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Original Article

Effect of Traditional East Asian Medicinal herbal tea (HT002) on insomnia: a randomized controlled pilot study

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ABSTRACT

Background: Complementary and alternative medicine treatment for insomnia has been sought due to the possible adverse effects of conventional pharmacotherapies. We performed a preliminary evaluation of the feasibility of using, and of the effect of a herbal tea (HT002), based on Traditional East Asian Medicine, in mild-to-moderate insomnia.
Methods: Patients ($n = 40$) with mild-to-moderate insomnia were randomized to the HT002 ($n = 20$) or waitlist ($n = 20$) groups. The HT002 group consumed HT002 twice daily for 4 weeks. Outcomes were assessed using the Insomnia Severity Scale (ISI), Pittsburgh Sleep Quality Index (PSQI), and 12-item Short Form Health Survey (SF-12) at baseline and after 4 and 8 weeks.
Results: The ISI score differences from baseline at weeks 4 and 8 were significantly greater in the HT002 than that in the waitlist group (week 4: -4.0 ± 0.8 vs. -0.4 ± 0.8, $p < 0.05$; week 8: -4.8 ± 0.7 vs. -0.9 ± 0.7, $p < 0.05$). Changes in PSQI and SF-12 physical component scores in the HT002 group were significantly greater at weeks 4 and 8 ($p < 0.05$), while SF-12 mental component scores were only significantly larger at 4 weeks ($p < 0.05$). HT002 was well-tolerated, with only one (5.0%) dropout, and no significant mean liver and renal function test changes post-treatment.
Conclusion: Our preliminary results suggest that a 4-week treatment with HT002 may reduce the severity of insomnia symptoms and improve the quality of life. Further studies devoid of the limitations of our protocol may provide stronger conclusions.
Trial registration: Clinical Research Information Service (CRIS), KCT0001900.

1. Introduction

Insomnia is a common complaint, with approximately 30% of the general population reporting symptoms such as difficulty falling asleep, difficulty maintaining sleep, poor quality of sleep, or waking up too early.[1] Insomnia is often associated with the development of various somatic and psychological disorders. Owing to its chronic nature, insomnia is also associated with significant impairments in an individual's quality of life and work productivity, as well as with an increased occurrence of work-related and vehicle accidents.[1–3] For these reasons, insomnia imposes a huge economic burden on society, not only because of the direct medical expenses, but also because of the socio-professional consequences.[4]

Conventional treatments for insomnia are usually either pharmacotherapies or psychological treatments. Commonly used medications for insomnia include non-benzodiazepine sedative–hypnotic drugs. Although these are often deemed to be safer than benzodiazepines given their shorter half-life and reduced disruption of normal sleep architecture, adverse effects, such as amnesia, psychomotor performance impairment, daytime fatigue, tolerance, and addiction, can still occur.[5] Psychological and behavioral therapies have been shown to be effective, but their use has been compromised because of the constraints of time, cost, and effort.[6] For these reasons, a few complementary and alternative medicine approaches have been sought for treating insomnia. According to a national survey in the United States in 2002, over 1.6 million adults reported having used complementary and alternative medicine to treat insomnia in the previous year, of

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which biological approaches, such as natural herbs, folk medicine, diet-based therapies, or nutritional medicine, were the most commonly used interventions.[7]

In this study, we aimed to evaluate the effectiveness of a herbal tea (HT002), which is composed of plants used in Traditional East Asian Medicine (TEAM), for mild-to-moderate insomnia,[8–10] and to evaluate the feasibility of a large sample study. The plants used in HT002 are as follows: *Ziziphus jujuba* var. *spinosa* (Bunge) Hu ex H. F. Chow (Ziziphi Semen, Sanjoin), *Rehmannia glutinosa* (Gaertn.) DC. (Rehmanniae Radix, Jihwang), *Z. jujuba* var. *inermis* (Bunge) Rehder (Zizyphi Fructus, Daejo), and *Gardenia jasminoides J. Ellis* (Gardeniae Fructus, Chija). These constituents were carefully selected on the basis of TEAM theory and from published basic research reports.[10–14] Animal studies have found that *Z. jujuba* var. *spinosa*, the herb most frequently used for insomnia, increased the GABA content in the hypothalamus, modulated stress-induced sleep changes, and improved total sleep time as well as slow wave sleep.[10,11] *R. glutinosa* has been reported to possess a significant sedative effect, by acting on the ascending reticular activating system of the brainstem and pallia.[12] *Z. jujuba* var. *inermis* is known to have sedative effects in animals,[13] and *G. jasminoides* has been reported to have an anxiolytic effect.[14]

2. Methods

2.1. Setting and participants

This was a parallel group, randomized, controlled pilot trial, performed at the Kyung Hee University Korean Medicine Hospital in Seoul, Korea, between February 2016 and May 2016. The study was approved by the Kyung Hee University Korean Medicine Hospital (KOMCIRB-151019-HRBR-044), and informed consent was obtained from all participants prior to the study. The study protocol was registered at the Clinical Research Information Service (http://cris.nih.go.kr) (registration number: KCT0001900) and conformed to the tenets of the Declaration of Helsinki.

Participants were recruited through newspaper advertisements and signs posted at the hospital. Individuals were included if they were between the ages of 30 and 49 years, experienced sleep problems for at least 3 days a week (such as taking at least 30 min to fall asleep or to return to sleep after waking up at night, or having difficulty staying asleep), and had mild-to-moderate insomnia as indicated by a score of 8–21 on the Insomnia Severity Index (ISI).

Individuals were excluded if they had any of the following: received medical treatment for insomnia during the last month; received medical treatment for any neuropsychiatric disorder (e.g., depression, anxiety or dementia) during the last month; had been diagnosed with secondary insomnia (e.g., sleep apnea syndrome, hypnolepsy, or restless leg syndrome); had experienced alcohol abuse or dependence during the last 6 months; worked overnight, night shifts, or had a severe workload; or were pregnant, breastfeeding, or planning a pregnancy in the next 6 months. Those, who were taking medication that might affect the study, or who were not able to follow the instructions properly, were also excluded.

2.2. Randomization

Randomization was performed by a statistician using a computer-generated randomization list prior to participant enrolment, with a group assignment ratio of 1:1, and a block size of four. Information on the group allocation for each participant was enclosed in sealed opaque envelopes with consecutive numbers to conceal the group allocation from the research nurse. After participants had satisfied all inclusion criteria and completed the baseline assessment, the envelopes were opened in consecutive order by the research nurse, and participants were allocated to either the HT002 (intervention) group or the waitlist control group.

2.3. Intervention

The herbal tea, HT002, was specifically manufactured by Tea Therapy, Ltd. for the present study. The herbs used were as follows: *R. glutinosa* (Gaertn.) DC, radix (900 mg); *Z. jujuba* var. *inermis* (Bunge) Rehder, fructus (900 mg); *G. jasminoides* J. Ellis, fructus (600 mg); and *Z. jujuba* var. *spinosa* (Bunge) Hu ex H. F. Chow, semen (600 mg). The components were cleaned, dried, roasted at 150 °C, divided into 3-g portions, parceled into 1–2 mm-diameter constituents, and sealed in a teabag.

For the HT002 group, participants were provided with standard tumblers (equivalent to 250 mL) and were instructed to infuse the teabag in hot water in the tumbler for more than 3 minutes, and then to drink the tea without removing the teabags. They were instructed to drink the tea twice a day: once in the morning (before noon) and once in the afternoon (between noon and bedtime), for 4 weeks. Participants in the waitlist group received no intervention during the 8-week study period. Upon completion of the study, however, they were offered the HT002 with the same instructions.

2.4. Outcomes

Patient outcomes were recorded at baseline, after the end of the 4-week treatment, and at the 4-week post-intervention follow-up (a total study period of 8 weeks). The primary outcome of this study was the ISI score.[15] The ISI includes seven items, rated on a 0–4 point scale, which investigate the severity of sleep onset problems, sleep maintenance difficulties, early morning awakenings, satisfaction with the current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and the level of distress caused by the sleep problem. The possible ISI score ranges from 0 to 28, with higher scores indicating more severe insomnia. The score was interpreted as follows: 0–7, absence of insomnia; 8–14, mild insomnia; 15–21, moderate insomnia; 22–28, severe insomnia. The ISI has been reported to be reliable, valid, and sensitive to changes in clinical trials of insomnia.[15,16]

Secondary outcomes included the Pittsburgh Sleep Quality Index (PSQI) score and the 12-item Short Form Health Survey (SF-12). The PSQI measures sleep quality and disturbances during the previous month and comprises 19 items that assess a broad range of domains related to sleep quality, which constitute seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). Each component score has a range of 0–3, with higher scores indicating more severe sleep complaints. The sum of the seven components yields a global score ranging from 0 to 21. The PSQI has been reported to be reliable and valid for evaluating sleep quality in clinical practice and research.[17,18]

The SF-12, which is a summarized version of the 36-item Short Form Health Survey (SF-36), was used to assess quality of life. The SF-12 is a generic health-related quality of life measure that assesses overall mental and physical functioning. It is composed of 12 questions, rated on a 5-point Likert scale, and eight scales that are used to construct the physical component summary (PCS; physical functioning, physical role, bodily pain, and general health) and the mental component summary (MCS; emotional role, vitality, social functioning, and mental health). Higher scores indicate a greater quality of life. Scores of the SF-12 have been reported to be reliable and have a high degree of correspondence with those of the SF-36.[19–21]

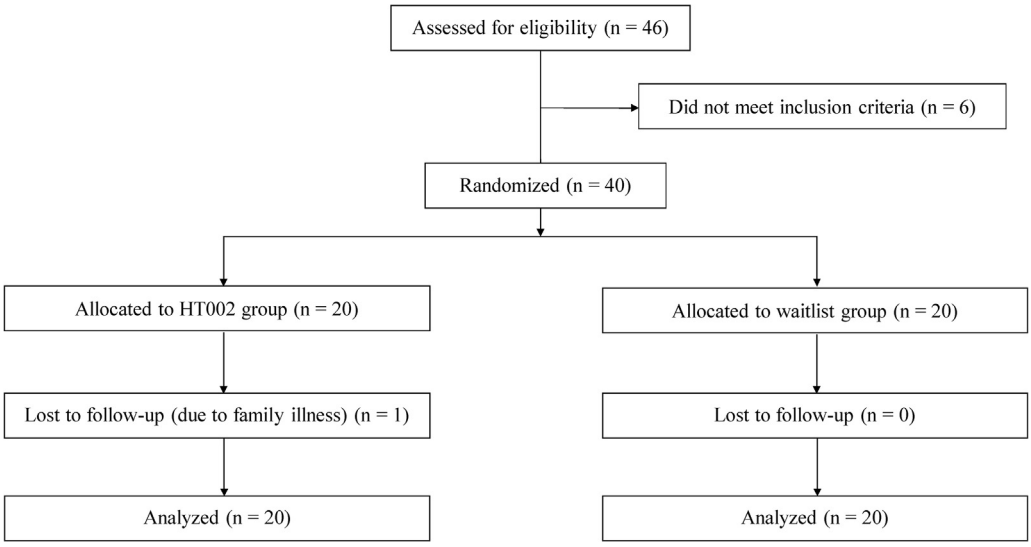

Fig. 1. Flow chart of the study participants.

Compliance with the HT002 regime was assessed based on returned tea bag counts after the treatment, whereby participants were considered compliant if they had consumed at least 70% of the HT002. Data on any adverse events were collected at each visit. Laboratory tests on liver and renal function were conducted at baseline and after the 4-week treatment; these included levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBR), blood urea nitrogen (BUN), and creatinine.

2.5. Statistical analysis

This study was designed as a pilot study to determine the appropriate sample size for future randomized clinical trials. Therefore, a minimum of 20 participants were assigned to each group, considering a 20% dropout rate, based on a previous study.[22]

Data for baseline characteristics of study participants are presented as the mean and standard deviation for continuous variables and as the frequency for categorical variables. Baseline characteristics between two groups were compared using Student *t*-test and the Mann–Whitney *U* test for normally and non-normally distributed data, respectively. Significant changes in primary and secondary effectiveness outcomes after 4 and 8 weeks were analyzed using analysis of covariance (ANCOVA) with the change in scores from the baseline set as the dependent variables, the baseline scores as the covariates, and the group as a fixed effect. If the data were not normally distributed, the analysis was conducted using a rank ANCOVA. The effectiveness outcome variables were analyzed on an intention-to-treat basis. Missing values were imputed by the last observation carried forward method. For the evaluation of HT002 safety, changes in liver and renal function were analyzed using a paired *t*-test, and all variables were investigated to determine whether any values were elevated by more than 1.5 times the upper limit of the reference range. A *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

Fifty-six individuals were assessed for eligibility. Of these, 40 participants met the inclusion criteria and were thus randomly allocated to the HT002 group or waitlist group. One participant in the HT002 group was lost to follow-up due to family illness, and hence 39 participants completed the study (Fig. 1).

Baseline characteristics of the participants are presented in Table 1. The mean age of participants was 37.5 ± 5.4 years, and 57.5% were female. The sociodemographic characteristics between the two groups were well-balanced ($p > 0.05$). The duration and severity of insomnia and the level of quality of life also did not differ significantly between groups at baseline ($p > 0.05$). The compliance rate of all participants in the HT002 group who completed the study ($n = 39$) was higher than 70% (mean: 88.1%; range: 75.9–100%); thus, they were all considered compliant.

Table 1
Baseline Characteristics of Study Participants

	HT002 ($n = 20$)	Waitlist ($n = 20$)	*p* value
Sex: female	9 (45.0)	14 (70.0)	0.110
Age (years)	37.7 ± 4.8	37.3 ± 6.0	0.602
BMI (kg/m^2)	23.9 ± 3.4	22.6 ± 3.0	0.242
Education			0.749
High school or university	11 (55.0)	12 (60.0)	
≥Graduate school	9 (45.0)	8 (40.0)	
Marital status			0.110
Married	14 (70.0)	9 (45.0)	
Not married	6 (30.0)	11 (55.0)	
Duration of insomnia (months)	34.9 ± 35.4	34.0 ± 23.6	0.602
ISI	13.0 ± 3.8	11.9 ± 2.4	0.369
PSQI			
Global score	8.5 ± 1.8	8.8 ± 2.1	0.461
Subjective sleep quality	1.9 ± 0.4	1.9 ± 0.4	0.820
Sleep latency	2.5 ± 0.6	2.4 ± 0.7	0.904
Sleep duration	1.2 ± 0.8	1.2 ± 0.9	1.000
Habitual sleep efficiency	0.3 ± 0.4	0.6 ± 0.8	0.157
Sleep disturbances	1.3 ± 0.6	1.1 ± 0.2	0.583
Use of sleeping medication	0.1 ± 0.2	0.1 ± 0.2	1.000
Daytime dysfunction	1.4 ± 0.9	1.6 ± 0.9	0.565
SF12			
PCS	49.5 ± 8.0	49.9 ± 7.0	0.862
MCS	43.7 ± 11.4	49.5 ± 5.7	0.051[a]

BMI, body mass index; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; SF-12, 12-item Short Form Health Survey; PCS, Physical Component Score; MCS, Mental Component Score.
Values are presented as *n* (%) for sex, education, and marital status, and as mean ± SD for the other factors.
[a] Student *t*-test, all other *p* values for continuous variables are based on Mann–Whitney *U* test.

Table 2
The Change of Outcome Measures at Each Visit

		HT002 ($n=20$)	Waitlist ($n=20$)	p value
ISI	Week 4	−4.0 ± 0.8	−0.4 ± 0.8	0.018*
	Week 8	−4.8 ± 0.7	−0.9 ± 0.7	0.001**
PSQI				
Global score	Week 4	−2.6 ± 0.4	0.3 ± 0.4	<0.001**,a
	Week 8	−2.6 ± 0.5	0.3 ± 0.5	0.001**,a
Subjective sleep quality	Week 4	−0.5 ± 0.1	0.0 ± 0.1	0.006**
	Week 8	−0.6 ± 0.1	−0.1 ± 0.1	0.005**
Sleep latency	Week 4	−1.0 ± 0.1	−0.3 ± 0.1	0.001**
	Week 8	−1.1 ± 0.1	−0.2 ± 0.1	<0.001**
Sleep duration	Week 4	−0.5 ± 0.2	0.4 ± 0.2	0.004**
	Week 8	−0.3 ± 0.2	0.5 ± 0.2	0.009**
Habitual sleep efficiency	Week 4	−0.3 ± 0.1	0.0 ± 0.1	0.154
	Week 8	−0.1 ± 0.2	0.3 ± 0.2	0.251
Sleep disturbances	Week 4	−0.1 ± 0.1	0.1 ± 0.1	0.134
	Week 8	−0.1 ± 0.0	−0.1 ± 0.0	0.351
Use of sleeping medication	Week 4	−0.1 ± 0.0	−0.1 ± 0.0	b
	Week 8	−0.1 ± 0.0	0.0 ± 0.0	0.165
Daytime dysfunction	Week 4	−0.2 ± 0.1	0.3 ± 0.1	0.043*
	Week 8	−0.3 ± 0.2	−0.1 ± 0.2	0.203
SF-12				
PCS	Week 4	2.2 ± 0.9	−2.5 ± 0.9	0.004**
	Week 8	3.6 ± 1.0	−3.0 ± 1.0	<0.001**,a
MCS	Week 4	3.6 ± 2.1	−3.5 ± 2.1	0.024*,a
	Week 8	−0.5 ± 1.6	0.1 ± 1.6	0.793a

ISI, Insomnia Severity Index; MCS, Mental Component Score; PCS, Physical Component Score; PSQI, Pittsburgh Sleep Quality Index; SF-12, 12-item Short Form Health Survey. Values are expressed as Mean ± Standard Error (SE).

* $p<0.05$.

** $p<0.01$.

[a] ANCOVA, all other p values for continuous variables are based on a rank ANCOVA.

[b] Could not be calculated due to lack of variability in the data.

3.2. Primary endpoint

After the 4-week treatment, the mean change in the ISI score was greater in the HT002 group than that in the waitlist group, and the difference between groups was statistically significant (−4.0 ± 0.8 vs. −0.4 ± 0.8, $p=0.018$). The changes in ISI remained similar at the 8-week follow-up, and the difference between the groups also remained statistically significant (−4.8 ± 0.7 vs. −0.9 ± 0.7, $p=0.001$) (Table 2).

3.3. Secondary endpoints

The change in mean PSQI global score was significantly different between the groups at week 4 (−2.6 ± 0.4 vs. 0.3 ± 0.4, $p<0.001$) and week 8 (−2.6 ± 0.5 vs. 0.3 ± 0.5, $p=0.001$). Among the component scores of the PSQI, subjective sleep quality, sleep latency, sleep duration, and daytime dysfunction exhibited a significantly larger reduction in the HT002 group than in the waitlist group ($p<0.05$, all).

The changes in mean SF-12 PCS and MCS were significantly different between the groups at week 4 (PCS: 2.2 ± 0.9 vs. −2.5 ± 0.9, $p=0.004$; MCS: 3.6 ± 2.1 vs. −3.5 ± 2.1, $p=0.024$). PCS changes at week 8 were significantly different between groups, while MCS changes at week 8 were not (PCS: 3.6 ± 1.0 vs. −3.0 ± 1.0, $p<0.001$; MCS: −0.5 ± 1.6 vs. 0.1 ± 1.6, $p=0.793$) (Table 2).

3.4. Safety

No adverse events were reported. In the HT002 group, there were no significant changes in the levels of liver and renal function after treatment as compared to baseline, and no participant experienced elevation of values to more than 1.5 times the upper limit of the reference range.

4. Discussion

This preliminary randomized clinical trial evaluated the feasibility and the preliminary effects of HT002 in patients with mild-to-moderate insomnia. This result suggests that HT002 is generally well tolerated, with only one (5%) dropout, and with no significant changes in the liver and renal function test results. The change in the ISI score after 4 weeks of treatment and at the 8-week follow-up compared to baseline was significantly greater in the HT002 group than that in the waitlist group. Similar improvements were also shown in terms of PSQI scores and SF-12 PCS. The findings were consistent with those of the studies evaluating herbal formulae that contain *Z. jujuba* var. *spinose* (FSZR) for insomnia, which reported that FSZR as a monotherapy was superior to placebo, and that its use as an adjunct therapy was superior to use of diazepam alone.[11]

In the HT002 group, the mean ISI scores at week 4 and week 8 were reduced by approximately 4–5 points as compared to baseline. This change was significantly greater than that of the waitlist group; however, this figure is slightly smaller than the recommended reduction of 6 points for representing a clinically meaningful improvement in individuals with primary insomnia.[23] The smaller change might be ascribed to the exclusion of severe insomnia patients, whose ISI score was higher than 21; we only included patients whose ISI score was between 8 and 21 (mild-to-moderate insomnia). We opted for this distinction to make the group more homogeneous, but this leaves less room for improvement than would a study involving participants with severe insomnia. However, the use of HT002 demonstrated a statistically significant reduction in terms of ISI, and the effects of HT002 persisted for 4 weeks after the end of the treatment (week 8). In addition, the PSQI score showed similar changes at both weeks 4 and 8, including the global score and the four component scores, involving subjective sleep quality, sleep latency, sleep duration, and daytime dysfunction.

Insomnia has been reported to be associated with low scores in both physical and mental health-related quality of life, and treatment for insomnia might improve several aspects of quality of life.[24–26] We found improvements in quality of life in the HT002 group after the treatment. Compared to baseline, the PCS and MCS of the SF-12 both showed greater increases in the HT002 group at week 4. At week 8, the PCS score of the HT002 group still showed significantly greater increases than the waitlist group as compared to baseline. In the four PCS subscales, the changes of scores regarding physical functioning and physical role were significantly greater in the HT002 group than in those of the waitlist group, at both week 4 and week 8, while the changes of scores regarding bodily pain and general health were not significantly different between groups (data not shown). These results indicate that HT002 treatment positively affected physical functioning in patients with insomnia, whereas popular sleep medications, such as benzodiazepine and non-benzodiazepine hypnotics, are known to have adverse effects on physical functioning and have been associated with myorelaxant effects and next-day hangover effects.[3,25]

Although decoction (a preparation involving boiling herbs with water or other solvents) has long been the favored prescription-type for herbal medicine in TEAM, tea bags, such as those used for the HT002, are lighter and more portable than decoction pouches. In addition, in patients with relatively mild insomnia, a familiar modality, such as tea, may be preferred over medication, such as pills or decoction pouches. Given that the rate of reporting insomnia symptoms to physicians is low, and given that few of those individuals with insomnia who do consult a physician are prescribed any medication,[27] an effective herbal tea may be a possible acceptable alternative treatment for patients with insomnia.

This study has several limitations that should be noted. Firstly, participants knew which group they belonged to. Unlike a placebo-controlled study using double-blinding, this may have led to an overestimation of HT002 effectiveness; because we used self-rated outcomes, the existence of a reporting bias cannot be excluded. This limitation is inherent to studies, in which an appropriate placebo is difficult to make, such as studies that evaluate exercise, psychological and behavioral treatment, or acupuncture; given that the tea used in this study had a unique color and flavor, it was not possible to make an appropriate placebo for the control group. Future studies evaluating the clinical value of HT002 may overcome this limitation to some extent by comparing it with other widely used modalities, and by using objective outcome measures, such as polysomnography or actigraphy. Secondly, we did not use the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Sleep Disorders (ICSD) as the inclusion criteria for insomnia. Although the inclusion criteria of our study, including the content of the ISI, corresponds in part to the diagnostic criteria of the DSM and ICSD, the latest versions of diagnostic criteria (i.e., DSM-V and ICSD-3) require that the duration of sleep difficulty should be at least 3 months. We did not specify the duration of sleep difficulty as an inclusion criterion. Although all the participants in our study reported a duration of 3 or more months (range: 3–150, mean 34.4, SD 29.7), the duration should be clearly specified as inclusion criteria in future research. Thirdly, work productivity is one of the important dimensions that might be influenced by insomnia. A future study with a longer follow-up should include evaluation of the effect of treatment on work productivity, such as absenteeism and self-report work efficiency, especially for studies focusing on working participants. Lastly, HT002 is obtained from four plant sources. There may be other active components related to the pharmacological efficacy of HT002 in insomnia. Thus, identification of the active compound in the HT002 and further pharmacokinetic evaluation of HT002 are necessary.

In conclusion, the preliminary results of the current protocol suggest that 4-week treatment with HT002 may reduce the severity of insomnia symptoms and improve the quality of life. However, further studies devoid of the limitations of our protocol may provide stronger conclusions.

Conflicts of interest

The authors declare that they have no competing interests.

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