	0.91	(0.33, 2.49)	N/A	0.86	N/A

Abbreviations: RCTs, randomized controlled trials; DRCT, double-blinded randomized controlled trials; P^a, *P* value of effect size; P^b, *P* value of heterogeneity; N/A, Not applicable.
*Statistical significance.

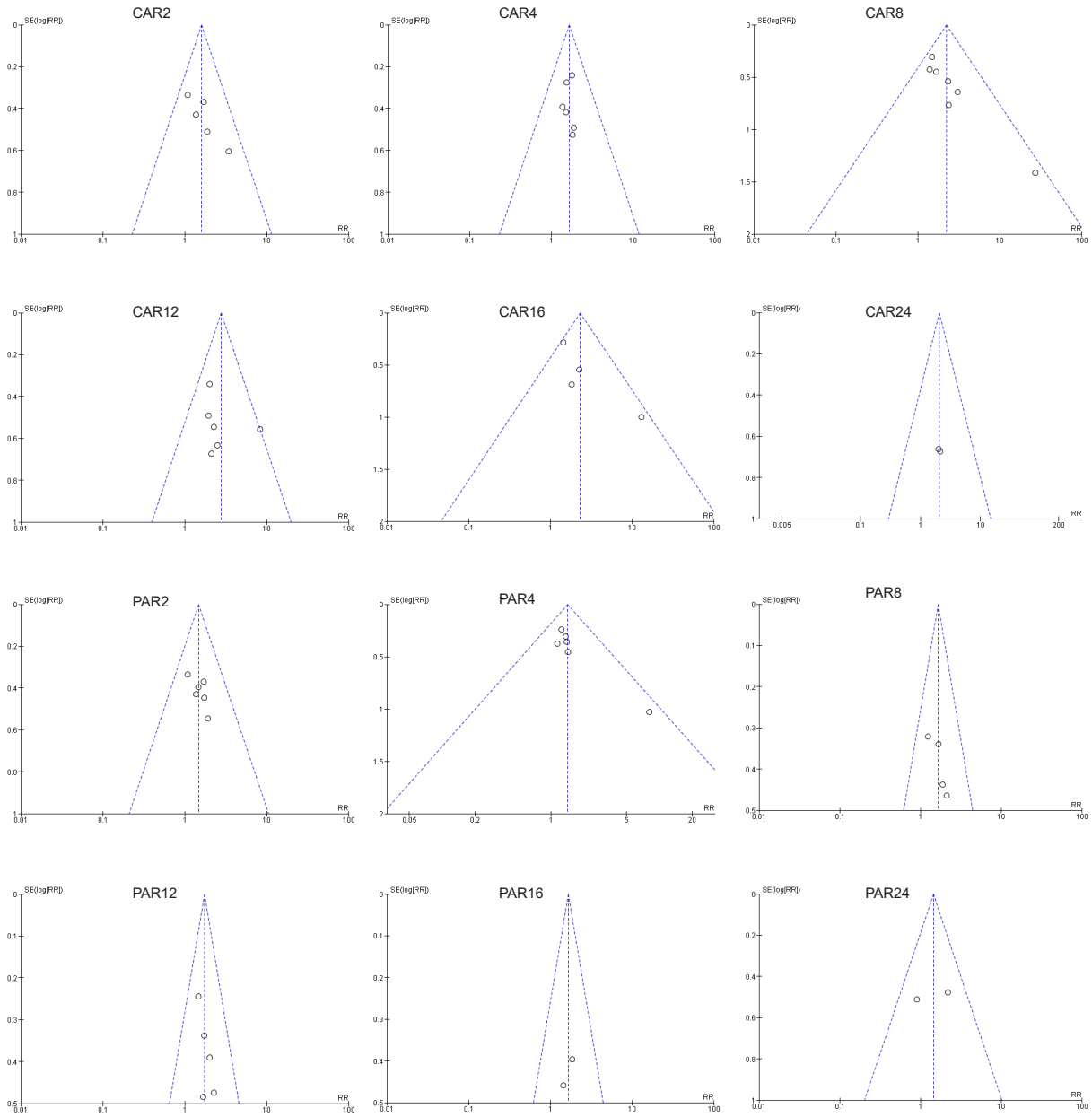

Figure 3. Publication bias. Abbreviations: CAR, Continuous abstinence rate; PAR, prevalence abstinence.

positive control groups (non-smokers). Furthermore, our study included only RCTs that compared VC and placebo and did not compare VC with other drugs used for smoking cessation. All of the included RCTs were conducted in Thailand, and all of them were performed in a small number of participants. Hence, our results may not be generalizable to a large number of clinical practices, for example, in other parts of the world.

Conclusion

Based on current evidence, VC therapy is predicted to be an effective and safe treatment to aid smoking cessation. However, the recruited RCTs had a small number of mild-to-moderate smokers. Therefore, well-designed, large, multi-center, randomized placebo- or active-controlled trials investigating the long-term effects of VC products on smoking cessation are needed to further substantiate the current findings.

Authors' contributions

WP, RS, BS reviewed and contributed to data collection and preparation of the manuscript. The first draft was prepared by WP, RS, KS. All authors read the final version and confirmed it for publication.

Conflict of interest

None declared.

Ethical considerations

Not applicable.

Funding/Support

This research project was financially supported by Mahasarakham University (Grant No. 2565).

References

1. Rosenberg SR, Kalhan R, Mannino DM. Epidemiology of chronic obstructive pulmonary disease: prevalence, morbidity, mortality, and risk factors. Semin Respir Crit Care Med. 2015;36(4):457-69. doi: 10.1055/s-0035-1555607.
2. Flor LS, Reitsma MB, Gupta V, Ng M, Gakidou E. The effects of tobacco control policies on global smoking prevalence. Nat Med. 2021;27(2):239-43. doi: 10.1038/s41591-020-01210-8.
3. Kondo T, Nakano Y, Adachi S, Murohara T. Effects of tobacco smoking on cardiovascular disease. Circ J. 2019;83(10):1980-5. doi: 10.1253/circj.CJ-19-0323.
4. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer. 2004;45 Suppl 2:S3-9. doi: 10.1016/j.lungcan.2004.07.998.
5. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax. 2015;70(10):984-9. doi: 10.1136/thoraxjnl-2015-206780.
6. Rezaei S, Karami Matin B, Kazemi Karyani A, Woldemichael A, Khosravi F, Khosravipour M, et al. Impact of smoking on health-related quality of life: a general population survey in West Iran. Asian Pac J Cancer Prev. 2017;18(11):3179-85. doi: 10.22034/apjcp.2017.18.11.3179.
7. World Health Organization. Encouraging People to Stop Smoking. Available from: https://www.who.int/mental_health/evidence/stop_smoking_whomsdmdp01_4.pdf. Accessed August 15, 2021.
8. Paeratakul O. Chemical constituents, biological activity of *Vernonia cinerea* (L.) Less., and its formulation development as a smoking cessation aid. J Thai Tradit Altern Med. 2010;8(1):81-92. [Thai].
9. Wongwiwatthananukit S, Benjanakaskul P, Songsak T, Suwanamajo S, Verachai V. Efficacy of *Vernonia cinerea* for smoking cessation. J Health Res. 2009;23(1):31-6.
10. Pitiporn S, Chotigeat U, Poonsub S, Chaiprasertsud P, Trakarnjunsiri J, Tong-on W, et al. Efficacy and safety of *Vernonia cinerea* (L.) Less. and *Boesenbergia rotunda* (L.) Mansf. oral sprays in light cigarette smokers with behavioral counseling for smoking cessation: a preliminary study. J Health Sci Res. 2019;13(2):117-27.
11. Tripopskul W, Sittipunt C. Efficacy of *Vernonia cinerea* for Cessation in Thai Active Smokers. 2016. Available from: http://www.trc.or.th/trcresearch/subpage/RP/TRC_Re_53-01-18.pdf. Accessed November 8, 2020. [Thai].
12. Lertsinudom S, Sawanyawisuth K, Srisoi S, Areemit J, Hansuri N, Tawinkan N, et al. *Vernonia cinerea* pastilles is effective for smoking cessation. Tradit Complement Med. 2021;11(2):90-4. doi: 10.1016/j.jtcme.2019.09.006.
13. Puttarak P, Pornpanyanukul P, Meetam T, Bunditanukul K, Chaiyakunapruk N. Efficacy and safety of *Vernonia cinerea* (L.) Less. for smoking cessation: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2018;37:37-42. doi: 10.1016/j.ctim.2018.01.009.
14. Higgins JP. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration; 2008.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, w64. doi: 10.7326/0003-4819-151-4-200908180-00135.
16. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Ann Intern Med. 2006;144(5):364-7. doi: 10.7326/0003-4819-144-5-200603070-00013.
17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. doi: 10.1016/0197-2456(95)00134-4.
18. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi: 10.1136/bmj.d5928.
19. iggins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557.
20. Quach BC, Bray MJ, Gaddis NC, Liu M, Palviainen T, Minica CC, et al. Expanding the genetic architecture of nicotine dependence and its shared genetics with multiple traits. Nat Commun. 2020;11(1):5562. doi: 10.1038/s41467-020-19265-z.
21. Punyaratabandha M, Chuanchaum P, Somwatasun S. Efficacy of *Vernonia cinerea* for smoking compared with tea (*Camellia sinensis*). Chonburi Hosp J. 2009;34(3):133-40. [Thai].
22. Leelarungrayub D, Pratanaphon S, Pothongsunun P, Sriboonreung T, Yankai A, Bloomer RJ. *Vernonia cinerea* Less. supplementation and strenuous exercise reduce smoking rate: relation to oxidative stress status and beta-endorphin release in active smokers. J Int Soc Sports Nutr. 2010;7:21. doi: 10.1186/1550-2783-7-21.
23. Kuwivattanachai P, Moto S. A comparison of *Vernonia cinerea* and placebo for smoking cessation. Srinagarind Med J. 2017;32(6):542-6. [Thai].
24. Kitpaiboontawee S. Efficacy of *Vernonia cinerea* Lozenge as an Adjunct to Pharmacist Counseling on Smoking Abstinence Rate: A Randomized Controlled Trial. IJPS. 2016; 2016. Available from: http://www.trc.or.th/trcresearch/subpage/TS/TRC_Th_55-001-01.pdf. Accessed November 15, 2016. [Thai].
25. Thuksin T. Effects of Smoking Cessation Program by Medications Use Reduction Tobacco Dependence Type Nicotine Gum and *Vernonia cinerea* Lozenge with an Intensive Counseling and Behavioral Therapies at Home: A Case Study of Roi-Et Province [thesis]. Thailand: Mahasarakham University; 2019. [Thai].
26. Srisoi S, Lertsinudom S, Areemit J, Hansuri N, Nasatid A, Pranboon S, et al. Efficacy and safety of *Vernonia cinerea* pastilles for smoking cessation in low and moderate nicotine dependence. Isan J Pharm Sci. 2018;14(4):68-78. doi: 10.14456/ijps.2018.40. [Thai].

27. Prasopthum A, Pouyfung P, Sarapusit S, Srisook E, Rongnoparut P. Inhibition effects of *Vernonia cinerea* active compounds against cytochrome P450 2A6 and human monoamine oxidases, possible targets for reduction of tobacco dependence. Drug Metab Pharmacokinet. 2015;30(2):174-81. doi: 10.1016/j.dmpk.2014.12.005.
28. Barboza JL, Patel R, Patel P, Hudmon KS. An update on the pharmacotherapeutic interventions for smoking cessation. Expert Opin Pharmacother. 2016;17(11):1483-96. doi: 10.1080/14656566.2016.1197203.
29. Teaktong T, Praputbut S. Effect of *Vernonia cinerea* Less. Extract on Dopamine 2 and NMDA Receptors in Mouse Brains. Thailand: Naresuan university; 2012. [Thai].
30. Berrettini WH, Lerman CE. Pharmacotherapy and pharmacogenetics of nicotine dependence. Am J Psychiatry. 2005;162(8):1441-51. doi: 10.1176/appi.ajp.162.8.1441.
31. Jain R, Mukherjee K, Balhara YP. The role of NMDA receptor antagonists in nicotine tolerance, sensitization, and physical dependence: a preclinical review. Yonsei Med J. 2008;49(2):175-88. doi: 10.3349/ymj.2008.49.2.175.