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Systematic review

External Application of Herbal Medicines for Acne Vulgaris: A Systematic Review and Meta Analysis

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Key Words
acne vulgaris, herbal medicine, external application, systematic review, meta-analysis, randomized controlled trial

Abstract

Aim of the study: The objective of this systematic review is to critically evaluate the evidence of the effectiveness and safety of external application of herbal medicines (EAHM) for acne vurgalis (AV).

Methods: English, Chinese and Korean language databases were searched up to May 2018. Randomized clinical trials (RCTs) that reported the effects of EAHM for AV were included and analysed.

Results: A total of 10 randomized trials with 656 AV patients were identified. A meta-analysis of two RCTs indicated that EAHM had a significant effect on improving primary outcome 'global assessment' compared with placebo (mean difference (MD) = -2.62, confidence interval (CI) = -4.84 to -0.40, p = 0.02). Furthermore, data extracted from two RCTs showed that EAHM significantly reduce primary outcome 'inflammatory lesion count of acne' (MD = -1.25, CI = -1.68 to -0.83, p < 0.00001) and 'non-inflammatory lesion count of acne' (MD = -1.32, CI = -1.75 to -0.90, p < 0.00001). No significant difference was observed between groups in secondary outcome 'sebum of skin' (MD = -0.21, CI = -0.53 to 0.11, p = 0.20) and 'patient-reported changes in symptom' (relative risk (RR) = 2.56, CI = 0.43 to 15.22, p = 0.30). No severe adverse events (AEs) were found and no treatment was stopped due to AEs of EAHM.

Conclusions: EAHM seems to have affirmative effects, but quality of evidence, and non-standardized use of EAHM make our conclusion weak. Our suggestion is rigorously designed RCTs and standardization of EAHM are required in the future.

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1. Introduction

Acne vulgaris (AV) is the most common dermatologic disease and affects not only 80% of adolescents, but also 54% of adult women and 40% of adult men [1-3]. The mortality of AV was not reported, but AV can cause physical and psychological morbidity such as acne scar, poor self-image, depression and anxiety [4]. In the United States, costs associated with the treatment of AV approximate 3 billion dollars per year [5].

Based on clinical guidelines, the conventional medicines (CM), such as oral medications (e.g., systemic antibiotics, hormonal agents and isotretinoin) and/or topical medications (e.g., benzoyl peroxide, topical antibiotics and topical retinoids), were applied for managing AV [4, 6, 7]. In a recent published multicenter observational study, topical medications were prescribed for 93% of AV patients and oral medications were used for 71% of cases in Japan [8].

However, these drugs have the potential side effects from local irritation to systemic symptoms including

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liver function abnormalities and teratogenic effects [9]. Traditional herbal medicines have been developed on the basis of unique theories and used to treat various diseases both internally and externally for thousand years [10, 11]. External treatment involves applying drugs on the surface or point of illness [12]. And external application of traditional herbal medicine has been perceived as inexpensive, safer and low cost than CM [12, 13].

The recent published systematic review on complementary therapies for AV reported that herbal medicine can be improving symptoms of acne [14]. However, no published systematic reviews have evaluated whether the external application of herbal medicine (EAHM) for AV is safe and effective.

Therefore, we conducted a systematic review following the PRISMA recommendations [15]. The aim of this systematic review is to evaluate the evidence of the effectiveness and safety of the EAHM for AV.

2. Methods

2.1. Protocol and registration

Our protocol of systematic review was registered in an international prospective register of systematic reviews under the registration number PROSPERO 2016: CRD42016050898 (Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016050898)
Protocol registration number: CRD42016050898

2.2. Data Sources and Searches

We searched the following electronic databases up to May 2018: Pubmed, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL Plus. We also searched six Korean databases (Korea Institute of Science and Technology Information, Korean traditional knowledge portal, KoreaMed, OASIS, RISS and the National Library of Korea) and two Chinese databases (CNKI and Wanfang). We did not limit publication languages. Furthermore, we also conducted non-electronic searches of conference proceedings, our own files of articles and nine traditional Korean medical journals (Journal of Korean Medicine, the Journal of Korean Acupuncture and Moxibustion Society, Korean Journal of Acupuncture, Journal of Acupuncture and Meridian Studies, Journal of Pharmacopuncture, Journal of Oriental Rehabilitation Medicine, the Journal of Korean Chuna Manual Medicine for Spine and Nerves, Korean Journal of Oriental Physiology and Pathology and the Journal of Korean Oriental Internal Medicine). References of references were reviewed and grey literature was not fully explored.

The search terms were as follows: "acne vulgaris OR acne" AND "external application OR external treatment OR external use OR topical application OR topical use OR topical treatment OR dermal OR skin OR gel OR ointment OR cream OR spray OR oil OR cosmetic product" AND "herb OR herbal medicine OR plant OR plant extract OR ethnobotany OR traditional Chinese medicine OR traditional Korean medicine OR kampo medicine" AND "randomized controlled trial OR randomized clinical trial" in each database language.

2.3. Study Selection

2.3.1. Types of Studies

We included parallel or cross-over randomized controlled trials (RCTs) to assess the efficacy of EAHM for AV. Non-RCTs, animal studies, survey and reviews were excluded.

2.3.2. Types of Participants

Patients within any age and gender group diagnosed with AV and participated in the RCTs were included. RCTs applying EAHM in healthy persons were excluded.

2.3.3. Types of Interventions

EAHM interventions as any type of intervention in which herbal medicine ingredients were applied to illness area were eligible for inclusion. There is no limitation on the number of herbs, dosage or duration of treatment. We defined herbal medicines as any types of products that originated from botanical sources such as whole plants or their adjuncts [16]. We excluded studies that EAHM interventions were orally administered. We also excluded trials on the combined effects of EAHM and other interventions (e.g., EAHM plus oral administration of herbal medicine, acupuncture or CM).

2.3.4. Types of Comparisons

Clinical trials comparing EAHM with placebo or CM were included. CM included zinc sulphate solution, benzoyl peroxide gel. Unqualified control interventions (e.g., herbal medicine) were excluded because their efficacy was not proven.

2.3.5. Types of Outcome Measures

The primary outcomes were physician-assessed acne lesion count and physician-assessed global assessment. The secondary outcomes considered in this review were the sebum of skin, moisture of skin, patient-reported changes in symptom, quality of life, anti-bacterial activity test and adverse events (e.g. itching, irritation, erythema and desquamation).

2.4. Data Extraction

Three authors (S.H. Sung, G.H. Choi and N.W. Lee) independently screened and selected the included studies and extracted data according to the predefined data extraction form. Data consisted of composition of herbs, used form and amount of EAHM, sample size, EAHM treatment regimens and comparators, outcome measures, reported results and adverse events. Insufficient outcome date were obtained by contacting corresponding authors whenever possible. Disagreements were resolved by discussion among authors (S.H. Sung and B.C. Shin) to reach consensus.

2.5. Assessment of Risk of Bias (ROB)

We used the method for assessment using Cochrane Collaboration's risk of bias tool [17]. This tool includes seven domains, but we assessed the ROB including random sequence generation, allocation concealment, blinding of participants or personnel, blinding of assessors, incomplete outcome data and selective outcome reporting. Two independent authors (S.H. Sung and G.H. Choi) assessed the risk of bias in each study. Any disagreements were resolved by discussion or consultation with a third author (B.C. Shin).

2.6. Data Analysis

We used Review Manager (RevMan) software (Version 5.3.5 for windows; the Nordic Cochrane centre, Copenhagen, Denmark) to conduct the meta-analysis. Dichotomous data were presented as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous outcomes were expressed as mean differences (MDs) with 95% CIs. Random-effects model was used in order to combine data into RRs or MDs. I2 tests were used to address the heterogeneity among the included studies. An I2 values > 50% or P values < 0.10 were considerable heterogeneity among studies.[17] A summary of the findings was presented in the results when statistical pooling was not assessed.

3. Results

3.1. Study Selection and Description

Our search generated a total of 312 potentially relevant studies, finally, 10 RCTs (English databases: n = 6; Chinese databases: n=1; Korean databases: n=3) [18-27] met our inclusion criteria (Fig. 1). The characteristics of the included RCTs are shown in Table 1. We converted each name of herb into the scientific name.

Three [18, 20, 23] of the 10 trials were conducted in Korea and published in Korean. For the remaining seven studies, two were conducted in Iraq and published in English [25, 26], and five were conducted in Italy [19], Iran [21], Pakistan [22], India [24] and China [27], respectively.

Table 1 Characteristics of the included RCTs for acne vulgaris

First author, year	Composition of herb(s), used form of EAHM, amount used	sample size (randomized/analysed)	Experimental group (intervention, regimen)	Control group (intervention, regimen)	Outcome measures	Main results	AEs
Baek, 2011[18]	*S. flavescens*, Lotion, n.r.	30/30	(A) EAHM lotion (containing *S. flavescens*), n=15, 56 sessions (2 times per day for 28 days)	(B) Placebo lotion (containing *S. flavescens*), n=15, 56 sessions (2 times per day for 28 days)	(1) Sebum of skin (2) Anti-bacterial activity test	(1) Significant difference in (A)[a] but not in (B) (2) NS	Itching (1in group(A)), irritation (1 in group (A))
Capitanio, 2012[19]	*L. digitata*, Cream, n.r.	60/60	(A) EAHM cream (containing *L. digitata*), n=30, 102 sessions (2 times per day for 8 weeks)	(A) Placebo cream (without *L. digitata*), n=30, 102 sessions (2 times per day for 8 weeks)	(1) Acne lesion count ① Inflammatory lesions ② Non- Inflammatory lesions (2) Sebum of skin	(1) ① (A) better than (B) but NS ② Positive[b] (2) Improved in (A) and (B) but NS between groups	None
Du, 2004[20]	*H. cordata*, Pack, n.r.	65/44	(A) EAHM pack (containing *H. cordata*), n=24, 56 sessions (2 times per day for 28 days)	(B) Placebo pack (without *H. cordata*), n=20, 56 sessions (2 times per day for 28days)	(1) Acne lesion count □ Inflammatory lesions □ Non- Inflammatory lesions (2) patient–reported changes in symptom	(1) ① Significant difference in (A)[c] but not in (B) ② Significant difference in (A)[c] but not in (B) (2) Positive[a]	Itching (2 in group(A)), irritation (2 in group (A)), pigmentation (1 in group (A))
Enshaieh, 2007[21]	*M. alternifolia*, Gel, n.r.	60/60	(A) EAHM gel (containing *M. alternifolia*), n=30, 90 sessions (2 times per day for 45 days)	(B) Placebo gel (without *M. alternifolia*), n=30, 90 sessions (2 times per day for 45 days)	(1) Acne lesion count ① Inflammatory lesions (papules) ② Inflammatory lesions (pustules) ③ Non-inflammatory lesions (comedones) (2) Global assessment	(1) ① Positive[a] ② Positive[b] ③ Positive[c] (2) Positive[c]	Pruritus (3 in group (A), 2 in group (B)),burning sensation (1 in group (A), 2 in group (B)), scaling (1 in group(A))
Khan, 2014[22]	*H. rhamnoides*, Emulsion, total 500 mg	50/50	(A) EAHM emulsion (containing *H. rhamnoides*), n=25[d], 112 sessions (2 times per day for 8 weeks)	(B) Placebo emulsion (without plant extract), n=25[d], 112 sessions (2 times per day for 8 weeks) *(c) EAHM emulsion (containing C. fistula), n=25[d], 112 sessions (2 times per day for 8 weeks)*	(1) Global assessment (2) Sebum of skin (3) Anti-bacterial activity test	(1) Unclear (2) (A)[a], (B)[a] significantly better than (C) (3) Anti-bacterial activity was observed in (A) and (B) but not in (C)	Itching and irritation(4 in group (A), 7 in group (B))
Park, 2013[23]	*B. platyphyllae*, Foaming cleanser total 170 ml, toner total 200ml, ampule total 60ml	60/60	(A) EAHM product (containing *B. platyphyllae*), n=30, 102 sessions (2 times per day for 56 days)	(B) Placebo product (without *B. platyphyllae*), n=30, 102 sessions (2 times per day for 56 days)	(1) Global assessment (2) Sebum of skin (3) Moisture of skin (4) Quality of life (skindex29)	(1) Positive[a] (2) NS (3) NS (4) NS	None

Parveen, 2009[24]	13 herbs[e], Cream, n.r.	30/30	(A) EAHM cream, n=20, 120 sessions (2 times per day for 60 days)	(B) Placebo cream, n=10, 120 sessions (2 times per day for 60 days)	(1) Global assessment	(1) Significant difference in (A)[a] but not in (B)	n.r.
Sharquie, 2006[25]	*C. sinensis*, Lotion, n.r.	60/49	(A) EAHM lotion (containing C. sinensistea leaves), n=25, 60 sessions (2 times per day for 30 days)	(B) Placebo solution(without C. sinensistea leaves), n=24, 60 sessions (2 times per day for 30 days)	(1) Acne lesion count ① Inflammatory lesions (papules) ② Inflammatory lesions (pustules) (2) patient–reported changes in symptom	(1) ① Positive[a] ② Positive[a] (2) Positive[b]	None
Sharquie, 2008[26]	*C. sinensis*, Lotion, n.r.	47/40	(A) EAHM lotion (containing C. sinensis), n=20, 120 sessions (2 times per day for 60 days)	(B) Zinc sulphate solution, n=20, 120 sessions (2 times per day for 60 days)	(1) Global assessment (2) Acne lesion count ① Inflammatory lesions (papules) ② Inflammatory lesions (pustules)	(1) (A) better than (B) (2) ① Significant difference in (A)[c] but not in (B) ② Significant difference in (A)[c] but not in (B)	Itching (5 in group (A), 2 in group (B)),burning sensation (5 in group (B))
Zeng, 2012[27]	*S. baicalensis* + P. *amurense* + *I. tincoria*, Pack, n.r.	233/233	(A) EAHM pack, n=113, 8 sessions (2 times per week for 4 weeks)bs	(B) Benzoyl peroxide gel, n=120, 28 sessions (1 time per day for 28 days)	(1) Acne lesion count (2) patient–reported changes in symptom	(1) Positive[a] (2) Positive[a]	AEs (2 in group (A), 3 in group (B))

[a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$; [d] cheeks of same patients with acne received (A) versus (C), and (B) versus (C) respectively; [e] 13 herbs: *A. barbadensis* + *A. indica* + *A. sarcocolla* + *B. serrata* + *C. myrrha* + *C. rotundus* + *C. zizanoides* + *J. officinale* + *L. ensata* + *M. chamomilla* + *N. arbor-tristis* + *O. europaea* + *P. dulcis*

A. barbadensis, *Aloe barbadensis*; *A. indica*, *Azadirachta indica*; *A. sarcocolla*, *Astragalus sarcocolla*; AEs, Adverse events; *B. Platyphyllae*, *Betulae platyphyllae*; *B. serrata*, *Boswellia serrata*; *C. fistula*, *Cassia fistula*; *C. myrrha*, *Commiphora myrrha*; *C. rotundus*, *Cyperus rotundus*; *C. sinensis*, *Camellia sinensis*; *C. zizanoides*, *Chrysopogon zizanoides*; EAHM, External application of herbal medicine; *H. cordata*, *Houttuynia cordata*; *H. rhamnoides*, *Hippophae rhamnoides*; *I. ensata*, *Iris ensata*; *I. tinctoria*, *Isatis tinctoria*; *J. officinale*, *Jasminum officinale*; *L. digitate*, *Laminaria digitata*; *M. alternifolia*, *Melaleuca alternifolia*; *M. chamomilla*, *Matricaria chamomilla*; *N. arbor-tristis*, *Nyctanthes arbor-tristis*; NS, No significant difference; *O. europaea*, *Olea europaea*; *P. amurense*, *Phellodendron amurense*; *P. dulcis*, *Prunus dulcis*; *S. baicalensis*, *Scutellaria baicalensis*; *S. flavescens*, *Sophora flavescens*.

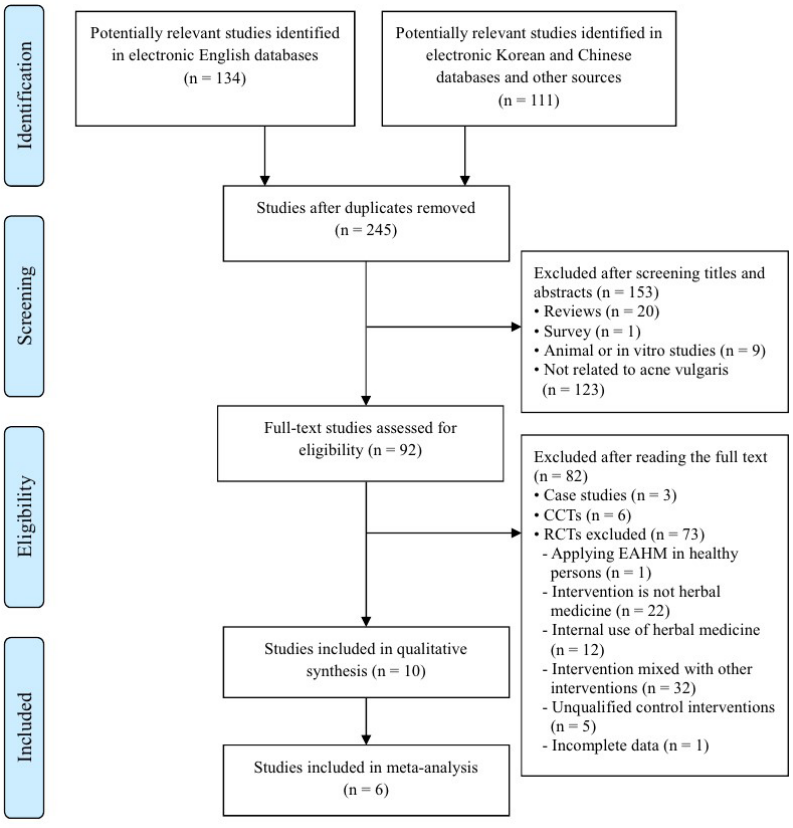


Figure 1 Flowchart of the RCT selection process. CCTs: Controlled Clinical Trial s ; RCTs: Randomized Controlled Trial s ; E AHM: External Application of Herbal Medicine

3.2. Participants

A total of 656 participants were included in 10 trials. The sample sizes in each group ranged from 15 to 113 in the EAHM group and from 10 to 120 in control group. The median sample sizes per arm were 33 in the EAHM group and 32 in the control group. One study [22] reported cheeks of same patients with AV received EAHM (containing Hippophae rhamnoides) versus placebo, and EAHM (containing Cassia fistula) versus placebo respectively.

3.3. Interventions

The types of EAHM were very diverse . Eight [18-23, 25, 26] reported single herbal medicine products : two studies [25, used Camellia sinensis ; Sophora flavescens [18], Laminaria digitata [19], Houttuynia cordata [20], Melaleuca alternifolia [21], Hippophae rhamnoides [22] and Betulae platyphyllae [23] were used in one study respectively . The other two studies [24, externally applied mixed herbal medicine products on AV patients : one study [used unani herbomineral formulation (Aloe barbadensis Azadirachta indica, Astragalus sarcocolla Boswellia serrata Commiphora myrrha Cyperus rotundus Chrysopogon zizanoides Jasminum officinale Iris ensata Matricaria chamomilla Nyctanthes arbor tristis Olea europaea Prunus dulcis); another study [used Chinese medical formulation Scutellaria baicalensis , Phellodendron amurense , Isatis tinctoria) Eight trials [18-25] compared EAHM interventions with placebo interventions. The remaining trials, one study [26] compared effects of EAHM to zinc sulphate, and another trial [27] contrasted EAHM treatment to benzoyl peroxide intervention.

3.3.1. Types of EAHM forms

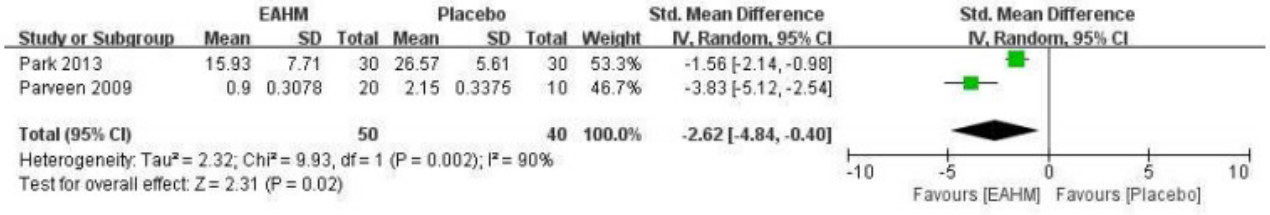
Various types of EAHM form were used in 10 included studies. Of these, three studies [18, 25, 26] applied EAHM lotion to AV patients. Cream [19, 24] and pack [20, 27] types were utilized in two studies. One study was for gel [21] and emulsion [22] respectively. One study [23] used three types of forms including foaming cleanser, toner and ample, with same ingredients on AV patients.

3.3.2. Amount of EAHM Used

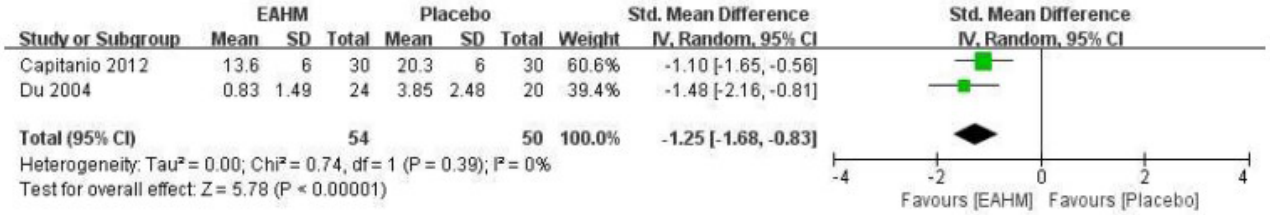
The amount of EAHM used was reported in only two studies: one study [22] utilized total 500 mg of EAHM. A total 170 ml of EAHM foaming cleanser, 200 ml of EAHM toner and 60 ml of EAHM ampule were used in the other study [23].

3.4. Outcome Measures

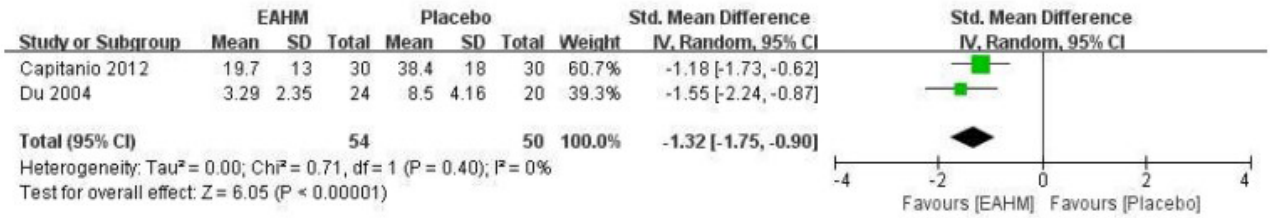
Six studies [18-20, 23-25] that placebo was used as a comparison were available for meta-analysis (Fig. 2). We summarized the results of the studies that statistical pooling was not assessable.



(a) Global assessment



(b) Inflammatory lesion count of acne



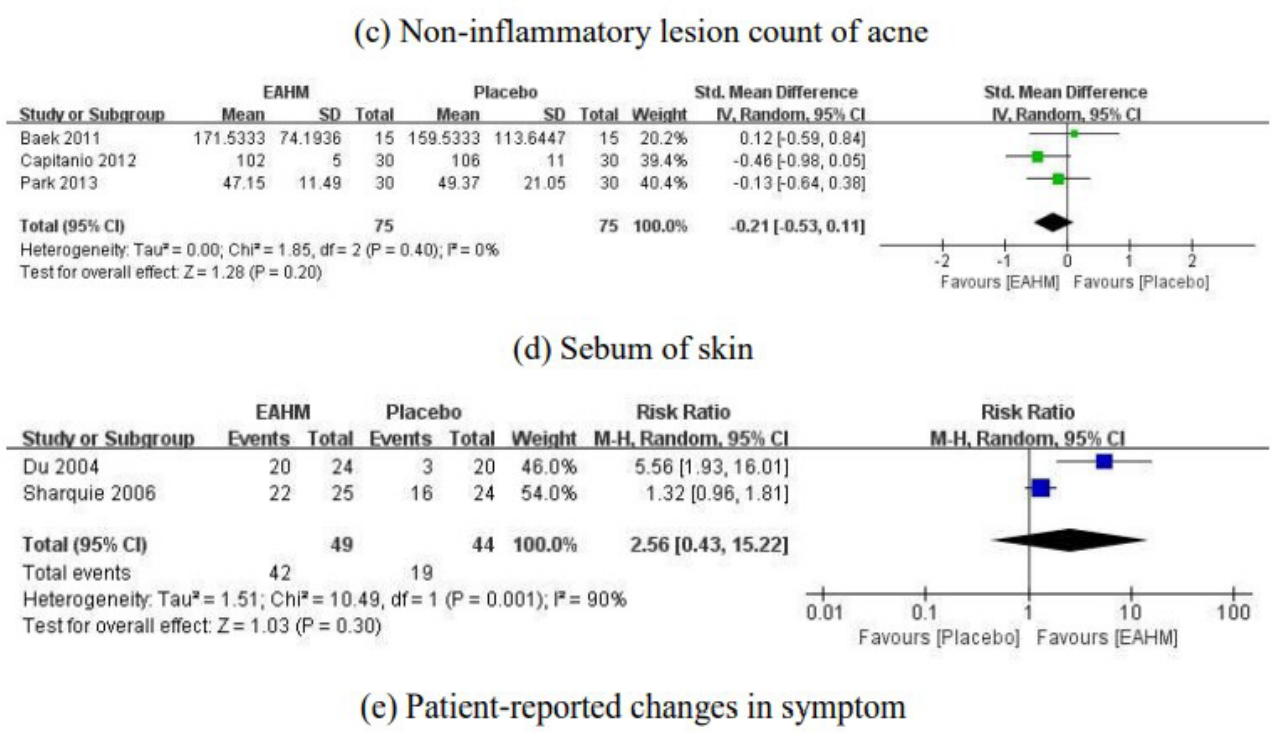


Figure 2 Meta analysis of EAHM versus placebo. EAHM; External Application of Herbal Medicine; CI: Confidence Intervals; SD: Standard Deviation.

3.4.1. EAHM versus Placebo

Of the eight studies [18-25] that compared EAHM with placebo interventions, six studies [18-20, 23-25] provided data for statistical pooling.

Four studies [21-24] compared primary outcome 'global assessment' between EAHM and placebo; two studies [23, 24] of meta-analysis showed significant effect on improving the global assessment [Fig. 2(a), MD = -2.62, CI = -4.84 to -0.40, P=0.02] with high heterogeneity (P = 0.002, I2 = 90%); in the study by Enshaieh et al. [21] reported significant difference in two groups (P < 0.001); we did not assess result of one trial due to insufficient data. [22] Park et al. [23] divided face into six parts, and assigned scores for each part.

For primary outcome 'lesion count of acne', data extracted from two studies [19, 20] showed a significant superior improvement in EAHM compared to placebo in inflammatory lesion count of acne [Fig. 2(b), MD = -1.25, CI = -1.68 to -0.83, P < 0.00001, I2 = 0%] and non- inflammatory lesion count of acne [Fig. 2(c), MD = -1.32, CI = -1.75 to -0.90, P < 0.00001, I2 = 0%]. As meta-analysis was impossible in the other two trials, we described the result of the studies as follows; one trial [21] showed significant improvement in inflammatory lesion count of papules (P < 0.05), inflammatory lesion count of pustules (P < 0.01) and non-inflammatory lesion count of comedones (P < 0.001); in another trial [25], EAHM treatment significantly reduced inflammatory lesion count of papules (P < 0.05) and pustules (P < 0.05) compared with placebo.

Among eight studies that contrasted EAHM with placebo, four trials assessed secondary outcome 'sebum of skin'; meta-analysis on three studies [18, 19, 23] showed no significant difference between the groups [Fig. 2(d), MD = -0.21, CI = -0.53 to 0.11, P = 0.20, I2 = 0%]; in the study by Khan et al. [22] reported EAHM group was more effective than placebo group in sebum of skin (P < 0.05).

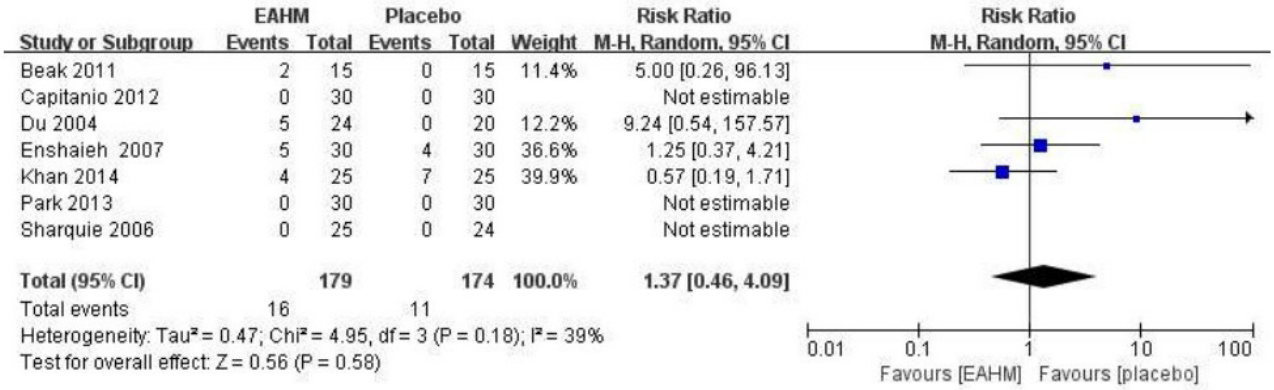
The pooled data from two trials [20, 25] indicated no significant effect in secondary outcome 'patient-reported changes in symptom' [Fig. 2(e), RR = 2.56, CI = 0.43 to 15.22, P = 0.30, I2 = 90%].

In the trial of Baek *et al.* [18], the effect was not significant in secondary outcome 'anti-bacterial activity test'. Anti-bacterial activity was observed in EAHM group but not in placebo group.[22] There were no significant differences between groups in secondary outcome 'quality of life'. [23]

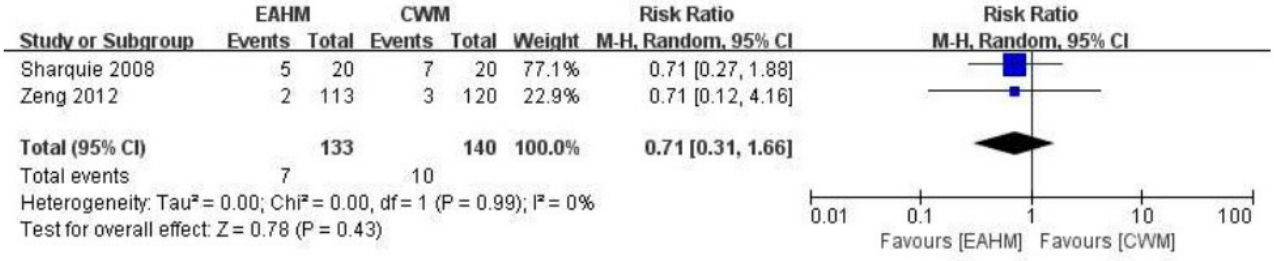
3.4.1.1. Adverse Events

Seven studies [18-23, 25] reported AEs; Baek *et al.* [18] reported minor AEs, such as itching and irritation in EAHM group; we found itching, irritation and pigmentation as minor AEs of EAHM treatment [20]; one trial [21] reported pruritus, burning sensation and scaling occurred in the EAHM group, pruritus and burning sensation presented in the control group; Khan *et al.* [22] reported four cases of itching and irritation occurred in the EAHM group, and seven cases of itching and irritation presented in the placebo group; AEs did not occur in another three studies [19, 23, 25]. One study [24] did not mention AEs. We pooled

data from seven trials [18-23, 25], EAHM group reported more AEs than placebo group but no statistically significant differences were observed between groups [Fig. 3(a), RR = 1.37, CI = 0.46 to 4.09, P = 0.58, I2 = 39%].



(a) EAHM versus placebo



(b) EAHM versus CM

Figure 3 Meta-analysis of adverse events; EAHM: External Application of Herbal Medicine; CI: Conficence Intervals; CM: Conventional Medication.

3.4.2. EAHM versus CM

We summarised the results of two studies [26, 27] compared EAHM with CM intervention because data pooling was not assessable.

Two trials [26, 27] evaluated the effectiveness and safety of EAHM compared with CM; in the study by sharquie [26] that compared EAHM lotion (*containing Camellia sinensis*) with zinc sulphate reported an improvement in global assessment. A significant improvement at acne count of inflammatory lesion (P < 0.001) and non-inflammatory lesion (P < 0.001) were observed in EAHM group but not in control group; the results of study [27] that contrasted EAHM pack with benzoyl peroxide indicated significant difference in acne lesion count and patient-reported changes in symptom (P < 0.05).

3.4.2.1. Adverse Events

There were no severe AEs in all participants; one study [26] reported five cases of itching occurred in the EAHM group, and two cases of itching and five cases of burning sensation represented in the control group; another study [27] mentioned two cases of AEs occurred in the treatment group, and three AEs presented in the control group. The results of AEs did not show a significant difference between the groups (Fig. 3(b), RR = 0.71, CI = 0.31 to 1.66, P = 0.43, I2 = 0%).

3.5. Cochrane risk of bias assessment

Overall, the included RCTs had a low methodological quality (Table 2). Only one trial [21] reported adequate random sequence generation using computer number generator, whereas two trials [19, 23] reported inappropriate method (sequence generated by patients entered the study).

Allocation was properly concealed in two trials. One study [19, 21] reported that allocation was properly conducted using identical appearance that is sealed randomization code. Another study [21] reported that allocation was performed by and independent person.

The participant and practitioner were blinded in five trials [18-21, 23]; Double-blinded RCTs were conducted in two trials [19, 21] and same form of intervention was used in the EAHM and control groups. [18, 20, 23] Single-blinded studies were employed in four studies [22, 24-26] and one study [27] used different types of intervention form in both groups. Only one trial [20] reported the details of the blinding of outcome assessment.

Most of the included studies [18, 19, 21, 23, 24-27] had low risk of bias addressing incomplete outcome data (e.g., no missing outcome data or missing outcome data, but the drop-out rate did not exceed 20% for short-term follow-up). Two trials [20, 22] had high ROB; one [20] had missing data and the drop-out rate exceeded 20% for short-term follow-up, and another [22] reported that the number of patients was different when we compared pre-treatment with post-treatment in outcome measure of global assessment.

Regarding selective outcome reporting, only one [22] studies reported their protocol before conducting the RCTs.

4. Discussion

This systematic review examined the effectiveness and safety of EAHM for treating AV. To the best of our knowledge, this is the first systematic review to provide current available evidence about EAHM for managing AV. From the eight studies [18-25] that compared EAHM with placebo, the positive outcomes and meta-analysis for primary outcomes were found. In the results of the studies that contrasted EAHM with CM [26, 27], the treatment group showed more effective than the control group in primary outcomes. The median sample sizes per arm were 33 in the EAHM group and 32 in the control group. All of the included trials involved small sample sizes; there were only one study [27] with ≥40 participants in each group. Based on the results, especially one high quality RCT [21], EAHM appear to improve primary outcome 'acne lesion count' and 'global assessment'. However, it is not conclusive due to the low methodological quality, and small number of included studies.

In terms of safety, more AEs were observed in EAHM groups compare to placebo groups [18-25], the difference between groups was not statistically significant. Fewer AEs reported among patients treated with EAHM relative to CM [26, 27]; however, no significant differences were observed between groups. The goals of acne treatment are to lessen the acne lesions, improve appearance and minimise potential AEs.[28] Finally, EAHM does not appear to be related to severe AEs, suggesting that EAHM might be safe for AV patients. However, the number of RCTs was too small, so this finding should be interpreted with caution.

Although all the included studies stated that the patients were randomly assigned, only one trial [21] used computer randomization and allocation concealment was stated in two trials [19, 21]. Only one study [21] had a low risk of bias for blinding of participants, personnel and outcome assessors. Bias resulting from inadequate random sequence generation, allocation concealment, or lack of blinding was related to over-positive estimates of intervention effects for subjectively assessed outcomes [29, 30]. For this reason, the potential risk of bias should be minimized to accurate evaluation of EAHM interventions. Among 10 included trials, three studies [18, 20, were conducted in Korea. Although various types of complementary and alternative medicine (CAM) RCTs (e.g. herbal medicine, acupuncture, tuina) were published in the Korea, Korean CAM RCTs were generally excluded from systematic review because Korean trials were not indexed in English data bases such as MEDLINE, EMBASE or Cochrane library [The unbiased search of various databases without a language restriction is important to avoid language bias. The difference that compared active treatment group with placebo group is called the specific effect of that treatment [32]. To measure specific effects, it is necessary to conduct placebo-controlled RCTs [32]. Even though eight studies [18-25] compared EAHM with placebo, the consideration of placebo that had the same level of flavours as the EAHM treatment was not mentioned. The unique flavours

Table 2 Risk of bias assessment.

First author, year	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Baek, 2011 [18]	U	U	L	U	L	U
Capitanio, 2012 [19]	H	L	L	U	L	U
Du, 2004 [20]	U	U	L	U	H	U
Enshaieh, 2007 [21]	L	L	L	L	L	U
Khan, 2014 [22]	U	U	H	U	H	L
Park, 2013 [23]	H	H	L	U	L	U
Parveen, 2007 [24]	U	U	H	U	L	U

of herbal medicine are potentially leading to the failure of participant and practitioner blinding.[33] Therefore, future studies should investigate appropriate placebo intervention that considered the identical shape and scent as experimental EAHM.

We reviewed the 10 included studies that used in the diverse types of EAHM form, ingredient and dosage. Although our review presented positive results, the standardisation of EAHM intervention was not performed. Therefore, Standardization of EAHM that considered following factors is necessary to apply EAHM to AV patients; (1) types of EAHM form and ingredient; (2) duration of treatment and number of treatment sessions based on the each EAHM intervention; (3) EAHM dosage for total treatment and one session; (4) Appropriate placebo model. Future trials need to adhere to 'consolidated standards of reporting trials (CONSORT) for traditional Chinese medicine' [34].

Only two studies [22, 23] reported total EAHM dosage during treatment. The same EAHM formulations might have different effects according the EAHM dosage. This is due to the lack of dosage guideline of EAHM on AV. For establishing EAHM dosage guideline for AV, further research should be conducted based on these results.

The strength of our review is that we searched various databases without language restriction; thus, researchers could assess papers published in East-Asian (Chinese and Korean). Furthermore, the screening and data extraction of East-Asian studies were conducted by Traditional Korean Medicine (TKM) doctors (S. H. S. and G. H. C.) and TCM doctor (N. W. L.). However, this systematic review has some limitations. From the 10 included RCTs, we conducted meta-analysis of six studies; however, due to clinical heterogeneity of control intervention and outcome measure, we performed statistical pooling of two to three trials for each outcome measures. Also, we analyzed the collected RCTs without setting the definition and scope of herbal medicines. The interpretation of the effectiveness of herbal medicines for AV may vary depending on the definition and scope of herbal medicines. In addition, it is difficult to recommend EAHM as a clinical practice guideline for the treatment of AV because of low methodological quality, small sample size and insufficient information of EAHM dosage.

In Future, lager, more rigorous and adequately powered multi-centre RCTs considering these limitations should be investigated.

5. Conclusion

The EAHM seems to have beneficial effectiveness and safe treatment in patients with AV. However, the evidence is insufficient to conclude the effectiveness and safety of EAHM treatment because the analyses were based on a small number of included studies and sample size. Therefore, well-designed, high quality and multi-centre RCTs are needed to provide evidence-based treatment in AV.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contribution

S.H. Sung, B.C. Shin, N.W. Lee and G.H. Choi designed the review. S.H. Sung, G.H. Choi and N.W. Lee completed the literature search, study selection and data extraction. S.H. Sung and G.H. Choi evaluated the methodological quality. They were checked by B.C. Shin, G.H. Choi and B.C. Shin performed the meta-analysis. S.H. Sung and G.H. Choi wrote the article. B.C. Shin revised the manuscript. All authors have read and approved the final manuscript.

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