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

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**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 ThaiLi. 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.

**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

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**Implication for health policy/practice/research/medical education:**

This meta-analysis demonstrated that *Vernonia cinerea* product is an alternative treatment for smoking cessation.

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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).

I² 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 I² 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 hospitals.
Vernonia cinerea for smoking cessation

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 (I²<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% CI = 0.65, 2.08).
### 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, PAR, AE   | 2           |
| Wongwiwatthanakit et al (9)     | 2009 | RCT          | Hospital                 | 2 weeks           | 40.9±11.6   | 19.36±10.45   | 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           |
| Kitpaiboonawee 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           |
| Kuivivattanachai et al (23)    | 2017 | DRCT         | Hospital                 | 2 weeks           | 48.67±12.56 | 11-20 (n=111) | 12-19 (n=110) | 20-30 (n=111) | 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 | 5.76±2.33     | 31.77±13.15 | VC pastilles (extract 575.34 mg) (57) | Placebo pastilles (54) | CAR, PAR, AE | 5           |
| Thuksin (25)                   | 2019 | RCT          | Home visit               | 12 weeks          | 36.34±13.21 | 26.08±9.76    | 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  | 10-20 (n=9)   | 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      | 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.
Vernonia cinerea for smoking cessation

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 | Sensitivity analysis | References |
|----------|---------------|----------------------|------------|
|          | RR (95% CI; P value); I\(^2\) | RR (95% CI; P value); I\(^2\) |             |
| 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; 0.0066); 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 |
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 Puttarat et al (13), who demonstrated that VC could improve CAR 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, 8, 12 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 oxidase (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 dopamine 2 receptor activity while decreasing NMDA receptor activity. Previous studies have shown that smokers with nicotine addiction have decreased levels of dopamine 2 receptor activity while decreasing NMDA receptor activity. Previous studies have shown that smokers with nicotine addiction have decreased levels of dopamine 2 receptor activity while decreasing NMDA receptor activity. Previous studies have shown that smokers with nicotine addiction have decreased levels of dopamine 2 receptor activity while decreasing NMDA receptor activity. Previous studies have shown that smokers with nicotine addiction have decreased levels of dopamine 2 receptor activity while decreasing NMDA receptor activity. Previous studies have shown that smokers with nicotine addiction have decreased levels of dopamine 2 receptor activity while decreasing NMDA receptor activity. Previous studies have shown that smokers with nicotine addiction have decreased levels of dopamine 2 receptor activity while decreasing NMDA receptor activity.

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 heavy smokers and heavy smokers.

**Table 3. Adverse effects of Vernonia cinerea vs comparators**

| Adverse events (references) | Risk ratio | (95% CI); P | P<sub>b</sub> | P<sub>a</sub> |
|----------------------------|------------|-------------|-----------|-----------|
| 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 |
| Dizziness (10-12, 24, 26) | 1.15 | (0.80, 1.65); 47.0% | 0.46 | 0.10 |
| Diarrhea (11, 24) | 1.84 | (0.94, 3.63); 0.0% | 0.08 | 0.79 |
| Dry mouth (10-12, 24, 26) | 4.05 | (0.98, 16.78); 0.0% | 0.05 | 0.34 |
| Muscle pain (11, 26) | 0.67 | (0.35, 1.30); 18.0% | 0.24 | 0.30 |
| Craving reduction (9, 11, 12, 24, 26) | 0.67 | (0.11, 3.97); 28.0% | 0.65 | 0.24 |
| Aversion to the taste and smell of cigarette smoke (9, 11, 12, 24, 26) | 1.29 | (0.90, 1.84); 0.0% | 0.16 | 0.95 |

Remark: Pa: P value of effect size; Pb: P value of heterogeneity; N/A: not applicable.
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 |
| Pastilles | 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 |
| Outcomes | No. of trials | RR     | 95% CI       | I² (%) | \(p^a\)  | \(p^b\)  |
|----------|---------------|--------|--------------|--------|---------|---------|
| 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.
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.
Phimarn et al

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