Author’s response to reviews

Title: Sedative and hypnotic effects of Compound Anshen essential oil inhalation for insomnia

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled “Sedative and hypnotic effects of Compound Anshen essential oil inhalation for insomnia” (ID: BCAM-D-19-00899R2). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:
Responds to the Editor comments:

María Celina Elissondo (Editor)

1. Response to comment: I now received comments from two contributing scientists (see comments below). One of the experts again requests to specify the novelty of the study. Please clarify.

Response: In many cases, the role of a single medicine is limited and cannot completely solve the complex and multivariate conditions of insomnia patients. Insomnia is caused by a variety of pathogenic factors. Insomnia patients are usually accompanied by different degrees of depression and anxiety. Therefore, the use of a single essential oil maybe only achieves the effect of sedative and hypnosis, and cannot completely solve the problem of sleep disorders. Multi-herb therapy basing on Traditional Chinese Medicine theory is one of the most important characteristics of Traditional Chinese Medicine clinical practice. Traditional Chinese medicine believes that insomnia is caused by dysfunction of organs. Clinically, it is more common in patients with Insomnia due to liver depression, which is the main cause of insomnia. Qi-regulating drugs have the effect of dispersing stagnated liver qi to relieve depression, and thus may be an effective medicine for treating insomnia. In traditional Chinese medicine, Sweet orange, Sandalwood, Rose, Frankincense, Agarwood, Orange blossom are Qi-regulating drugs, which have the effect of dispersing stagnated liver qi to relieve depression. Sweet orange (Orange peel) and Agarwood are classic Herb pairs, which have the effect of relieving qi stagnancy in liver and resolving stagnation for tranquilization. From the perspective of Western medicine, Lavender has sedative-hypnotic effects and anti-anxiety effects, Sandalwood and Agarwood have sedative-hypnotic effects, Sweet orange, Rose, Frankincense and Orange Blossom all have antidepression effects. In this study, the Lavender essential oil, a commonly used in the treatment of insomnia, was combined with the Qi-regulating drugs’ essential oil to prepare the Compound Anshen essential oil and its effect on sedative and hypnotic effects with inhalation administration were studied. Based on the theory of aromatherapy of traditional Chinese medicine, this experiment is aiming at treating insomnia from the perspective of relieving qi stagnancy in liver and resolving stagnation for tranquilization. The purpose of the study is to investigate the potential treatment on insomnia of Compound Anshen essential oil.

On this basis, the composition of Compound Anshen essential oil was analyzed by gas chromatography-mass spectrometry (GC-MS). A total of 30 chemical constituents were identified, accounting for 93.39% of total volatile oil. The main components of Compound Anshen essential oil are esters, alcohols, alkenes, alkyls and other compounds, with the highest content of D-limonene (24.07%), Linalool (21.98%), Linalyl acetate (15.37%), α-Pinene (5.39%) and α-Santalol (4.8%). D-limonene, Linalool, Linalyl acetate and α-Santalol have been reported to have central nervous sedative effect. In addition, D-limonene has anti-anxiety and soothing effects, Linalool has anti-anxiety and depression-like effects and α-Pinene has anti-anxiety and stress-relieving effects. It is speculated that the sedative and hypnotic effect of Compound Anshen essential oil is related to its main chemical composition and activity. Based on the network pharmacology, the active components, targets and pathways of the Compound Anshen essential oil were predicted. The results of the network pharmacology analysis were published. Among the volatile chemical constituents of the compound anshen essential oil traced by GC-MS, the active ingredients related to insomnia were screened and the relevant targets and pathways were predicted. The study found that Dibutyl phthalate, Caryophyllene, Geranyl acetate, Linalool, α-Terpinel, and Terpinen-4-ol played a key role in the treatment of insomnia in the Compound Anshen essential oil. The chemical components with the highest content tracked by GC-MS were D-Limonene, Linalyl acetate, α-Pinene, which were also correlated with treatment of insomnia. It is predicted that the compound anshen essential oil mainly exerts pharmacodynamic effects through related target proteins such as ESR1, GABRA1, GABRA2,
GABRA3, GABRA4, GABRA5, NR1H4, CHRM1, SLC6A2, SLC6A3, SLC6A4, CYP3A4, DRD1, DRD2, OPRD1, OPRM1, HCRTR1, HTR2A, etc. It is mainly related to Calcium signaling pathway, Neuroactive ligand-receptor interaction, Cholinergic synapse, GABAergic synapse and other pathways. Based on the network pharmacology method, the active ingredients of the Compound Anshen essential oil have sedative, hypnotic, anti-anxiety and anti-depression effects, and the correlation between the active ingredients and the target and pathway. To some extent, the reliability of the study on the sedative and hypnotic effects of the Compound Anshen essential oil and the reliability of the GC-MS analysis of the chemical components were confirmed.

We have made correction according to the Editor’s comments.

(e.g. Background section, line 3, page 5) Inhalation is a fast and effective aromatherapy that induces central nervous system response in just 4 seconds. It uses respiration to start from the absorption of volatile molecules through the nasal mucosa, while volatile molecules enter the circulatory system after gas exchange into the lungs [21]. The olfactory pathway not only conducts the sense of smell, but also regulates the memory, emotions, visceral activities, and advanced functions of the brain such as alertness and sleep through olfactory regulation. The neurotransmitter of olfactory transmission information and the Orexin neuronal system in the lateral region of the hypothalamus initiate neurons such as brain stem, basal forebrain, and hypothalamus, producing gamma-aminobutyric acid (GABA), Serotonin (5-HT), etc [22]. These transmitters are closely related to the pathogenesis of insomnia and other diseases. Inhalation administration is a nondestructive way of administration, which minimizes toxic and side effects. Therefore, it may be an effective way to control and treat insomnia and other psychiatric diseases.

(e.g. Background section, line 4, page 5) In many cases, the role of a single medicine is limited and cannot completely solve the complex and multivariate conditions of insomnia patients. Insomnia is caused by a variety of pathogenic factors. Insomnia patients are usually accompanied by different degrees of depression and anxiety. Therefore, the use of a single essential oil maybe only achieves the effect of sedative and hypnosis, and cannot completely solve the problem of sleep disorders. Multi-herb therapy basing on Traditional Chinese Medicine theory is one of the most important characteristics of Traditional Chinese Medicine clinical practice [23, 24]. Traditional Chinese medicine believes that insomnia is caused by dysfunction of organs. Clinically, it is more common in patients with Insomnia due to liver depression, which is the main cause of insomnia [25]. Qi-regulating drugs have the effect of dispersing stagnated liver qi to relieve depression, and thus may be an effective medicine for treating insomnia [26]. In traditional Chinese medicine, Sweet orange, Sandalwood, Rose, Frankincense, Agarwood, Orange blossom are Qi-regulating drugs [25, 26], which have the effect of dispersing stagnated liver qi to relieve depression. Sweet orange (Orange peel) and Agarwood are classic Herb pairs, which have the effect of relieving qi stagnancy in liver and resolving stagnation for tranquility. From the perspective of Western medicine, Lavender [27,28] has sedative-hypnotic effects and anti-anxiety effects, Sandalwood [29] and Agarwood [30] have sedative-hypnotic effects, Sweet orange [31], Rose [32], Frankincense [33] and Orange Blossom all have anti-depression effects. In this study, the Lavender essential oil, a commonly used in the treatment of insomnia, was combined with the Qi-regulating drugs’ essential oil to prepare the Compound Anshen essential oil and its effect on sedative and hypnotic effects with inhalation administration were studied. Based on the theory of aromatherapy of traditional Chinese medicine, this experiment is aiming at treating insomnia from the perspective of relieving qi stagnancy in liver and resolving stagnation for tranquility. The purpose of the study is to investigate the potential treatment on insomnia of Compound Anshen essential oil.

Special thanks to you for your good comments.

Responds to the reviewer’s comments:
Tadaaki Satou (Reviewer 1)

1. Response to comment: I read a comment. However, I could not understand the necessity of blended essential oil (composition, ratio). Experimental results are only considered for blended essential oils. It is written as network pharmacology, but it is quite possible that it is the effect of one essential oil or one compound. When the effect of this blend essential oil is recognized as novelty, it is necessary to recognize the effect of another blended essential oil as novelty. Please show clear novelty.

Response: In many cases, the role of a single medicine is limited and cannot completely solve the complex and multivariate conditions of insomnia patients. Insomnia is caused by a variety of pathogenic factors. Insomnia patients are usually accompanied by different degrees of depression and anxiety. Therefore, the use of a single essential oil maybe only achieves the effect of sedative and hypnosis, and cannot completely solve the problem of sleep disorders. Multi-herb therapy basing on Traditional Chinese Medicine theory is one of the most important characteristics of Traditional Chinese Medicine clinical practice. Traditional Chinese medicine believes that insomnia is caused by dysfunction of organs. Clinically, it is more common in patients with Insomnia due to liver depression, which is the main cause of insomnia. Qi-regulating drugs have the effect of dispersing stagnated liver qi to relieve depression, and thus may be an effective medicine for treating insomnia. In traditional Chinese medicine, Sweet orange, Sandalwood, Rose, Frankincense, Agarwood, Orange blossom are Qi-regulating drugs, which have the effect of dispersing stagnated liver qi to relieve depression. Sweet orange (Orange peel) and Agarwood are classic Herb pairs, which have the effect of relieving qi stagnancy in liver and resolving stagnation for tranquilization. From the perspective of Western medicine, Lavender has sedative-hypnotic effects and anti-anxiety effects, Sandalwood and Agarwood have sedative-hypnotic effects, Sweet orange, Rose, Frankincense and Orange Blossom all have antidepressant effects. In this study, the Lavender essential oil, a commonly used in the treatment of insomnia, was combined with the Qi-regulating drugs’ essential oil to prepare the Compound Anshen essential oil and its effect on sedative and hypnotic effects with inhalation administration were studied. Based on the theory of aromatherapy of traditional Chinese medicine, this experiment is aiming at treating insomnia from the perspective of relieving qi stagnancy in liver and resolving stagnation for tranquilization. The purpose of the study is to investigate the potential treatment on insomnia of Compound Anshen essential oil.

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Special thanks to you for your good comments.

Thomas Heinbockel (Reviewer 2)
1. Response to comment: The authors have attempted to address my concerns and questions. The
manuscript has improved in quality. 
Response: Special thanks to you for your good comments. 

Other changes: We have studied reviewer’s comments carefully and have made revision in the paper.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Thank you and best regards!

Yours sincerely,
Yu Zhong

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