



Efficacy and safety of *Vernonia cinerea* (L.) Less. for smoking cessation: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background & objective: Several randomized controlled trials have investigated *Vernonia cinerea* (L.) Less. for smoking cessation but there remains no critical summary of overall findings. This study uses systematic review and meta-analysis to summarize the efficacy and safety of *V. cinerea*.

Methods: Nine databases were searched through November 2017. Randomized controlled trials that reported the smoking cessation effect of *V. cinerea* were included. Data were extracted by two independent researchers. Study quality was assessed using the Cochrane risk of bias and JADAD score. The estimates of pooled effects were calculated as relative risk (RR) with 95% CI using a random-effects model.

Results: Five trials with 347 smokers were included. *V. cinerea* treatment group was significantly associated with cessation rate higher than that in the control group with no evidence of heterogeneity for both continuous abstinence rate (CAR) at week 8 with risk ratio (RR): 1.69, 95% CI [1.00, 2.86]; week 12 RR: 2.18, 95% CI [1.17, 4.04]) and 7-day point prevalence abstinence rate (PAR) (week 8 RR: 1.51, 95% CI [1.01, 2.27]; week 12 RR: 1.93, 95% CI [1.24, 2.99]) at week 8 and 12, respectively. There was no significant difference of all adverse events between the treatment and the control groups.

Conclusion: Our study demonstrates that *V. cinerea* has potential efficacy for smoking cessation. Further well-design RCTs of standardized *V. cinerea* compared with standard treatment should be conducted to strengthen this evidence.

1. Introduction

Smoking is one of the major preventable causes of premature death and several diseases worldwide. Appropriate counselling with medication for smoking cessation treatment was recommended for higher cessation rate than either counselling or medication alone. Nicotine replacement (gum, inhaler, lozenge, nasal spray, patch) and non-nicotine replacement therapy (bupropion SR, varenicline, clonidine,

nortriptyline) were approved for smoking cessation therapy.¹ However, several smoking cessation medications are expensive, a main barrier to access especially in low- and middle-income countries.² In addition they are associated with increased adverse events such as dry mouth, nausea and sedation. Therefore, herbal medicine has been considered as a potential alternative option for smoking cessation treatment² which could be potentially more accessible, inexpensive and have fewer adverse effect.

Abbreviations: NLEMs, national list of essential medicines; AEs, adverse events; RCT, randomized controlled trial; PRISMA, preferred reporting items for systematic reviews and meta-analyses; CAR, continuous abstinence rate; PAR, 7-day point prevalence abstinence rate; FTND, Fagerstrom test for nicotine dependence; RR, risk ratio; CO, carbon monoxide; ROB, cochrane risk of bias; PK/PD, pharmacokinetic/pharmacodynamic

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Recently, clinical evidences supporting the use of herbal medicine for smoking cessation such as *Cytisus laburnum* (Cytisine), St. John's wort, herbal tea, or black pepper^{3,4} have been reported. Although cytisine was recommended as a low cost alternative plant-based medicines for smoking cessation, it is not be available in low- and middle-income countries.² One of the popular herbal medicines for smoking cessation in Thailand is *Vernonia cinerea* (L.) Less. *V. cinerea* (Asteraceae family), ya dok khao (Thai name), sahadevi, or little iron weed is widely spread as a weed in Africa, America, Asia and Australia especially in tropical and subtropical areas.⁵ *V. cinerea* has been traditionally used as diuretic, antipyretic, antitussive, anti-jaundice, anti-hepatitis, tonic, anti-hemorrhoid and indigestion treatment.^{6,7} In Thailand, *V. cinerea* tea is recognized as an alternative medicine for smoking cessation treatment since it has been included in National List of Herbal Medicine, Ministry of Public Health.⁸ The benefits of *V. cinerea* for smoking cessation were supported by evidence in preclinical studies. *V. cinerea* extract and its active constituents such as apigenin, chrysoeriol, luteolin, quercetin and hirsutinolides could inhibit CYP2A6-mediated nicotine metabolism which could result in decreased elimination rate of nicotine. Furthermore, *V. cinerea* extract and its active constituents also stabilized dopamine level through inhibition of MAOs during withdrawal period which decreased cigarette craving, smoking rate and alleviated withdrawal symptoms.⁶ *V. cinerea* also improved respiratory tissue in chronic nicotine treatment rat.⁹

Several randomized controlled trials have investigated *V. cinerea* for smoking cessation^{10,11} but there remains a lack of critical summary of overall findings. Systematic review and meta-analysis have been widely used to summarize efficacy and safety of several herbal medicines.^{12–14} This study aims to systematically review and perform a meta-analysis to determine the efficacy and safety of *V. cinerea* on smoking cessation.

2. Methods

This systematic review was conducted according to the Cochrane Collaboration framework guidelines,¹⁵ and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.¹⁶ The review protocol was registered with PROSPERO (registration number: CRD42017056116).

2.1. Search strategies and study selection

The following databases were used to search for original research articles from inception to November 2017: PubMed, AMED, CINAHL, Cochrane Central Register of clinical trial, Cochrane library, EMBASE, ASEAN Citation Index (ACI), ThaiLIS-Thai library integrated system, WHO trial registry, and www.clinicaltrial.gov. Strategic search terms used were *Vernonia cinerea* OR *Cyanthillium cinereum* (L.) H. Rob. OR little iron weed OR sahadevi OR poovamkurunnila OR “ya-dok-khao”. Search strategies were described in Supplementary Table S2. For other sources, online and offline sources such as libraries and references of papers derived for full text review were scanned to identify potential studies not indexed in the above databases. The experts were also contacted for additional trials.

Research articles were included if they met the following inclusion criteria: 1) randomized controlled trial (RCT) in smokers and 2) evaluating clinical effects and/or safety of *V. cinerea* for smoking cessation. There was no language restriction. PP and TM scanned all the titles and abstracts to determine whether the studies assessed the effects of *V. cinerea*. Full-text articles of the potential studies were subsequently assessed by PP and TM, independently. Disagreements and uncertainties regarding eligibility were resolved by discussions with NC, when necessary.

2.2. Data extraction and quality assessment

Data extraction was undertaken by PP and TM using a data extraction form in accordance with the CONSORT statement for reporting herbal medicinal interventions.¹⁷ The data extracted included: study design; number of participants; age of participants; smoking habit; Fagerstrom Test for Nicotine Dependence (FTND); characteristics of the intervention; and outcomes measurement. The primary outcomes are continuous abstinence rate (CAR) and 7-day point prevalence abstinence rate (PAR) at week 12. Secondary outcomes are CAR and 7-day PAR at week 2, 4, 8, acceptability (all-cause of discontinuation),¹⁸ tolerability (all-cause of discontinuation due to AEs),¹⁸ and adverse events (AEs).

Studies included in this review were assessed for methodological quality by PP and TM using the Cochrane risk of bias tool,¹⁵ and JADAD score.¹⁹ The Cochrane risk of bias evaluates bias in intervention studies based on a number of criteria including: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each study was classified as having low risk (low risk of bias for all key domains), high risk (high risk of bias in at least one domain or some concerns for multiple domains), or some concerns (some concerns in at least one domain). Overall JADAD score of < 3, = 3, > 3 indicates low, moderate or high methodological quality, respectively. Disagreements between the reviewers were settled through discussion and consensus.

2.3. Outcome measure and statistical analyses

Data from all studies were pooled in a meta-analysis to determine the overall effect size with 95% confidence interval. Pooled effects were calculated using risk ratio (RR). Statistical heterogeneity between studies was assessed using the chi-squared test and I^2 .¹⁵ Thresholds of I^2 were interpreted in accordance with the magnitude and direction of effects and strength of evidence of heterogeneity (eg. p-value) as follows: might not be important (0%–30%); moderate heterogeneity (30%–50%); substantial heterogeneity (50%–75%); and considerable heterogeneity (75%–100%).¹⁵ The Dersimonian and Laird random-effects model was employed for all analyses. Fixed-effected model also used for sensitivity analysis.²⁰ Meta-analyses were conducted using STATA[®] version 14 (STATA Corp, College Station, TX, USA).

3. Results

3.1. Study selection

Of the 229 articles found from the databases and one article identified through other sources (contact content expert for additional articles), 230 articles were eligible for screening. Based on title and abstract screened of studies after duplication removal, eight articles were retrieved for full text review. Three articles were excluded because of non-clinical study or non-RCT, leaving five randomized controlled trials to be included in this systematic review and meta-analysis (Fig. 1).

3.2. Study characteristics

All five RCTs^{10,11,21,22,23} (Table 1) involving 347 smokers were conducted in Thailand to investigate the effects of *V. cinerea* on smoking cessation. The age of participants in all included studies ranged from 34.6 to 36.1 years. The major participants are male (90–100%) which related with Thailand smoking prevalence.²⁴ Three studies^{10,22,23} reported the number of year for smoking which was about 22.3–30.0 years. All subjects in all trials were also evaluated for Fagerstrom test for nicotine dependence (FTND) score with the score ranging from low to high (2.9–7.6) nicotine dependence.

The dosage forms and doses of *V. cinerea* used varied across studies.

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