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Efficacy and safety of Wuling capsule, a single herbal formula, in Chinese subjects with insomnia: A multicenter, randomized, double-blind, placebo-controlled trial

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ABSTRACT

Ethnopharmacological relevance: Wuling Capsule is a single herbal formula from *mycelia of precious Xylaria nigripes* (*Kl.*) *Sacc* and its pharmacological function have a tranquilizing effect on the central nervous system. The aim of the study to evaluate the efficacy and safety of Wuling capsule in treatment of insomnia.

Materials and methods: We performed a multicenter, randomized, double-blind, placebo-controlled study. The participants received either placebo ($n=92$) or Wuling capsule ($n=94$) for 4 weeks and a follow-up period for 2 weeks.

Results: Compared between pre-treatment and post-treatment, the global Pittsburgh sleep quality index (PSQI) scores in both Wuling capsule group and placebo group improved significantly ($P<0.01$). However, there was no significant difference between Wuling capsule group and placebo group ($P>0.05$). Scores of clinical global impressions scale (CGI-I) at each week in Wuling capsule group was similar to those in placebo group ($P>0.05$). Compared between pre-treatment and post-treatment, scores of the four components of world health organization on quality of life brief scale (WHOQOL-BREF) in both Wuling capsule group and placebo group improved significantly ($P<0.01$). However, there were no difference between the two groups ($P>0.05$). The rate of adverse events was 10.10% in Wuling group, and 6.73% in placebo group ($P>0.05$).

Conclusions: Wuling capsule can improve insomnia when compared with pre-treatment for 4 weeks and be a well tolerated by all the patients at the 6 weeks of study period. However, there are no significant in the results of the variables tested when compared with placebo control. Further additional rigorous randomized clinical trials are still required.

0. Introduction

Insomnia is a highly prevalent and often debilitating condition. The American Academy of Sleep Medicine Work Group defines insomnia disorder as sleep difficulties associated with daytime impairment or distress about the difficulty sleeping (Edinger et al., 2004). Prevalence estimates of chronic insomnia ranged from 10% to 15% in the adult population who suffers from insomnia with the presence of symptoms for at least 1 month, while an additional 25% to 35% have transient or occasional insomnia (Doghramji, 2006). Evidence-based management of insomnia may include pharmacological treatments and the collectively nonpharmacological approaches (Morgan et al., 2011). Currently, the results of the Bettering the Evaluation and Care of Health (BEACH) program from April 2006 to March 2008 showed that medications are prescribed to 95.2% of insomniac cases, even as high as 81.7% of new insomniac cases (Charles et al., 2009). However, hypnotic medicines might have a pool of potential harms such as hangover effects, drug tolerance, rebound insomnia, and risk of addiction.

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In addition, chronic users of hypnotic medications for insomnia have more regular nighttime awakenings than insomniacs not taking medications (Ohayon and Caulet, 1995). Thus, there are rising number of insomniac patients resort to various kinds of complementary and/or alternative medicine (CAM) worldwide. An analysis of the United States National Health Interview Survey data from 2002 by Pearson et al. (2006) revealed that 4.5% of adult population had used CAM to treat insomnia or trouble sleeping during the previous 12 months. However, the only extensively researched herbal medicine for insomnia to date is valerian (either as a monotherapy or in combination with kava or hops), suggesting that further research on other herbal medicines with potential hypnotic effects is encouraged as current research in these areas is in their infancy (Sarris and Byrne, 2011).

The most appreciable distinction between China and the west in treating insomnia is the use of traditional Chinese medicine (TCM) therapy, which includes Chinese herbal medicine (CHM), acupuncture and other nonmedication therapies. TCM has played an important role in the medical care of insomnia patients for thousands of years in China. For example, *Suan Zao Ren* decoction has a long history of use as part of the traditional *Chinese pharmacopoeia* first documented in the classical Chinese text *Jin Gui Yao Lue* (essential prescriptions from the golden cabinet) about 210 A.D. by Zhong-Jing Zhang (Yeh et al., 2011). In modern time, herbs are still prevalent attractive CAMs to many patients with sleep disorders (Gyllenhaal et al., 2000; Sarris et al., 2011). Wuling capsule is a single herbal formula from *mycelia of precious Xylaria nigripes (Kl.) Sacc* and was approved in 1999 by the China State Food and Drug Administration (Authorized Document Number: Z19990048 in Chinese medicine) for the treatment of neurasthenia (insomnia, amnesia, neurosis, vertigo, exhaustion syndrome) and depression, anemia, women's menstrual disorder, diseases during climacterium and geriatric of men as well as women. As a modern Chinese patent herbal preparation, Wuling capsule carried out standard for quality and purity according to *Chinese Pharmacopoeia* (version 2005) and now *Chinese Pharmacopoeia* (version 2010). On the basis of the *Chinese Pharmacopoeia*, content determination of polysaccharides and adenosine has been proposed as the quality control of Wuling capsules. Thus, the processing of the product was subjected to strict quality control, and the ingredients were subjected to standardization. Recently, some new methods were reported for determining the chemical composition and/or for quality control of Wuling capsules. For example, Chen et al. (2012) established a method for the content determination of multiple constituents, including 5-methylmellein, 5-hydroxymellein, 5-carboxylmellein and genistein, in Wuling capsules simultaneously by high performance liquid chromatography (HPLC); Lu et al. (2011) established a method of specific chromatogram analysis of chemical constituents by reverse phase-HPLC with diode array detector for the quality control of Wuling capsules, and 5-methylmellein was extracted as the characteristic component of Wuling capsules; He and Liu (2010) established an analytical method for detecting 14 kinds of amino acid in Wuling capsule by HPLC with fluorescence detection.

Wuling capsule has been used in clinic for many years and claimed to be effective in improving the signs of insomnia and cognitive deficits (Li et al., 2011). The preliminary evidences from clinical studies suggested the significant benefits of Wuling capsule for some patients with insomnia (Yin and Zhang, 2011).

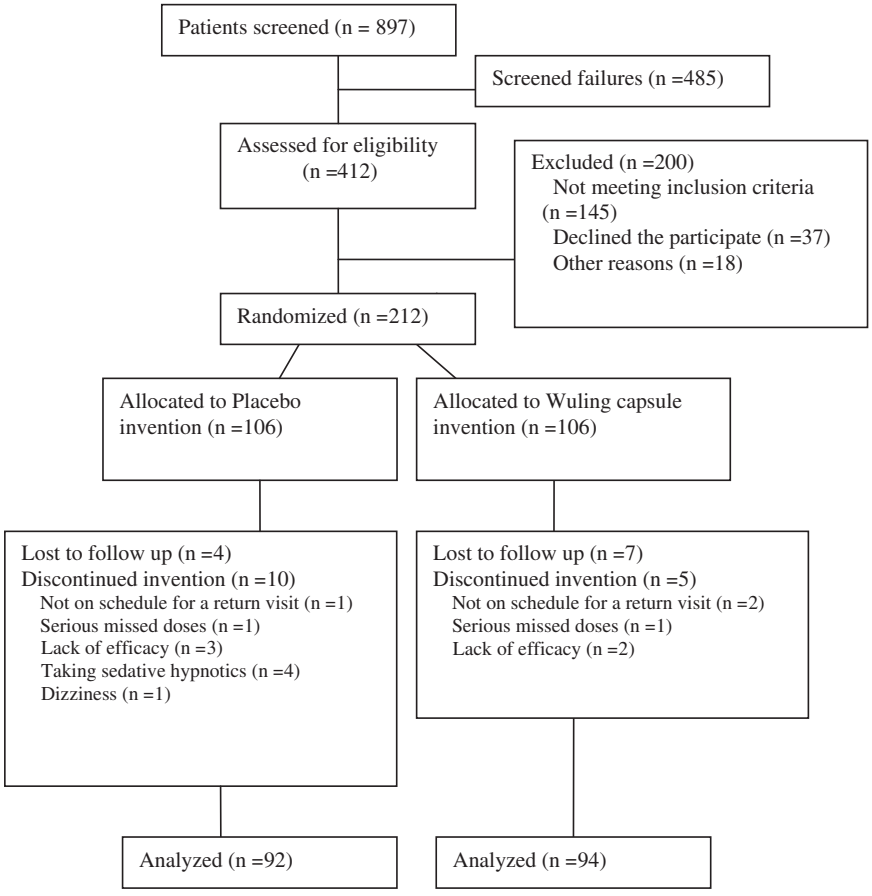

Fig. 1. Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis).

For the mechanisms of the tranquilizing effect of Wuling Capsule on the central nervous system, some researchers found that Wuling capsule could increase the brain intake of glutamic acid and γ-aminobutyric acid (GABA) and reinforce the activity of glutamate decarboxylase, thus increase the synthetic amount of the inhibitory neurotransmitter of GABA in the cerebral cortex (Ma et al., 1999). To date, however, a randomized, double-blind, placebo-controlled trial is still absent.

1. Methods

1.1. Trial design

This clinical study was designed as a multicenter, randomized, double-blind, placebo-controlled trial, and was conducted between June 2008 and February 2009 in China. The trial used the two-group parallel design where 212 cases of insomniac patients were randomized in a 1:1 ratio to receive a Wuling capsule or a placebo treatment for a total of 4 weeks. The efficacy and safety of Wuling capsule was assessed after 4 weeks treatment and at 2-weeks follow-up after drug withdrawal. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and China's regulations and guidelines on good clinical practice. Ethical clearance for the trial was obtained from the Ethics committee of the first affiliated hospital of Wenzhou medical college. All participating centers obtained approval of their local Ethical Review Board. Written informed consent was obtained from all subjects.

1.2. Participants

This study was performed in Chinese adults at six hospitals' centers. Subjects were considered eligible to be enrolled in the study only when all of the following inclusion criteria were met: (1) aged between 18–60 years old; (2) junior high school and higher educational level; (3) a diagnosis of insomnia according to the 10th revision of the international classification of diseases and related health problems diagnostic criteria (ICD-10) and the following one or more symptoms present: Difficulty initiating sleep, difficulty maintaining sleep, nonrestrictive sleep, waking up too early, nocturnal awakenings, uncomfortable after waking up, fatigue/malaise or daytime sleepiness, concerns or worries about sleep; (4) the symptom of insomnia that has been present for three or more times a week and persist for at least a month; (5) marked distress due to discontent about the quantity and quality of sleep, or social/vocational dysfunction; (6) one global score of the Pittsburgh sleep quality index (PSQI) ranged from 8 to 15; (7) All subjects must participate of their own free will and signed an informed consent form.

The following exclusion criteria were applied: (1) severe chronic insomnia: little or no sleep most nights associated with impairments of daytime work, for more than 6 months; (2) secondary insomnia: caused by or co-morbid with moderate anxious or depression (scores of the self-rating anxiety scale (SAS) ≥ 60 points or scores of the self-rating depression scale (SDS) ≥ 63 points), and other sleep disorders such as restless legs syndrome, sleep apnea syndrome; (3) major life events within 2 weeks such as death of a loved one, a family tragedy, emotional attack, unemployment, criminal trial, involved in disputes, family economic change, emigration; (4) alcohol or drug abuse: a history of substance abuse or dependence such as alcohol, opium, benzedrine within the past year; (5) patients who had been using antidepressants, anti-anxiety and hypnotic medications in latest 2 weeks; (6) laboratory tests showed the following results: (A), high blood pressure at or above 140 mmHg and/or 90 mmHg; (B), fasting blood glucose ≥ 7.0 mmol/L or random blood glucose ≥ 11.1 mmol/L; (C), elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 1.5 times the upper limit of normal;(D), an abnormal blood routine test or abnormal thyroid function or abnormal electrocardiogram (EKG) with requirements for clinical care; (7) any patients who had participated in another clinical trial within the latest one month; (8) allergic constitution; (9) pregnancy or breast-feeding women; (10) those who refuse to sign an informed consent form.

1.3. Interventions

The study period for all eligible patients was 6 weeks, during which time the patient underwent treatment period for 4 weeks and a follow-up period for 2 weeks. Patient visits were required as frequent as once a week. During the treatment period, eligible patients were randomly assigned to take either Wuling capsule (0.33 g per-capsule and 63 capsules in one bottle) or identical placebo capsule according to a randomization schedule. Placebo capsule was the same size, shape, color, and taste as Wuling capsule. Each bottle was labeled with randomization number, the number of capsules for each follow up period, instruction for use and storage requirement. Patients were instructed to take 3 capsules orally, 3 times daily. At each visit, patients returned the bottle for the previous week, and the study staff recorded the number of remaining capsules along with the dates of omitted doses. This trial is not to be combined with any of the following intervention, including other sleep medications and psychotherapy, antipsychotics and antidepressants, drugs acting upon the central nervous system, and any drugs (including herb medicine), or health care products, food and beverages that may cause insomnia or hypnotic effects. It was forbidden to take any beverages that contain alcohol during treatment period. It is acceptable if patients had already taken other drugs that did not affect the central nervous system before the trial. Yet, all combined administration should be recorded in case report form (CRF).

1.4. Outcomes

The primary efficacy variable was the score on the PSQI at baseline and after 4 weeks treatment. The PSQI included one global score and scores of seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

The secondary efficacy variables were the scores on the clinical global impressions scale (CGI-I) and world health organization on quality of life brief scale (WHOQOL-BREF). There were specific doctors to follow up and finished CGI-I evaluation on each weekend. Scoring the WHOQOL-BREF included four major domains: physical, psychological, social and environment by trained appraisers who were blinded to the treatment group at baseline and after 4 weeks treatment.

1.5. Safety assessments

Safety was assessed by physical examinations, vital signs and laboratory results including heart rate, blood pressure, body weight, blood routine test, liver function and kidney function, and EKG both at baseline time and at the end time of treatment, and by documentation of spontaneously reported or observed adverse events throughout the study. There are specific persons in charge of the inspection of safety information after 106 patients have been grouped. At the end of the 6th week of this study,

a follow up was done to gather the information of patients' sleep and record the adverse reactions.

1.6. Sample size

Calculation of sample size was based on previous reports that the total effective rate of Wuling capsule in treatment of insomnia was mostly 80∼90% (Ma et al., 2003; Li and Pan, 2006; Chen and Fan, 2007). We set level of testing as $\alpha=0.025$ (1-sided), power $(1-\beta)=0.90$, superiority test $\delta=15\%$, and the effective rate of Wuling capsule group was to take 85%. Based on the *Sample Size Estimation in Clinical Research* by Chow et al. (2003), the formula $N=2\,(u\alpha+u\beta)^2\cdot\,P\,(1-P)/\delta^2=2\times(1.645+1.282)^2\times0.85\,(1-0.85)/(0.15)^2\approx97$ (cases). Allowing a 10% increase in sample to account for variation in rates or 10% more for possible attrition, it was decided to enroll 106 cases per group.

1.7. Randomization

Randomization was performed stratified and blocked according to study center. Center is the factor as a stratification variable that 6 centers were divided into 6 stratifications. Each center was further divided into two groups by using blocked-randomization. Based on the result of estimates of sample size, subjects were randomly assigned by each center. An appointed person was responsible for the process of randomization by using the SAS procedure PROC PLAN to generate the random numbers. The random numbers for each research center were sealed in opaque envelopes. The researcher opened the envelope only to start the intervention. The results of randomized allocation were sent by distribution systems of responsible department to each research center. Each patient's random number and his/her drug number was the same, and this unique number lasted till the end of the trial. The process of randomization was managed by quality control in clinical medicine research process.

1.8. Blinding

Investigators, outcome assessors and patients remain blinded to group assignment during the entire intervention and data analysis. Result for group randomization was grade 1 blinded and corresponding group of drug was grade 2 blinded, which were preserved by appointed persons, respectively. The whole blinded process was on the record. After the trial has finished, the unblinding of the first stage was conducted to reveal A and B group for statistical analysis by SPSS software package. After statistical analysis, the unblinding of the second stage was carried out by revealing the final result of Wuling capsule group and placebo group.

1.9. Statistical methods

All data was processed by SPSS16.0. Qualitative data was described by percentage and component proportion ratio, while quantitative data by frequency, median number (interquartile range), average number ± standard deviation. *T*-test, rank-sum test, chi-square test and repeated measurement variance analysis were used. Statistical tests were completed blind, and were two tailed at the 5% level of significance.

2. Results

2.1. Participant flow

Based on enrollment criteria, 897 patients were prescreened and 485 patients excluded. Eligibility of the remaining 412 patients was further assessed and 200 patients excluded due to not meeting inclusion criteria, declined to participate, and/or other reasons. 212 patients signed informed consent, finished baseline evaluation and entered random process. During the trial, 11 out of the 212 patients have been excluded due to loss to follow-up, and 15 have discontinued intervention, with 10 cases in placebo group (dropout rate: 9.8%) and 5 cases in Wuling capsule group (dropout rate: 5.05%). Ultimately, statistical analyses were conducted on the results from 92 patients of placebo group to 94 patients of Wuling capsule group (Fig. 1).

2.2. Recruitment

Patients were recruited through doctors' recommendation, newspapers and posts in each medical center. After a short telephone interview, possible patients were invited for further assessments in outpatient department. After the patients have adequately understood the study and have signed informed consent, a fixed clinical interview including the current treatment, course of disease, the former history of insomnia, and family history of insomnia was carried out by a trained doctor, and then finished the PSQI evaluation. The baseline evaluation was recorded and assessed by responsible doctor in research group, including name, gender, age, marriage status, profession, education, income, workplace, home address, telephone number. The participant himself/herself completed the SAS and SDS. All of the patients should take lab tests, including blood routine, liver and kidney function, blood glucose, thyroid function, EKG, blood pressure, heart beat and body weight. The qualified subjects finished WHOQOL-BREF evaluation and were randomly divided into groups.

Patients could withdraw from the study at any time and for any reason. Study staff recorded the reasons for withdrawal or early discontinuation and made every effort to have the patients stick to the treatment plan. There is a special hotline telephone for patients' inquiry of problems that occur during the treatment period. If any of intolerable adverse events happened, we will decide whether he/she should withdraw from the trial.

The terminal criteria were as follows: (1) patients who do not obey the trial plan to take medicine or being followed up; (2) patients who take other medicine during the trial that will affect the trial results or cause adverse effects; (3) patients who terminate the treatment due to adverse effects.

2.3. Baseline data

Comparing Wuling capsule group with placebo group, the data of demographic baseline that include age, sex, marital status, education level and professional status showed no statistical significance ($P>0.05$). No statistically significant difference was found between the two groups in the characteristic of insomnia-specific baseline, including PSQI score, SAS score, SDS score, and the sleep duration, history of insomnia, family history of insomnia, and smoke and alcohol use,($P>0.05$), (Table 1).

2.4. Outcomes and estimation

Compared between pre-treatment and post-treatment, the global PSQI scores in both Wuling capsule group and placebo group improved significantly ($P<0.01$) (Table 2). However, no statistical significance showed the difference in the total score and scores of the 7 components of PSQI compared between Wuling capsule group and placebo group ($P>0.05$) (Table 3). Scores of CGI-I at each week in Wuling capsule group was similar to those in placebo group ($P>0.05$) (Table 4). Compared between pre-treatment and post-treatment, scores of the four components

Table 1
Baseline of demographic and clinical characteristics.

Variables		Wuling capsule group ($n=99$)	placebo group ($n=102$)	Statistics	P value
Age composition (years)	18–30	45	51	−0.89	0.64
	31–40	26	25		
	41–50	15	18		
	51–60	13	8		
Sex	Male	28	26	0.28	0.60
	Female	71	76		
Marital status	Married	35	38	0.03	0.86
	Single	64	64		
Education level	Junior high school	19	18	−0.04	0.97
	High school or college	17	18		
	Undergraduate college or university	47	52		
	Postgraduate	16	14		
Professional status	Worker	12	15	7.43	0.28
	Farmer	0	2		
	Administrative	11	6		
	Services	16	21		
	Intellectual	26	27		
	Freelance	6	2		
	Others	28	29		
PSQI		11.79 ± 2.08	11.63 ± 2.19	0.51	0.61
SAS		45.13 ± 7.99	44.06 ± 7.43	0.99	0.32
SDS		45.78 ± 9.39	45.58 ± 8.55	0.16	0.87
Sleep duration (months)	1–3	21	26	−0.92	0.38
	3–6	22	26		
	6–12	28	23		
	>12	28	27		
History of insomnia	Yes	27	25	0.27	0.60
	No	72	77		
Family history	Yes	25	31	0.53	0.47
	no	74	72		
Smoke	Yes	4	5	0.00	1.00
	No	95	97		
Alcohol use	Yes	10	7	0.75	0.39
	No	89	95		

Note: PSQI: Pittsburgh sleep quality index; SAS: self-rating anxiety scale; SDS: self-rating depression scale.
The rank-sum test for two independent samples was used for age, age composition and educational level. Chi-square test for gender, marriage and occupation. *Note*: T test for two independent samples for PSQI, SAS and SDS. The rank-sum test for two independent samples for course of insomnia. Chi-square test for insomnia history, family history and alcohol use. Corrected Chi-square test for smoking.

Table 2
Clinical evaluation of global PSQI score before and after treatment ($\bar{x} \pm s$).

Group	global PSQI score		t	P value
	Pre-treatment	Post-treatment		
Wuling capsule group ($n=94$)	11.78 ± 2.80	7.53 ± 3.11	11.00	0.00
Placebo group ($n=92$)	11.55 ± 2.10	7.60 ± 3.20	9.86	0.00

Note: PSQI: Pittsburgh sleep quality index.
T-test for two independent samples was used.

Table 3
Clinical evaluation of PSQI score between two groups.

Variable definition	difference score of PSQI		Statistics	P value
	Wuling capsule group ($n=94$)	placebo group ($n=92$)		
Subjective sleep quality	−1(−1, 0)	−1(−1, 0)	−0.55	0.59
Sleep latency	−2(−1, 0)	−1(−2, 0)	−1.37	0.17
Sleep duration	−1(−1, 0)	−0.5(−1, 0)	−0.27	0.79
Habitual sleep efficiency	0(−1, 0)	−0.5(−1, 0)	−0.99	0.32
Sleep disturbances	0(−1, 0)	0(0.25, 0)	−1.18	0.24
use of sleeping medication	0(0, 0)	0(0, 0)	−1.12	0.26
Daytime dysfunction	−1(−1, 0)	−1(−1, 0)	−0.24	0.81
Global PSQI score	4.24 ± 3.02	4.05 ± 3.54	−0.40	0.69

Note: PSQI: Pittsburgh sleep quality index.
T-test for two independent samples was used for PSQI total score. Rank sum test for two independent samples for the 7 component scores.

of WHOQOL-BREF, including physical, psychological, social and environment domains, in both Wuling capsule group and placebo group improved significantly ($P<0.01$). However, there were no difference compared between the two groups ($P>0.05$) (Tables 5,6).

2.5. Harms

The majority of adverse events were mild in severity and no death of subjects or other serious adverse events occurred during in this study. Of the 212 patients, treatment-emergent adverse events were reported by 17 patients in both groups, including headache, dizziness, limb numbness, dry mouth, constipation, abdominal distention, stomachache, diarrhea and sleepiness after drug administration at noon (Table 7). The rate of adverse events was 10.10% in Wuling group, and 6.73% in placebo group. There were no statistical significance between two groups by chi-square test of four-fold table, $\chi^2=0.751$, $P=0.386$. Compared between two groups or between pre-treatment and post-treatment, blood routine test, hepatonephric function, blood pressure, heart rate and body weight showed no statistical significance (Tables 8,9). 1 patient in Wuling group and 2 patients in placebo group

Table 4
Clinical evaluation of CGI score between two groups.

Group	Time	Significant progress	Progress	Little progress	No change	Slightly worse	Total	*Z* value	*P* value
Wuling capsule group ($n=94$)	1st week	4	15	42	37	1	99		
	2nd week	6	23	47	21	0	97		
	3rd week	5	31	47	14	0	97		
	4th week	9	40	27	18	0	94		
	6th week	7	34	31	21	1	94		
Placebo group ($n=92$)	1st week	5	15	44	39	2	102	−0.80	0.42
	2nd week	1	23	50	19	1	94	−0.29	0.77
	3rd week	6	29	41	16	1	93	−0.35	0.73
	4th week	10	43	25	14	0	92	−0.81	0.42
	6th week	8	38	27	20	1	92	−0.59	0.56

Note: CGI-I: Clinical global impressions scale.
Rank sum test for two independent samples was used.

Table 5
Clinical evaluation of WHOQOL-BREF score before and after treatment ($\bar{x} \pm s$).

	Domains	Pre-treatment	Post-treatment	*t*	*P* value
Wuling capsule group ($n=94$)	Physical	13.15 ± 2.15	14.38 ± 2.08	−3.98	0.00
	Psychological	13.35 ± 2.02	14.02 ± 2.01	−2.30	0.02
	Environment	13.07 ± 2.09	13.53 ± 1.78	−1.62	0.11
	Social relationships	13.45 ± 2.05	13.96 ± 1.87	−1.77	0.08
Placebo group ($n=92$)	Physical	13.07 ± 1.88	14.51 ± 1.85	−5.41	0.00
	Psychological	13.25 ± 1.81	14.12 ± 1.75	−3.24	0.00
	Environment	12.57 ± 1.90	13.27 ± 1.85	−2.41	0.02
	Social relationships	13.23 ± 2.02	13.90 ± 1.92	−1.91	0.06

Note: WHOQOL-BREF: world health organization on quality of life brief scale.
T-test for two independent samples was used for compare of the life quality before and after treatment.

Table 6
Clinical evaluation of WHOQOL-BREF score between two groups ($\bar{x} \pm s$).

Variable definition	Difference score of WHOQOL-BREF		*Z*	*P* value
	Wuling capsule group ($n=94$)	placebo group ($n=92$)		
Physical	−1.20(−2.30,0)	−1.20(−2.88,0)	−0.71	0.48
Psychological	−0.70(−1.40,0)	−0.70(−1.40,0)	−0.30	0.76
Environment	−0.50(−1.50, 0.50)	−0.50(−1.50, 0)	−0.59	0.55
Social relationships	0.00(−1.40,0)	0.00(−1.40,0)	−0.60	0.55

Note: WHOQOL-BREF: world health organization on quality of life brief scale.

Table 7
Adverse reactions.

Adverse events	Wuling capsule group ($n=94$)	Placebo group ($n=92$)
Dizziness	2	1
Numbness in hands and feet	1	0
Dry mouth	2	2
Constipation	1	1
Stomach Bloating	2	0
Stomach pain	1	1
Diarrhea	1	1
Drowsiness after medication at noon	0	1

showed abnormal ECG but no clinical magnificence after 4-weeks treatment period. Two weeks after drug withdrawal, patients showed no obvious insomnia rebound. Scores of CGI-I at 4th weeks during treatment period and follow-up 2 weeks after drug withdrew in Wuling capsule group showed no significant difference compared with those in placebo group ($P > 0.05$), (Table 4).

3. Discussion

To our knowledge to date, this is the first multicenter, randomized, double-blind, placebo-controlled trial of herbal medicine in the treatment of adult insomnia. A systematic review of CAM treatments for insomnia revealed evidence in support of the use of acupressure, tai chi and yoga, mixed evidence for the use of acupuncture and L-tryptophan, but weak evidence for the use of herbal medicines such as valerian and Kava (Sarris and Byrne, 2011). Unfortunately, our findings replicated the findings of Valerian, the most studied herbal medicine worldwide, on the week evidence for natural pharmacotherapies in the treatment of insomnia (Bent et al., 2006; Taibi et al., 2007; Fernández-San-Martín et al., 2010). In present study, Wuling capsule improved insomnia compared between pre-treatment and post-treatment, but its efficacy was equal to placebo. Why was this study negative whereas several smaller single-center RCTs showed a positive treatment effect in China (Yin et al., 2011)? The main reasons might be many methodological weaknesses in these study such as unsuitable or no randomization, blinding, placebo controlled, sample size, and analysis of data. Further rigorously designed and large sample study into efficacy of herbal medicine for insomnia is still required.

Mycelia of precious Xylaria nigripes (*Kl.*) *Sacc* have been traditionally and widely used by Chinese population for health care and is known with no or low toxicity. The present study showed that Wuling capsule is generally safe in insomina patients. Likewise, the others studies also did not usually mention the possible adverse effects of Wuling capsule (Han and Gao, 2007). Moreover, although benzodiazepines is a relatively safe class of medication, concerns exist over dependency (Lader, 2011), and currently most guidelines endorse only short-term use for insomnia (Sarris and Byrne, 2011). The present study supported the safety of Wuling capsule. Thus, Wuling capsule may be potentially used in adjuvant therapy for insomnia.

Table 8
Compare of routine blood test, liver and kidney function before and after treatment.

	Item	Pre-treatment	Post-treatment	Statistics	*P* value
Wuling capsule group ($n=92$*)	RBC	4.39 (4.17,4.73)	4.39 (4.17,4.84)	−0.59	0.55
	HB	135.20 ± 14.67	137.16 ± 18.16	−1.00	0.32
	WBC	5.9 (4.63,7.03)	6.16 (4.90,7.50)	−1.38	0.17
	PLT	224.00 ± 53.94	233.14 ± 58.80	−0.81	0.42
	ALT	16 (12, 20.25)	16 (12, 23)	−0.83	0.41
	AST	19 (17, 23)	20 (17, 23)	−0.90	0.37
	BUN	4.55 (3.80, 5.34)	4.64 (3.91, 5.36)	−0.31	0.76
	CR	68.40 ± 15.37	69.13 ± 16.64	−0.31	0.76
Placebo group ($n=90$*)	RBC	4.66 (4.18, 4.89)	4.49 (4.16, 4.80)	−0.48	0.64
	HB	135.26 ± 15.14	136.28 ± 18.94	−0.68	0.51
	WBC	6.0 (4.58, 6.6)	5.82 (4.74, 6.84)	−0.28	0.81
	PLT	228.00 ± 49.58	218.15 ± 60.30	−0.62	0.53
	ALT	16 (12, 22)	15 (11, 22)	−1.14	0.30
	AST	20 (16, 25)	20 (17, 23)	−0.80	0.49
	BUN	4.44 (3.80, 5.44)	4.40 (3.90, 5.28)	−0.30	0.78
	CR	66.40 ± 13.57	64.13 ± 14.12	−0.32	0.75

ALT:Alanine aminotransferase; AST:Aspartate aminotransferase; BUN: Blood urea nitrogen; Cr:Creatinine; HB: Hemoglobin; PLT: Blood platelet; RBC: Red blood cell; WBC: White blood cell.

* 4 patients did not conduct laboratory tests at the end of treatment.

Table 9
Compare of blood pressure, heart rate, body weight before and after treatment.

	Item	Pre-treatment	Post-treatment	Statistics	*P* value
Wuling capsule group ($n=92$*)	Body weight	53 (49, 62)	53 (49, 60)	−0.55	0.58
	Systolic blood pressure	110.27 ± 9.98	110.30 ± 9.22	−0.02	0.98
	Diastolic blood pressure	71.99 ± 8.49	72.81 ± 7.10	−0.76	0.45
	Heart rate	70.93 ± 8.82	70.63 ± 7.36	0.14	0.89
Placebo group ($n=92$)	Body weight	50.5 (44.25, 58)	55 (49, 60)	−1.11	0.27
	Systolic blood pressure	111.08 ± 11.15	110.42 ± 9.89	−0.10	0.92
	Diastolic blood pressure	72.56 ± 8.02	72.11 ± 7.28	−0.13	0.90
	Heart rate	70.58 ± 7.7	71.38 ± 8.25	−0.16	0.51

* 2 patients did not conduct physical examinations at the end of treatment.

Modern pharmacological studies indicate that Wuling Capsule has a role in regulating the functioning of nervous system, immune and endocrine system, and anti-anemia, and widely used in the psychiatric and mental illness, nervous system diseases, and digestive diseases (Wang et al., 2010). Mood, anxiety, and sleep disorders are prevalent and highly comorbid psychiatric conditions (Kessler et al., 2005). A randomized, positive parallel controlled trial indicated that Wuling capsule was effective in treating female climacteric patients with depression and anxiety state (Wang et al., 2009). Therefore, Wuling Capsule would be potentially used in "comorbid (No authors listed, 2005)" insomnia. Further studies using Wuling capsule adjuvant with conventional interventions are warranted.

Several potential limitations of the present study should be addressed. First, one limitation of this study was the absence of polysomnographic sleep parameters. Our study relied only on subjective sleep outcomes, which mainly are assessments of patient reports of improved sleep and well being. Future studies are needed to address these issues. Another limitation of this study is the lack of compliance monitoring. Although we instructed our subjects to avoid eating, drinking caffeine and alcohol, or exercising for 2 h before bedtime, there was no way to be certain of their compliance. Third, this study did not conduct a clinical trial registration, because at that time in 2006 we considered that this study was a non-commercial clinical trial under the supervision of the national fund. Moreover, full details of the trial protocol can be found in the documentation of the National Ministry of Science and Technology *Eleventh Five-Year* project of China. However, the registration of all interventional trials is a scientific, ethical and moral responsibility (De et al., 2004). We hope this limitation is minimal and improve in further study.

In conclusion, Wuling capsule can improve insomnia when compared with pre-treatment for 4 weeks. Moreover, adverse effect data indicate a well tolerated by all the patients at the 6 weeks of study period. However, the present findings were not found to be significant in the results of the variables tested when compared with placebo control. Further additional randomized clinical trials are still required with more experimentation into study design and duration.

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