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Effects of *Passiflora incarnata* Linnaeus on polysomnographic sleep parameters in subjects with insomnia disorder: a double-blind randomized placebo-controlled study

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The purpose of the present double-blind randomized placebo-controlled clinical study was to investigate the effects of Passionflower on polysomnographic sleep parameters in subjects with insomnia disorder. A total number 110 adult participants (mean age = 40.47 ± 11.68, Female = 53.6%) met the inclusion criteria of insomnia disorder according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders). After randomization, patients received either the Passionflower extract or the placebo for 2 weeks. Patients underwent an overnight polysomnography and completed sleep diaries, Insomnia Severity Index, and Pittsburgh Sleep Quality Index. Within group comparisons were analyzed with paired *t*-tests or Wilcoxon's signed rank tests, and between-group comparisons were analyzed with independent t-tests or Mann–Whitney U Tests, as appropriate. Total sleep time (TST) was significantly increased in the Passionflower group compared with placebo (Passionflower vs placebo, 23.05 ± 54.26 vs –0.16 ± 53.12; *P* = 0.049). Sleep efficiency and wake after sleep onset (WASO) significantly improved after 2 weeks in the Passionflower group but there was no difference compared with the placebo group. The current study demonstrated the positive effects of Passionflower on objective sleep parameters including TST on polysomnography in adults with insomnia disorder. Further study is needed to investigate the clinical efficacy of Passionflower on insomnia. *Int Clin Psychopharmacol* 35: 29–35

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Keywords: herbal medicine, insomnia, *Passiflora incarnata*, Passionflower, polysomnography, sleep

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Introduction

Insomnia is a major health complaint prevalent in the general population and in clinical practice (Ancoli-Israel, 2006). Prevalence of insomnia as a disease entity is estimated to be between 10 and 20%, and the prevalence of insomnia as a symptom has been reported to be as high as 40% in the general population (Ancoli-Israel, 2006). Insomnia is a major health problem because it can deteriorate one's health and well-being by inducing reduced quality of life, impaired daytime functioning, and higher healthcare costs (Cunnington *et al*., 2013). Also, insomnia has been reported to increase risk of many diseases, including diabetes, cardiovascular disease, as well as many psychiatric disorders (Knutson and Van Cauter, 2008; Sofi *et al*., 2014).

The most common and effective treatment of insomnia is pharmacological therapies with hypnotics. Substances regarded as appropriate hypnotics are those which prevent continuous awakenings, shorten the period of latency for sleep initiation and increase sleep duration (Guerrero and Medina, 2017). Drugs that are most commonly used as hypnotics are benzodiazepines. These drugs increase the binding of gamma-aminobutyric acid (GABA) to $GABA_A$ receptors and enhance inhibitory signals to cell groups that promote arousal (Gottesmann, 2002). Benzodiazepines may be very effective in inducing sleep, but they often accompany adverse effects such as daytime sedation and risk of tolerance and dependence (Ashton, 2005). As a result, demands for a relatively more tolerable and safer remedy are high.

In recent years, research on herbal medicine in psychiatry has significantly advanced (García-García *et al*., 2008). There are several medicinal plants known for their sedative properties, mostly in preclinical in-vitro and in-vivo studies. Kava-kava, Valerian, aromatherapy (lavender, chamomile, and Ylang-Ylang), Melissa, and Passionflower are some herbal drugs that have been suggested as hypnotics (Wheatley, 2005).

Passiflora incaranata Linnaeus, commonly known as Passionflower, has a long history of use as traditional

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herbal medicine. Previous clinical studies have demonstrated potential effects of Passionflower on anxiety, insomnia, attention-deficit hyperactivity disorder, opiate withdrawal symptoms, and menopausal symptoms (Miroddi *et al*., 2013). While Passionflower has been used for various pharmacological purposes, the current most common use in clinical practice is in the treatment of insomnia and anxiety (Dhawan *et al*., 2004).

The passionflower extracts were found to contain GABA (Carratù *et al*., 2008). The sedative effects of Passionflower extract may result from the synergistic action of GABA, leading to the modulation of $GABA_A$ receptors (Miroddi *et al*., 2013). The sedative action of Passionflower has been demonstrated in preclinical studies. Passionflower extracts were shown to significantly lengthen the subhypnotic pentobarbital-induced sleep (Soulimani *et al*., 1997). Also, Guerrero and Medina (2017) administrated Passionflower extracts on six rats and polysomnographic recordings were taken after the administration. The results demonstrated a significant increase in the total sleep time (TST), and a decrease in wakefulness. However, scientifically validated evidence on the sedative effects of passionflower on human subjects is limited.

The present study investigated the effects of *Passiflora incarnata* on objective polysomnographic sleep parameters in subjects with insomnia disorder. Effects on subjective sleep parameters as well as self-reports on depression, anxiety, and stress were also explored. Additionally, the safety and tolerability of *Passiflora incarnata* were evaluated.

Materials and methods

Study design

The present study was designed as a prospective, double-blind, randomized, placebo-controlled study which was conducted to assess the efficacy and safety of passionflower extracts in adults with insomnia. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practice guidelines. The study was approved by the institutional review board of Soonchunhyang University Bucheon Hospital (SCHBC 2017-07-029-022).

Participants

Adults aged 18–59 years who met the diagnostic criteria of insomnia disorder according to the Diagnostic and Statistical Manual 5 criteria were recruited for this study through advertisements and clinical referrals (Association, 2013). Exclusion criteria included major psychiatric disorders (schizophrenia, major depressive disorder, bipolar disorder, and substance use disorder), developmental disorders (intellectual disability and autism spectrum disorder), neurocognitive disorders (delirium and dementia), neurologic disorders (epilepsy and cerebrovascular disease), any ongoing severe medical condition, history of suicidal attempt, severe obstructive sleep apnea, consumption of any kind of sleep medications during the past month, BMI >30 kg/m^2, severe snoring, and currently a shift-worker. Written informed consent was obtained from each subject prior to participation

Randomization

After an initial screening visit, subjects meeting inclusion and exclusion criteria were randomized 1:1 to either the passionflower group or the placebo group. A computer-generated random sequence was used to allocate the participants either to the passionflower or the placebo group. Investigators and the participants were blind to the allocated intervention. The random sequence was kept by the outside provider not involved in the study. Blinding was maintained until data analysis was completed.

Intervention

The passionflower group received a capsule containing 60 mg of passionflower extracts. The passionflower extracts contained 80% leaves and 20% fruits. Passionflower leaves and fruits were air-dried, ground and mixed with 60% ethyl alcohol. Then, they were heated to 80°C for 2 hours and were filtered. Finally, Passionflower leaves and fruits extracts were concentrated and spray-dried after the addition of dextrin. The dosage of passionflower extracts was relatively low, compared to commercially available products which mostly contain 250–900 mg of passionflower. Vitexins present in passionflower extracts were analyzed and quantitated using HPLC-UV.

The placebo group received a matching placebo capsule indistinguishable from the study treatment, mainly composed of soybean oil. The placebo and the passionflower capsule were identical in size, shape, color, and smell. The participants were to consume either the study treatment or the placebo every night for 2 weeks. No sleep medications were allowed during the study. Compliance was assessed by counting the leftover pills the participants returned to the investigators at the end of the study. Participants who consumed lower than 80% of assigned pills were considered noncompliant and were withdrawn from the study.

Outcome measures

Overnight polysomnography and self-report questionnaires were used to assess the objective and subjective sleep parameters at baseline and after 2 weeks. Polysomnographic sleep parameters included total sleep duration (TST), sleep efficiency, sleep latency, total arousal, and wake after sleep onset (WASO). Subjective sleep parameters including TST, sleep latency, total arousal, and WASO were obtained by the self-reported

sleep diaries. Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI) were also completed by the participants. Level of depression, anxiety, and stress were examined by Center for Epidemiologic Studies Depression Scale (CES-D), Beck Anxiety Inventory (BAI), and Global Assessment of Recent Stress Scale (GARS), respectively.

Safety and tolerability

All subjects underwent a physical examination, urinalysis, blood chemistry, and hematology at baseline and after 2 weeks. Adverse events were explored in all the participants who received the allocated treatment.

Statistical analysis

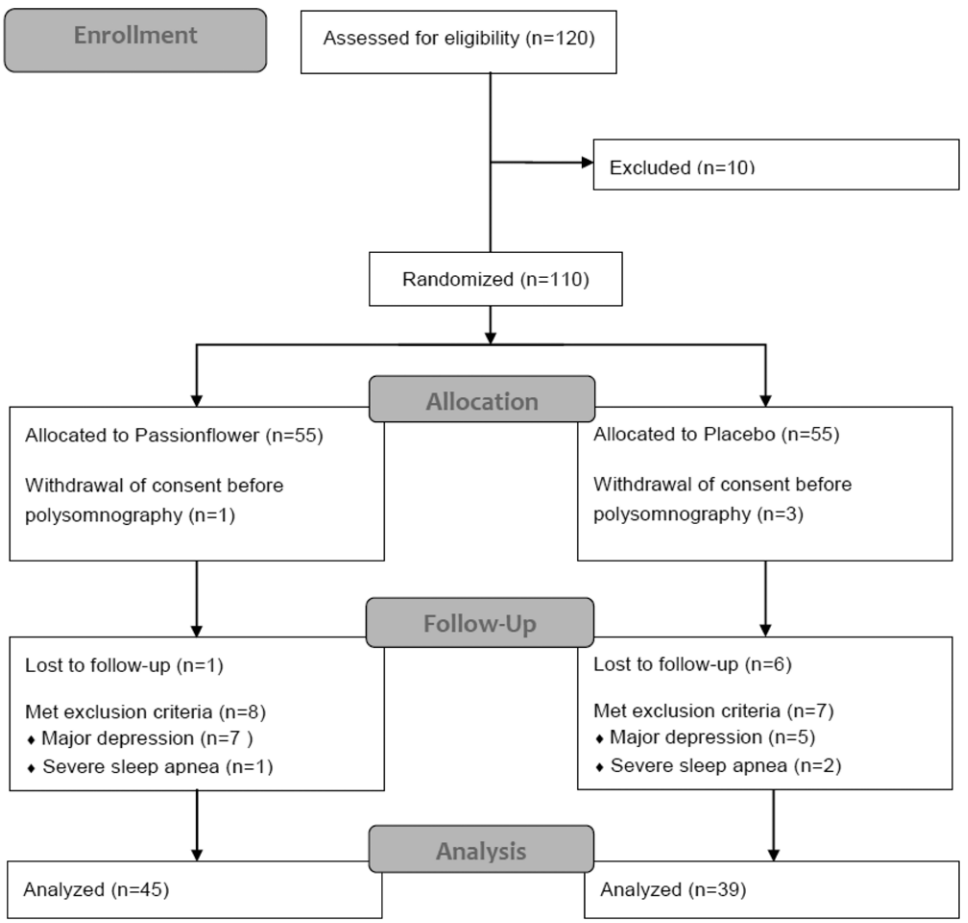
A sample size of 49 participants per group was required to achieve a statistical power of 80% at a level of 0.05. Considering a 10% drop-out rate, a sample size of 55 subjects in each group was calculated. Per-protocol analyses, excluding the subjects with major protocol deviation, were performed to examine the efficacy of the passionflower compared with the placebo.

Group differences on the demographic variables and baseline clinical data were analyzed using Pearson's Chi-squared tests, independent *t*-tests, or Mann–Whitney U tests, as appropriate. Within-group comparisons before and after treatment were performed using the paired *t*-tests or the Wilcoxon's signed rank tests, as appropriate. Between-group data were analyzed using the independent *t*-tests or Mann–Whitney U Tests, as appropriate. A two-tailed $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using the SPSS 20.0 (SPSS INC., Chicago, Illinois, USA).

Results

A total of 110 participants who met the eligibility criteria were enrolled in the study from November 2017 to December 2018. The diagram of the study flow is shown in Fig. 1. A total of 84 participants (45 in the passionflower group and 39 in the placebo group) completed the study without major protocol deviation: four prematurely withdrew, seven were lost to follow-up, and 15 were found to meet the exclusion criteria (12 had major depressive disorder and three had severe sleep apnea) during the study.

Fig. 1



Flow diagram of the study.

Demographic and baseline characteristics

Demographic characteristics and baseline measurements of clinical data of the passionflower group and the placebo group are summarized in Table 1. There was no significant difference between the two groups.

Polysomnography

The results of the polysomnography are shown in Table 2. The TST, which was the primary outcome measure, was significantly improved in the passionflower group compared with the placebo group ($P=0.049$). Compared with baseline scores, sleep efficiency and WASO were significantly improved in the Passionflower group ($P=0.008$, $P=0.025$). However, there was no significant difference compared with the placebo group. Sleep efficiency showed a trend of improvement in the passionflower group compared with the placebo group ($P=0.074$). Sleep efficiency is calculated by TST divided by total time in bed. All the subjects had the same amount of total time in bed during polysomnography, so increase in TST would result in increase in sleep efficiency, just in a smaller ratio.

Table 1 Demographic and baseline clinical characteristics of the participants (*N*=84)

Variables	Total (*N*=84)	Passionflower (*N*=45)	Placebo (*N*=39)	*P* value
Age, (year)	41.01±11.01	40.51±10.19	41.59±11.99	0.581
Female, (%)	50 (59.52%)	27 (60.00%)	23 (58.97%)	0.924
Education, (year)	15.27±2.14	15.37±2.50	15.15±1.64	0.579
Height (cm)	166.09±9.32	166.36±8.85	165.79±9.94	0.782
Weight (kg)	65.20±11.44	65.43±11.25	64.92±11.80	0.839
BMI (kg/cm^2)	23.46±2.60	23.58±2.68	23.32±2.54	0.641
Polysomnography				
TST (min)	403.05±57.99	395.28±58.84	412.01±56.40	0.092
Sleep efficiency (%)	84.24±12.31	82.88±12.73	85.82±11.76	0.209
Sleep Latency (min)	15.57±22.07	17.30±26.26	13.57±16.03	0.753
WASO, min	60.09±51.00	64.93±48.95	54.50±53.35	0.353
Total Arousal, No	108.68±50.40	105.8±44.99	112.0±56.42	0.577
Self-report scales				
ISI	13.74 ± 3.96	13.24 ± 3.65	14.31 ± 4.26	0.222
PSQI	8.40 ± 1.51	8.27 ± 1.60	8.56 ± 1.39	0.286
CES-D	9.52 ± 5.72	9.82 ± 5.80	9.18 ± 5.68	0.689
BAI	7.50 ± 5.47	7.02 ± 5.13	8.05 ± 5.85	0.456
GARS	21.02 ±9.92	19.82 ± 11.16	22.41 ± 8.18	0.069
Sleep Diary				
TST (min)	369.52±74.76	372.90±79.23	365.79±70.35	0.593
Sleep Latency (min)	35.87±36.52	35.17±36.73	36.64±36.77	0.962
WASO, min	19.39±25.58	15.25±18.07	24.19±31.79	0.120
Total Arousal, No	2.29±1.89	2.36±1.91	2.21±1.90	0.733

Data are presented as mean±SD. Independent *t*-tests or Chi-squared tests were used to determine the difference between the two groups.
BAI, Beck Anxiety Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; GARS, Global Assessment of Recent Stress Scale; ISI, insomnia severity index; PSQI, Pittsburgh sleep quality index; TST, total sleep time; WASO, wake after sleep onset.

Table 2 Polysomnography results in both groups (*N*=84)

Variables		Passionflower (*N*=45)	Placebo (*N*=39)	P value (between group)
TST, min	Baseline	395.28±58.84	412.01±56.4	–
	2 weeks	418.33±45.12	411.85±63.04	–
	Difference	23.05±54.26	−0.16±53.12	0.049#
	P value (within group)	0.005**	0.807	
Sleep efficiency, %	Baseline	82.88±12.73	85.82±11.76	–
	2 weeks	87.16±9.37	85.82±13.12	–
	Difference	4.28±11.27	0.01±11.04	0.074
	P value (within group)	0.008**	0.759	
Sleep latency, min	Baseline	17.30±26.26	13.57±16.03	–
	2 weeks	12.20±20.62	17.26±35.13	–
	Difference	-5.1±27.62	3.69±26.43	0.141
	P value (within group)	0.053	0.389	
Total arousal, No	Baseline	105.8±44.99	112.0±56.42	–
	2 weeks	156.49±289.76	108.74±49.23	–
	Difference	50.69±282.03	-3.26±38.37	0.240
	P value (within group)	0.234	0.599	
WASO, min	Baseline	64.93±48.95	54.50±53.35	–
	2 weeks	49.43±36.60	50.42±48.51	–
	Difference	−15.50±44.91	−4.08±45.23	0.25
	P value (within group)	0.025*	0.577	

Data are presented as mean±SD.
Independent *t*-tests or Mann–Whitney *U* Tests were used to determine the difference between groups. #$P<0.05$, ##$P<0.01$, ###$P<0.001$.
Paired *t*-tests or Wilcoxon signed rank tests were used to determine the differences within groups. *$P<0.05$, **$P<0.01$, ***$P<0.001$.
TST, total sleep time; WASO, wake after sleep onset.

Subjective sleep parameters

Self-reported sleep parameters on sleep diaries and self-reported scales including ISI and PSQI did not show any significant difference between the Passionflower group and the placebo group (Table 3).

Depression, anxiety, and stress

Compared with baseline, scores of CES-D, BAI, and GARS decreased after 2 weeks in the passionflower group ($P=0.002$, $P=0.009$, $P=0.024$). However, there was no significant difference compared with the placebo group (Table 4).

Safety and tolerability

No serious adverse events (AE) occurred during the study. Two AEs, which was somnolence and headache, were reported in the placebo group. No AE was reported in the Passionflower group. Laboratory results of the participants were all in the normal ranges and were not significantly different between groups.

Discussion

In the present study, the effects of Passionflower on the objective and subjective sleep parameters of subjects with insomnia disorder were assessed by a 2-week, double-blind, randomized, placebo-controlled clinical trial. The results showed that Passionflower improved polysomnographic sleep parameter, TST, compared with the placebo in subjects with insomnia disorder. The sleep efficiency also showed a trend of improvement in subjects who received passionflower compared with those who had placebo. Subjective sleep parameters and

Table 3 Results of the subjective sleep parameters in both groups (*N*=84)

Variables		Passionflower (*N*=45)	Placebo (*N*=39)	*P* value (between group)
ISI	Baseline	13.24±3.65	14.31±4.26	–
	2 weeks	9.93±1.61	9.87±1.52	–
	Difference	−3.31±3.6	−4.44±3.74	0.166
	P value (within group)	<0.001***	<0.001***	
PSQI	Baseline	8.27±1.60	8.56±1.39	–
	2 weeks	6.91±1.61	7.05±1.521	–
	Difference	−1.36±1.96	−1.51±1.14	0.26
	P value (within group)	<0.001***	<0.001***	
Sleep Diary				
TST, min	Baseline	372.9±79.23	365.79±70.35	–
	2 weeks	397.4±48.43	390.73±60.34	–
	Difference	24.03±75.61	25.83±63.08	0.47
	P value (within group)	0.046*	0.009**	
Sleep latency, min	Baseline	35.17±36.73	36.64±36.77	–
	2 weeks	24.18±15	20.87±14.25	–
	Difference	−11.73±31.13	−15.53±31.68	0.391
	P value (within group)	0.003**	<0.001***	
Total arousal, No	Baseline	2.43±1.96	2.24±1.77	–
	2 weeks	1.29±1.05	1.47±1.05	–
	Difference	−1.21±1.30	0.78±1.66	0.232
	P value (within group)	<0.001***	0.002**	
WASO, min	Baseline	15.41±18.40	24.42±31.54	–
	2 weeks	11.32±13.26	12.48±12.12	–
	Difference	−3.95±15.02*	−11.95±26.13**	0.107
	P value (within group)	0.018*	0.009**	

Data are presented as mean±SD.
Independent *t*-tests or Mann–Whitney U Tests were used to determine the difference between groups. #*P*<0.05, ##*P*<0.01, ###*P*<0.001.
Paired t-tests or Wilcoxon signed rank tests were used to determine the differences within groups. *P<0.05, **P<0.01, ***P<0.001.
ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time; WASO, wake after sleep onset.

Table 4 Results of depression, anxiety, and stress in both groups

Variables		Passionflower (*N*=45)	Placebo (*N*=39)	*P* value (between group)
CES-D	Baseline	9.82±5.80	9.18±5.68	–
	2 weeks	7.56±6.99	7.82±6.52	–
	Difference	−2.27±5.25	−1.36±5.52	0.273
	P value (within group)	0.002**	0.076	
BAI	Baseline	7.02±5.13	8.05±5.85	–
	2 weeks	5.36±5.10	7.03±5.21	–
	Difference	−1.67±4.12	−1.03±4.91	0.395
	P value (within group)	0.009**	0.212	
GARS	Baseline	19.82±11.16	22.41±8.18	–
	2 weeks	17.78±11.21	21.33±9.71	–
	Difference	−2.04±8.3	−1.08±8.33	0.587
	P value (within group)	0.024*	0.369	

Data are presented as mean ±SD.
Independent *t*-tests or Mann–Whitney U Tests were used to determine the difference between groups. #*P*<0.05, ##*P*<0.01, ###*P*<0.001.
Paired *t*-tests or Wilcoxon signed rank tests were used to determine the differences within groups. *P<0.05, **P<0.01, ***P<0.001.
BAI, Beck Anxiety Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; GARS, Global Assessment of Recent Stress Scale.

subjective reports of depression, anxiety, and stress did not show any significant difference compared with the placebo. The Passionflower was well tolerated, with no reports of any kind of adverse events.

There are very few previous clinical trials that investigated the effects of Passionflower on subjects with insomnia. Schulz *et al*. (1998) conducted a randomized double-blind placebo-controlled study on 12 females to study the effects of different medicinal herbs including Passionflower on sleep quality. In this study, Passionflower, diazepam, and placebo all exerted effects, producing a similar decrease in mental alertness. Electroencephalography did not show any effect of passionflower compared with placebo.

Another randomized double-blind placebo-controlled study by Ngan and Conduit (2011) was conducted to investigate the efficacy of *Passiflora incarnata* herbal tea on sleep quality of 40 participants. After 1 week of treatment period, sleep quality measured by sleep diaries showed a significantly better rating for Passionflower compared with placebo. However, the results of the 10 participants who underwent the polysomnography did not demonstrate any significant difference.

The present study is the first clinical trial that demonstrated the positive effects of Passionflower on sleep by polysomnographic results in subjects with insomnia. However, objective sleep parameters other than TST and the subjective sleep parameters did not show any difference compared with the placebo. There could be several reasons for this result. First, sedative effects of Passionflower have reported be dose-dependent, and 60 mg of Passionflower extract may have been insufficient to produce a greater difference that could be measured subjectively (Soulimani *et al*., 1997). The previous clinical study that showed significant result by sleep diaries administered tea with 2 g of Passionflower extract. Second, the participants of the present study were not comprised patients with severe insomnia as it can be shown by the mean objective and subjective TST at baseline which was more than 6 hours. Therefore, subjective sleep parameters could have had too little possibility for improvement due to the mild severity of the insomnia of the participants. Third, the relatively short period of treatment duration could have been insufficient, as Passionflower has been suggested to have a slow onset of action (Akhondzadeh *et al*., 2001).

Subjective reports of depression, anxiety, and stress did not show any significant difference compared with the placebo. Still, the scores of depression, anxiety, and stress all significantly improved after 2 weeks compared with baseline in the Passionflower group, while no significant change was observed compared with the placebo. Given that the anxiolytic effect is one of the most intensively investigated pharmacological roles of Passionflower (Miyasaka *et al*., 2007), the unexpected negative results could be attributed to the same reasons mentioned for the subjective sleep parameters. The Passionflower failed to show any significant difference on subjective reports of anxiety in the present study due to the relatively low dose of Passionflower extract, the mild severity of anxiety in the participants, and the short duration of treatment.

Limitations of the present study are that the clinical efficacy in insomnia remains to be explored because the subjective satisfaction is most important in clinical insomnia. Also, the treatment duration could have been too short to evaluate the adverse effects, especially the risk of tolerance and dependence. Last, only a single night of polysomnography was each conducted at before and after the treatment. A night at a sleep laboratory could be a very different environment compared with one's usual one. Therefore, it may result in worse sleep quality, which is called the first night effect (McCall and McCall, 2012). Subjects may become more comfortable during their second polysomnography test, yielding an improvement in sleep quality compared with their first test. However, in this study, the results of the polysomnography showed that only the sleep parameters in the passionflower group were significantly improved after the intervention, and the placebo group showed no improvement after receiving the placebo in all polysomnographic parameters (Table 2).

Conclusion

The current study is the first study to demonstrate positive effects of Passionflower on the polysomnographic sleep parameters in patients with insomnia disorder. The results demonstrated a significant increase in the TST on the polysomnography. More extensive clinical trials on larger populations with longer treatment period and different dosages of Passionflower are required. Additionally, Passionflower should be compared with conventional hypnotic drugs to elucidate its clinical efficacy in the treatment of insomnia.

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Conflicts of interest

There are no conflicts of interest.

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