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GAVIN PUBLISHERS

Journal of Sleep Disorders and Nervous System

Leung PC and Wing YK. J Sleep Disord Nerv Syst: JSDNS-102.

DOI: 10.29011/JSDNS-102/100002

Research Article

How is an Old Herbal Formula Converted to an Evidence-Based Medicinal Herbal Supplement for the Treatment of Sleep Disorder – A Review and Current Study

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Citation: Leung PC, Wing YK (2018) How is an Old Herbal Formula Converted to an Evidence-Based Medicinal Herbal Supplement for the Treatment of Sleep Disorder - A Review and Current Study. J Sleep Disord Nerv Syst: JSDNS-102. DOI: 10.29011/ JSDNS-102/100002

Received Date: 04 June, 2018; **Accepted Date:** 11 September, 2018; **Published date:** 18 September, 2018

Abstract

Insomnia is a common problem among the general population while people with advancing age seem to be more affected. Powerful drugs capable of sleep induction have never been popular for obvious reasons. Instead, those suffering from sleep disorder are yearning for specific medicinal supplements that could possibly help with better sleep.

Classic Chinese Herbal Formularies have an ancient formula consisting of 5 herbal items, the Suanzaorentang (Sour date seed decoction) that originated from the Han Dynasty and for over 2000 years, has consistently served Chinese people for sleep disorders. Unlike most herbal formulae which aim at a number of syndromes, this formula Suanzaorentang (SZRT) is unique in that it is focused on only one target of sleep disorder. Literature search has confirmed the sedative effects of the formula as well as some of its components.

We modified SZRT by removing two herbs that appeared to be less supportive for the clinical effects and replacing with three other items that have been described as "Body-Mind Harmonizers". We need to prove that the modification has not weakened its original efficacy and has potential of even enhanced effects.

The modified formula was put under a *Drosophila* platform to test its sleep promotion effects on fruit flies. The results were very positive.

The same formula was put on a randomized controlled trial involving 162 people suffering from primary insomnia. Result of four weeks' consumption showed that the subjective sleep quality and the perceived depth of sleep were significantly better in the treatment group.

We conclude that the modified SZRT was safe and effective for sleep improvement and the line of approach we took on the modification of an ancient formula to justify its modern use could serve as a model for similar endeavours.

Keywords: Chinese Medicine; *Drosophila*; Insomnia

Introduction

Insomnia is a common health issue affecting 10-20% of general population [1], and much higher rates have been reported among Americans (40%) [2] and clinical populations [3]. People with sleep disorder presented with difficulty falling asleep; frequent awakenings and daytime drowsiness tend to rely on alcohol, drugs and other remedies [4]. On the other hand, many affected people assume that insomnia is normal and are afraid of taking proper

medications for fear of addiction. Instead they use complementary and alternative medicine for management of their sleep problems [5].

In Hong Kong, the main Chinese Community favours Traditional Chinese Medicine provided in various forms of "Off the Counter" preparations. Among the popular medicinal products, one most frequently used herbal combination is a very ancient classical formula: Suanzaorentang or, literally "Sour-Date Nut Decoction" [6,7].

While we are earnestly developing an evidence-based medicinal supplement to help patients with sleep disorder, there is good reason to consider using this most popular ancient formula, giving it logical modifications, and putting it onto laboratory platforms and proper clinical studies in the process of validation for efficacy.

The Ancient Formula - Suanzaorentang

Suanzaorentang (SZRT) was recorded in the oldest traditional Chinese Formulary, Jin Guai (Han Dynasty) over 2600 years ago. It was composed of five herbs: *Semen Ziziphi Spinosae*, Caulis polygonic multi-flori, Poria cum radix pini, *Glycyrrhiza uralensis* and *Ligusticum chuanxiong* hort. It has been advocated for calming the mind and harmonizing body and mind. It has kept its popularity in the subsequent centuries for over 2000 years. One common practice in Traditional Chinese Medicine is using the best-known combination (i.e. SZRT) as the core treatment pillar, then adding freely some other herbs to intensify certain effects under specific clinical situations. Over the 20 centuries since the creation of SZRT, a few equally popular formulations had been created, all centralized on SZRT, in Tang, Sung, Ming and Qing Dynasties [8].

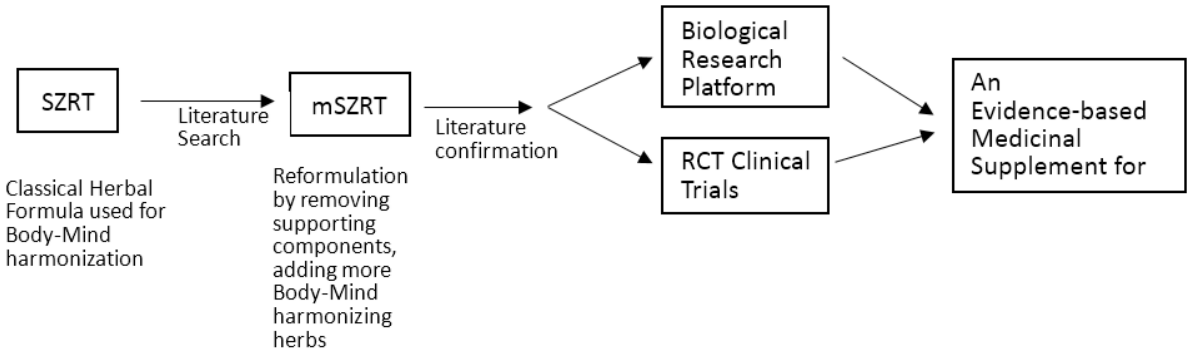
While we are confident that SZRT could be a reliable choice of herbal combination to alleviate sleep disorder, we intend to further enhance its mind-calming and body-mind harmonizing effects through a careful re-formulation according to current knowledge on other medicinal herbs known to possess the same effects. Two of the five herbs, viz. *Glycyrrhiza uralensis* and *Ligusticum chuanxiong* hort, presumably have been included in the SZRT to achieve co-ordinating effects between the major components. We decided to remove them and replace with three others traditionally used herbs for the same purpose of harmonizing and mind-calming, viz. *Polygonum mltiflorum*, *Radix Polygalae* and *Triticum aestivum*. We believe the modification would provide more specific benefits for sleep disorders. After all, the two eliminated herbs have been reported to be more prone for adverse effects in repeated consumptions and their inclusion in the original SZRT could have meant for wider indications other than sleep enhancements [9,10].

The Three Substituted Herbs have been Investigated Thoroughly in Available Literature to Justify their Mind-calming Effects

- ***Radix Polygalae*** appeared in the oldest classics as a potent anti-inflammatory mind calming and harmonizing agent. While its preparation from raw herb needs to be meticulously done to avoid toxicity, it has been widely used as an important component of mentality related formulations [11].
- ***Polygonum mltiflorum*** **thunb** is the aerial part of a well-known herbal root widely used for white hair and related aging problems. Experiments using mice have demonstrated its sleep supporting effects [12]. Its clinical use has been well-known in the psychiatric fields in China [13,14].
- ***Triticum aestivum*** is a special specie of wheat well-known for its mentally soothing effects, particularly used among women who experience feelings of mental stress, resulting from sleep disorders and dreams. It has also been used together with ziziphi to make a special calming tea [15].

With the revised formula ready we need to put it to carefully designed research platforms to establish objective evidence about its pharmacological effects. After this, carefully planned clinical trials are required to investigate its efficacy.

The Following Diagram gives a Schematic Explanation of the Comprehensive Approach



Laboratory Tests on SZRT's Pharmacological Effects

Prior to platform studies a careful literature search has been useful to establish preliminary confidence in the choice of the formula.

The key component semen *Ziziphi spinosae*, the seed of a sour date, has been found in the laboratory to exert sedative effects probably via molecular pathways related to 5HT1a, 5HT2 and GABA receptors [9,10,16]. Wang et al reported that a C-glycoside flavonoid, spinosin, extracted from *Ziziphi spinosae*, had potentiating effects on pentobarbital-induced sleep, and this effect could be related to post-synaptic 5HT(1A) [10].

While fruit flies have been endorsed as relevant animals for the studies on sleep, many publications are available for reference [17,18] Wang in 2009 reported the positive effects of SZRT on the support of sleep in fruit flies, so that male flies after consuming 2% SZRT food for 3 days were found to have a much longer sleep time compared with controls. Female flies given a 4% feed for 7 days demonstrated an even longer sleep period. The same SZRT consumptions equally improved sleep in flies under the adverse disturbances of strong light and noise. (Master thesis Wang Guang-wai, Chinese Medicine University, Heilungjiang, China 2009).

In Hong Kong Ko & Koon used a *Drosophila* platform to study the sedative effects of the modified SZRT [19].

Their Work Can Be Summarized as Follows

To assess the biological effects of the six-herb SZRT, caffeine-induced insomnia *Drosophila* model and short-sleep mutants were used: Caffeine-induced insomnia wild-type *Drosophila* and short-sleep mutant flies Minisleep (mns) and HyperkineticY (HkY) were used to assess the hypnotic effects. The night time activity, the amount of night time sleep and the number of sleep bouts were determined using a *Drosophila* activity monitoring system. Sleep was defined as any period of uninterrupted behavioral immobility (0 count per minute) lasting > 5 min. Night time sleep was calculated by summing up the sleep time in the dark period. Number of sleep bouts was calculated by counting the number of sleep episodes in the dark period. Result showed SZRT at the dosage of 50 mg/mL, effectively attenuated caffeine-induced wakefulness ($P<0.01$) in wild-type Canton-S flies as indicated by the reduction of the sleep bouts, night time activities and increase of the amount of night time sleep. SZRT also significantly reduced sleeping time of short-sleep HkY mutant flies ($P<0.01$). However, SZRT did not produce similar effect in mns mutants. Conclusion is made that SZRT might be able to rescue the abnormal condition caused by mutated modulatory subunit of the tetrameric potassium channel, but not rescuing the abnormal nerve firing caused by Shaker gene mutation.

The laboratory informations, though yet scanty, should have given reasonable suggestions on the biological and pharmacological effects of the modified SZRT, which lead us into the planning of proper clinical trials.

Reports on Clinical Trials on SZRT and Related Formulae

Chen & Hsieh in 1985 conducted a clinical trial on SZRT and reported good anti-insomnia results [20]. Xie et al. did a systemic review on the efficacy and safety of SZRT for primary insomnia using randomized controlled trials in 2013 and reported reasonable efficiency although the quality of the trials was not of high standard [21].

Many modified SZRT formulae had been made into proprietary medicine preparations and put into clinical trials. The diversities of modifications have made interpretation difficult. Moreover, the number of subjects could be very limited [22].

A recent report from China gives analysis of as many as 13 reported trials on different combinations of SZRT, some on which were also used together with sedative pharmaceuticals like diazepam. Authors made a conclusion that "SZRT caused fewer side-effects than that of diazepam and could be recommended as alterative treatment for insomnia" [21].

A proper Randomized Controlled Trial

To give clinical evidence to the modified SZRT, its efficacy and safety when used on primary insomnia patients over a period of four weeks a clinical study was organized using subjective as well as objective measurements. The randomized controlled trial was double-blinded, involving 162 primary insomnia subjects (mean age 46.5 years, ranged from 21 to 64 years and male/female 31.5/68.5). The study was carried out in 2 university affiliated sleep centers. 86% (139) completed the whole trial. Participants received either four weeks of modified SZRT or placebo by block randomization. After 4 week's treatment, the treatment group showed more improvement in the subjective sleep quality in the perceived depth of sleep (visual analog scale, mean differences (95% C1) = -16.0 (-22.1 to -9.9) vs -7.1 (-13.3 to -1.0), $p<0.05$) and refreshing sleep (mean differences 95% C1 = -12.0 (-18.2 to -5.8) vs -2.2 (-8.9 to -4.5), $p<0.05$) than the placebo group. However, the two groups did not show significant difference over the objective measures using Actiwatch 16 (mini Mitter Co. Inc) and the Insomnia Severity Index total scores. Adverse effects were not observed in both groups. A conclusion could therefore be made that the SZRT had a good safety profile and tolerability and that it improved perceived sleep quality [23].

Discussion

People suffering from insomnia could have rather complex causative background like hyperactivity of stress response

mechanisms; anxiety and depression, abnormalities in the circadian rhythm [24], all of which could be related to functional disorders of the hypothalamic-pituitary-adrenal axis [3]. Other precipitating and perpetuating factors like psychosocial features, fatigue and irritability, behavioral changes and cognitive alternations, also contribute. To harmonize the possibly co-existing functional disorders is obviously a difficult aspiration in contrast to drastic measures when potent drugs are used to totally knock down the consciousness to produce sleep.

Natural remedies commonly used in Europe and America include foods with tryptophan, cherry juice, seaweed, melatonin and valerian. Assumption are made that those natural products probably work via the serotonergic system [25]. However, proper clinical evidence on the efficacy of the natural products are lacking. The modified formula we used for insomnia contains Sanjoinine A, Jujuboside A, Spinosin and other flavonoids which could provide sedative effects via the GAB Aergic and Serotonergic systems [27,28]. Which are the exact mechanisms involved are not known. Since a large variety of chemicals must be involved, the speculation on the pharmacological effects of SZRT could be related to harmonizing the contrasting directions of the molecular mechanisms.

SZRT has a solid record of clinical application for over 2000 years. It is also one of the few ancient herbal formulae that consistently maintain its specific favour for use among patients with sleep disorders. This record is unique since most ancient Chinese herbal formulae are meant for multiple uses for a number of syndromes, not consistently focusing on just one symptom of sleep disorder. The formation of ancient Chinese herbal formulae follows a unique logic of having one or two components to play the major role while the other partners are incorporated as "smoothener" or "detoxicant". In the classical SZRT, two herbs viz. *Glycyrrhiza uralensis* and *Ligusticum chuanxiong* hort, fall into the "smoothener" group. In our attempt to create a more effective herbal combination from the classic, *Glycyrrhiza uralensis*, *Ligusticum chuanxiong* hort were removed and their positions were replaced with *Polygonum mltiflorum*, *Radix Polygalae* and *Triticum aestivum*, all of which have reported sedative effects in herbal classics and in recent scientific reports [26].

The modified SZRT in our clinical trial worked quite well which indicated that not only had the modification maintained its classical effects but it might have given it extra merits.

There was one interesting report in 2004 about the combined use of SZRT with venlafaxine, a common anti-depressant, when the adverse serotonin syndrome, resulted. This raised the concern about the safety use of SZRT, particularly when other drugs for mental disorders are being used. The same report might also indicate that SZRT affects the mind through the same serotonergic effects [29].

In our clinical trial using modified SZRT, safety was comfortably demonstrated [23]. The same trial also indicated that rebound of insomnia symptoms which is commonly reported in abrupt cessation of conventional treatment for insomnia, e.g. using diazepines, was not observed.

Conclusion

The modified SZRT, a formula aiming at increased potency of body-mind calming effects, has been proven to be safe and effective among people suffering from chronic insomnia with a mean duration of 10 years in a trial using fixed dosage in a short duration of four weeks. The mode of action is postulated to be harmonizing between the molecular mechanisms related to the hypothalamus-pituitary-endocrine axis. The modification has followed a logic of taking comprehensive reference from the classics, clearly defining the clinical indication for patient care, (i.e. insomnia) then add on other herbal items reported to have the same bio and clinical activities. The subsequent clinical trial designed according to the guideline of Randomized Controlled Trial has given essential evidences for the safe use of the modified formula. We believe that the complicated processes that have been described and taken for the justification of the modification and its subsequent clinical application, could serve as a working example for the upgrading of ancient Chinese Herbal Formulae to be accepted as evidence-based medicinal supplements with specific health indications.

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