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Original Research Article

Meta-analysis of the effectiveness of *Euodia rutaecarpa* Benth acupressure and Wendan decoction in the treatment of vertigo

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Abstract

Purpose: *To systematically assess the efficacy and safety of combining Euodia rutaecarpa Benth acupressure with Wendan decoction for the treatment of vertigo, thereby establishing a theoretical framework for informed clinical practice.*
Methods: *Computer-based search was conducted in PubMed, Embase, Scopus, Web of Science, and Cochrane databases to identify randomized controlled literature pertaining to efficacy and safety of Euodia rutaecarpa Benth acupressure in combination with Wendan decoction for management of vertigo. The experimental group received an intervention of Euodia rutaecarpa Benth acupressure combined with Wendan decoction. Articles that met set inclusion and exclusion criteria were screened and evaluated for quality based on Cochrane Quality Rating Scale. Baseline data, intervention data and outcome indicators of included studies were also extracted. Meta-analysis was performed using RevMan 5.4 software.*
Results: *The difference in symptom scores between groups was statistically significant (RR = -0.04, 95 % CI (-0.3, 0.23), p = 0.78). Meta-analysis of the outcome indicators showed heterogeneity at p < 0.0001, I^2 = 91 %. I^2 = 91 > 50 %. There was a statistically significant difference (p < 0.05) between groups in terms of total treatment efficiency (RR = 0.31, 95 % CI (-0.25, 0.88), p = 0.28). Heterogeneity of vertigo degree score showed p < 0.0001, I^2 = 98 %. I^2 = 98 % > 50 %, SMD = 2.34, 95 % CI (0.69, 3.99), p = 0.53.*
Conclusion: *The combination of clinical Euodia rutaecarpa Upright acupressure and Wendan decoction demonstrates significant clinical effectiveness in treating vertigo as evidenced by improvement of all indicators. Moreover, this treatment approach exhibits a high level of safety.*

Keywords: *Euodia rutaecarpa Benth, Acupressure, Wendan decoction, Vertigo, Safety, Meta-analysis*

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INTRODUCTION

Vertigo is a prevalent clinical condition characterized by a subjective sensory abnormality, which can arise from diverse etiologies [1]. Vertigo is a motion or kinesthetic illusion that causes the sensation of rotation, tilting and heaving, in response to the distortion of the spatial relationship between the person and surrounding environment in cerebral cortex

[3]. Etiology of vertigo is multifaceted, requiring involvement of various disciplines and can manifest in numerous diseases, with notable prevalence in hypertension, posterior circulation ischemia, and cervical vertigo [4]. Vertigo is clinically categorized as central vertigo, peripheral vertigo, and other forms of vertigo [5]. Given the high recurrence rate of vertigo symptoms and significant distress experienced by patients, effective management of vertigo holds paramount clinical importance in enhancing patients' quality of life and prognosis of associated conditions [6]. *Euodia rutaecarpa* Benth acupressure is an external Chinese medicine treatment based on meridian theory, the basic theory of Chinese medicine and Chinese herbal medicine [7]. Effectiveness of *Euodia rutaecarpa* Benth acupressure in treating vertigo, particularly when combined with Wendan decoction, has been evaluated in this study to determine its safety and efficacy. This non-invasive method, which involves applying a paste or cream of powdered medicine to acupuncture points, offers advantages such as affordability and ease of use. Patients generally exhibit good acceptance and compliance. However, comparative safety and effectiveness of *Euodia rutaecarpa* Benth acupressure treatment remains uncertain.

METHODS

Literature search

A comprehensive computer search was conducted to obtain literature from PubMed, Embase, Ovid, Web of Science, Cochrane, Library and other databases and collection time frame was from database establishment to February 3, 2023, for *Euodia rutaecarpa* Benth acupressure. This was combined with Wendan decoction Randomized controlled trials (RCTs) on effectiveness and safety of *Euodia rutaecarpa* Benth and Wendan decoction for the treatment of vertigo. The search terms were: "*Euodia rutaecarpa* Benth", "Wendan decoction", and "Vertigo" and their synonyms cum near-synonyms. This study included all randomized controlled trials of the effectiveness of *Euodia rutaecarpa* Benth acupressure combined with Wendan decoction for cervical vertigo with complete follow-up data and outcome indicators.

PICOS principles

Participant/patient

The study was conducted on patients with pathological diagnoses of vertigo regardless of age, race, education, or work environment. Various interventions were employed in experimental group including *Euodia rutaecarpa* Benth acupressure combined with Wendan decoction therapy, in conjunction with other Chinese medical methods. The control group received *Euodia rutaecarpa* Benth acupressure combined with Wendan decoction treatment therapy. Control group had the option to utilize Chinese medicine, conventional Western medicine or other treatment methods.

Parameters determined

Total effective rate (referring to efficacy assessment criteria for eating dizziness in Guidelines for Clinical Research on New Chinese Medicines), secondary outcome indicators including vertigo symptom score, vertebrobasilar artery blood flow velocity, vertebral artery pulse index (PI), serum fibrinogen (Fib) and total cholesterol (TC) were analyzed.

Inclusion criteria

Reports with vertigo as primary presenting symptoms, manifestations of transient brainstem ischemia including ocular symptoms (such as darkness, flashes, visual distortion, diplopia, etc.), inner ear pain, limb numbness or weakness, sudden collapse and syncope were included. Cases in which there exist minor and fluctuating indications of brainstem impairment, including reduced or absent corneal reflex, compromised convergence, nystagmus triggered by spontaneous or vertebral artery compression, positive pathological signs, and other similar symptoms, all of which have well-defined causes and exclude vertigo resulting from alternative disorders, including normal cranial magnetic resonance imaging were also included in this study.

Exclusion criteria

Literature reviews that reveal instances of data omission, wherein certain data were found to be missing and attempts to establish communication with original authors were unsuccessful including studies that focused on patients diagnosed with tumors, otologic diseases, cerebral death, and cerebral hemorrhage were excluded. Trials without controls or self-control, case reports, or case reviews, unpublished literature such as dissertations, conference papers, reviews, commentaries, case reports focusing on systemic diseases, or other malignancies, or any history of malignancy, where original text was not available, and individuals who have not adhered to the treatment protocols outlined in this study

due to a variety of reasons, including language barriers were all excluded from the study.

Retrieval strategy

The search words or phrases were "*Euodia rutaecarpa* Benth" or "Wendan decoction" or "Vertigo disease".

Literature screening and data extraction

Literature was independently screened by two investigators using Note Express software. Investigators read the abstract and full text and examined articles according to inclusion and exclusion criteria. Extracted information included details of authors, time of publication, sample size, randomization protocol, interventions, and outcome indicators, which were cross-checked one after the other. In case of a disagreement, a third investigator was consulted.

Quality evaluation

Evaluation criteria of SYRCLE Risk of Bias Assessment Tool for Animal Experiments were used to evaluate quality of articles. Each article was evaluated independently by two investigators and the results were checked against each other. In case of disagreement, a third investigator was consulted. The following items were evaluated: Adequacy of generation or application of allocation sequences was assessed. Additionally, the uniformity of baselines across all groups, adequacy of allocation concealment, random assignment of animals in experiment, random selection of animals for outcome evaluation, reporting of incomplete data and presence of any other biases were evaluated. Each category was assigned a "yes," "no," or "uncertain" designation, and corresponding results were reported.

Statistical analysis

Pooled data were statistically analyzed using Rev Man 5.4 software. Fixed effect model (Peto method) was used to combine data and pooled OR value was calculated. If there was significant heterogeneity among results, random effect model (D-L method) was used to combine data. After making the funnel plot, fail-safe coefficient = $(\sum z/1.64)^2$-k was calculated, where z was z score of each independent study obtained by checking the standard normal distribution table of *p*-value of each study, and k was number of included studies. The larger the fail-safe coefficient, the more stable the results and the less likely conclusions are to be overturned. Results of meta-analyses using different effect models were compared. Two independent sample *t*-tests were used to compare differences of point estimate and interval estimate of combined value between random effect model and fixed effect model and also to analyze the sensitivity.

RESULTS

Literature search results

After database search, 91 papers were initially retrieved and screened strictly according to inclusion and exclusion criteria. A total of 31 papers were eliminated based on evaluation of their titles and abstracts. Additionally, 30 papers were excluded from experimental literature due to their focus on experimental subjects. Furthermore, 10 papers were excluded from review and empirical literature, while 9 papers were eliminated as they were found to be duplicates. Three articles were excluded from the study due to inconsistencies in number of cases, duration of treatment, interventions, efficacy indexes, duplicate studies and non-randomized groups. Ultimately, a total of eight articles were included in this study. Figure 1 summarizes results of literature search.

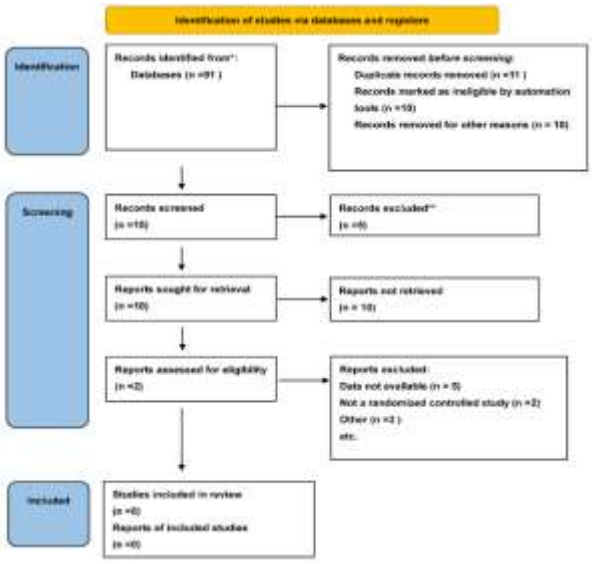

Figure 1: Literature screening process and results

Basic information on the included studies

Eight articles from literature screening totaling 703 patients with 353 patients in the experimental group and 350 patients in the control group were used for subsequent study. All 8 articles had clear diagnostic criteria and were balanced at baseline (Table 1).

Table 1: Basic characteristics of the included studies

Literature	Year of publication	Sample size (Experimental/Control)	Grouping	Baseline Information
[11]	2020	83 (43/40)	Random	Comparable
[12]	2010	90 (45/45)	Random	Comparable
[13]	2019	60 (30/30)	Random	Comparable
[14]	2022	88 (44/44)	Random	Comparable
[15]	2023	88 (44/44)	Random	Comparable
[16]	2022	60 (30/30)	Random	Comparable
[17]	2021	130 (65/65)	Random	Comparable
[18]	2019	104 (52/52)	Random	Comparable

Literature quality assessment

In accordance with Cochrane Systematic Assessor's Manual 4.2.6, two researchers independently read title and abstract of article and obtained full text of article to check whether inclusion criteria were met. At the end, two researchers cross-checked results separately and in case of disagreement, discussion was held or a third researcher decided whether to include article or not. Included article was evaluated using RevMan 5.4 tool, which included risk of bias, whether random assignment method and assignment protocol were hidden, whether treatment protocol, study population and determinant of study outcome were blinded, completeness of outcome data, other sources of bias and selective reporting of study results. If the study met quality criteria, it indicated least possibility of bias and was rated as grade A. If the study partially met quality criteria, it indicated a moderate possibility of bias and was rated as grade B. However, if the study did not meet quality criteria, it indicated a high possibility of bias and was rated as grade C. Results are represented in Figure 2 and Figure 3.

Symptom score

There was no statistical heterogeneity in the 8 articles selected (p < 0.0001, I^2 = 62 %). Fixed-effect model combined with effect size was used for analysis and results showed that there was a statistically significant difference in symptom scores between groups (RR = -0.04, 95 % CI (-0.3, 0.23), p = 0.78). The results are presented in Figure 4.

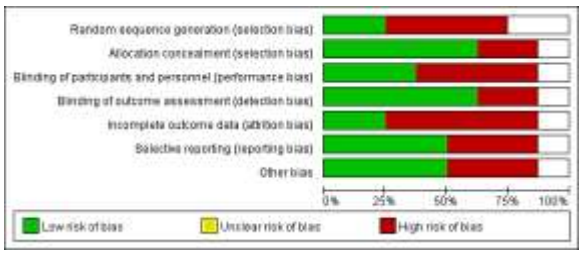

Figure 2: Incorporating Evaluating Literature Quality

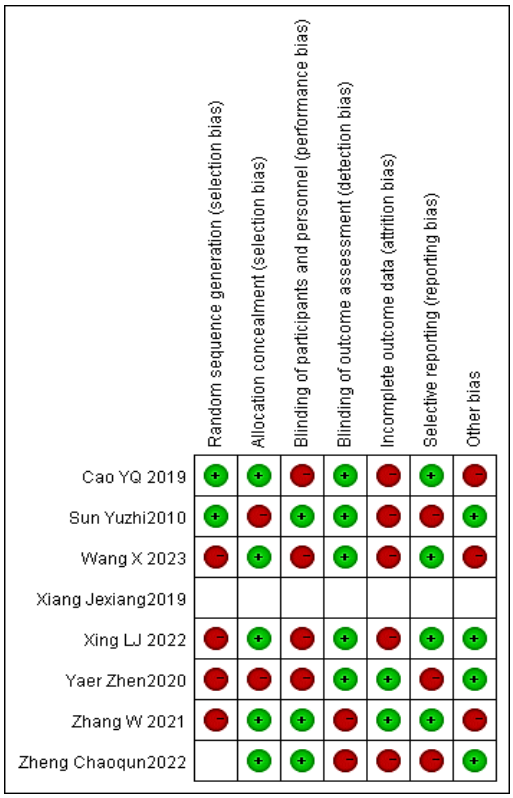

Figure 3: Risk assessment of literature bias

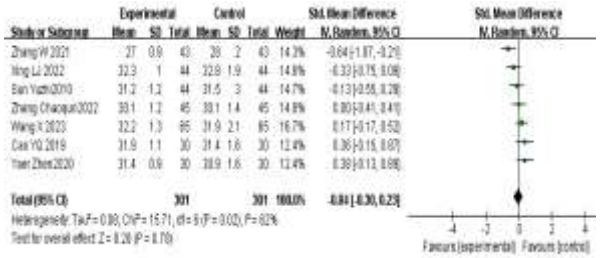

Figure 4: Meta-analysis of symptom score

Total response rate

Meta-analysis of outcome indicators showed p < 0.0001 and I^2 = 91 % for heterogeneity. I^2 = 91 % > 50 % and Q test suggested strong heterogeneity among included studies (Table 5). Literature was culled one by one for sensitivity analysis and detection and heterogeneity was

significantly reduced. Fixed effect model was used to conduct integration statistics and results showed that there was statistically significant difference in total response rate between groups (RR = 0.31, 95 % CI (-0.25, 0.88), p = 0.28).

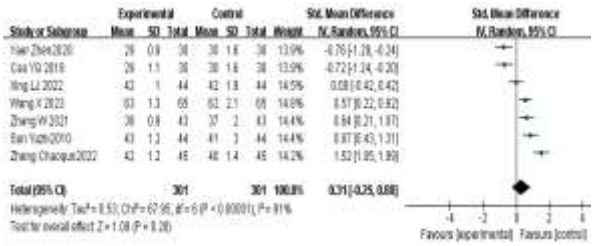

Figure 5: Meta-analysis of total treatment efficiency

Clinical syndrome score

Figure 6 shows meta-analysis of clinical evidence scores. Clinical syndrome score heterogeneity showed $p < 0.0001$, $I^2 = 93$ %. $I^2 = 93$ % > 50 %, and $p > 0.1$ of Q test. Fixed effect model was used to integrate statistics and results were as follows: SMD = -0.48, 95 % CI (-1.14, 0.19), p = 0.16 and difference was not statistically significant ($p > 0.05$).

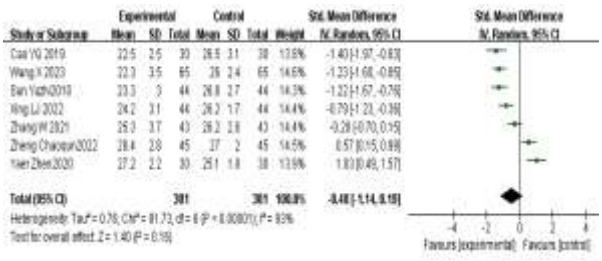

Figure 6: Meta-analysis of clinical evidence scores

Vertigo score

Meta-analysis of vertigo degree score is presented in Figure 7. Heterogeneity of vertigo degree score showed $p < 0.0001$, $I^2 = 98$ %. $I^2 = 98$ % > 50 %, and $p > 0.1$ of Q test. Fixed effect model was used to integrate statistics and SMD = 2.34, 95 % CI (0.69, 3.99), p = 0.53 were obtained. Differences was statistically significant ($p < 0.05$).

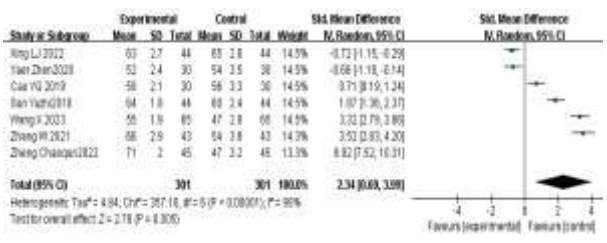

Figure 7: Meta-analysis of vertigo degree score

DISCUSSION

Euodia rutaecarpa Benth acupuncture point application therapy is guided by concept of Chinese medicine. It is based on the principles of internal and external treatment as well as upper and lower treatment of diseases. *Euodia rutaecarpa* Benth is a potent and thermogenic substance that possesses therapeutic properties of cold dispersion, pain relief, liver drainage, Qi stimulation, stain warming and suspension. Consequently, it finds extensive application in external medicinal treatments [19]. The Yongquan point, located on the kidney meridian, serves the purpose of nourishing yin and reducing fire, while also promoting mental clarity and tranquility. *Euodia rutaecarpa* Benth, known for its diverse therapeutic properties, is efficacious in alleviating symptoms such as headache, dizziness and fainting. Furthermore, its ease of administration and simplicity of use make it a frequently employed acupuncture point in acupressure therapy. External application of Wu Zhuyu to Yongquan acupuncture point effectively treats hypertension and improves clinical symptoms, early recovery time from isoproterenol anesthesia, quick re-awakening of patient and low incidence of post-anesthesia nausea. Isoproterenol has inhibitory effect on sympathetic excitation by slowing down heart rate and lowering blood pressure while Wendan decoction has sympathetic excitation effect such as increased heart rate and blood pressure.

In Wendan decoction, Fa Xian Xia is attributed to the three meridians of the card, stomach and lung, which can dry dampness, resolve phlegm, stop vomiting and dissipate knots to improve symptoms of vertigo. Fu Ling (*Poria cocos*) has the potential to enhance spleen function and promote mental tranquility thereby alleviating distressing symptoms of insomnia and dizziness. Chen Pi (*Citrus reticulate*) possesses ability to regulate qi flow and harmonize the qi mechanism, dissolve accumulated phlegm and facilitate digestion. Jieshi effectively disrupts qi stagnation and disperses pathological conditions. Licorice (*Glycyrrhiza glabra*) serves to tonify and nourish qi, while Huang Lian (*Coptis chinensis*) aids in drying dampness and clearing internal heat, thereby ameliorating symptoms associated with abdominal fullness, heat, and heart dryness. Additionally, ginger exhibits warming properties and can effectively alleviate symptoms of nausea. In the case of patients exhibiting various symptoms, application of dialectical addition and subtraction can effectively regulate their condition. For instance, individuals experiencing chest tightness and heart discomfort can benefit from the therapeutic properties of Yu Jin (*Radix*

curcumae), which promotes qi circulation, alleviates depression, clears heart and cools blood. Similarly, administration of Gua Ling can aid in clearing lungs, resolving phlegm, promoting qi flow and expanding the chest. In the context of patient care, the drug is utilized to augment or diminish treatment in order to achieve the desired outcome of regulating symptoms, alleviating illness, and enhancing overall bodily function. Euodia rutaecarpa Benth, known for its pungent taste, is classified as a thermally active medication and is particularly effective in reducing rebellious qi and regulating qi. Consequently, it can also be employed in the treatment of thermal diseases. In the management of such conditions, the distal acupuncture point method is predominantly employed, wherein the upper ailments are addressed by targeting the well point of the foot Shao Yin kidney meridian, specifically Yongquan, which is situated furthest from the human heart. Euodia rutaecarpa Benth exerts the effect of inducing heat with heat and fire to return to the source at this point, the floating yang is latent and the true yang returns to its place then the disease is cured. Results of modern pharmacological experiments also suggest that alkaloids in *Euodia rutaecarpa* Benth have medicinal effects. Among them, *Euodia rutaecarpa* Benth base has protective effect on gastric mucosa and anti-gastric mucosal damage. *Euodia rutaecarpa* Benth base may have direct junctional resistance to M cholinergic receptors, relieves gastrointestinal smooth muscle pain, inhibits intestinal motility and thus has antidiarrheal effect. *Euodia rutaecarpa* Benth is one of the antihypertensive active ingredients that can slow heart rate as well as vasodilation, analgesic and anti-inflammatory effects. Therefore, some scholars also believe that topical application of *Euodia rutaecarpa* Benth may rely on drug penetration through the skin and capillaries to reach internal organs through human blood circulation but exact mechanism of action is still controversial.

All 8 clinical trials in this study followed inclusion and exclusion criteria in case screening and assessed efficacy using common evaluation criteria. For each clinical trial, the underlying data of study subjects were not significantly different but accuracy of study results was limited by factors described below. None of the eight papers in this study stated the method of randomization, whether blinding was applied, or if concealment was assigned and quality of literature was low, making it difficult to verify the objectivity of randomization in these papers and possible bias in measurement, execution and selection. Most results in literature were positive and factors leading to this result may be better efficacy of sulforaphane in treatment of sudden vertigo. The availability of negative, unpublished results leads to publication bias. In this study, Chinese and English literature were designated as primary focus of literature search. However, only Chinese literature was incorporated, potentially leading to exclusion of literature in other languages. Therefore, it is unavoidable to influence study results. In order to guarantee precision and impartiality of study findings, it is imperative for clinical investigators to enhance the precision of trial design, including selection of accurate randomized grouping techniques. Additionally, it is highly recommended to employ a blinded method. Furthermore, it is crucial to promote the publication of negative results, rectify publication bias, and establish a more systematic assessment of drug efficacy.

CONCLUSION

Euodia rutaecarpa Benth acupressure combined with Wendan decoction for the treatment of vertigo shows significant clinical efficacy, improves all observed indicators, and has a high safety profile in patients.

DECLARATIONS

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Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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