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Research Article

STUDY OF AQUEOUS EXTRACTS OF ASPARAGUSON SLEEP MELIORATING EFFECT

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ABSTRACT

Insomnia is a prevalent sleep disorder that can profoundly impact a person's health. The pharmacological management of insomnia has lately become a challenge for researchers worldwide. Herbal medicine represents one of the great potentialson treatment of insomnia. However, the safety and efficacy of herbal medicine for the treatment of this disorder is currently uncertain.In the study, aqueous extracts of asparagus (AEA) was obtained, and its anti-insomnia effect and safety were investigated and evaluated. The results of this study suggested that AEA therapy might meliorate a variety of symptoms of insomnia, and no side effects were found. Therefore, AEAhas great potential and superiorityon insomnia therapy.

INTRODUCTION

Insomnia is a widespread problem in modern societies. In particular, insomnia is associated with various disorders including chronic stress, depression, and neurological symptoms, whichis a complex issue, and no single therapy is known to remove all symptoms(Palagini et al., 2016). Insomnia and sleep disturbance, most common mental illnesses worldwide, represent a prominent healthcare problem (Crawford et al., 2016; Zachariae et al., 2016).Hypnotics are among the first line of drugs that have been extensively used to treat several forms of insomnia(Tariq and Pulisetty, 2008). The conventional treatments approved for management of insomnia were benzodiazepines (BZDs) (estazolam, quazepam, triazolam, flurazepam and temazepam) and non-BZDs, also known as z-drugs (zaleplon, zolpidem, and eszopiclone), tricyclic antidepressant (TCA) doxepin as well as melatonin agonists, e.g. ramelteon. Although hypnotics have well-known benefits, their side effects are prominent (Akiko et al., 2015). These agents have been limited due to substantial side effects associated with them like hangover, dependence and tolerance, rebound insomnia, muscular atonia, inhibition of respiratory system, cognitive dysfunctions, and increased anxiety.The use of benzodiazepines such as diazepam and related drugs, or nonbenzodiazepine hypnotics e.g., zolpidem or zopiclone are preferred currently over older barbiturates which can cause death in cases of overdose (Tariq and Pulisetty, 2008).With respect to benzodiazepines, although a relatively safe class of medication, concerns exist over dependency, and currently most guidelines endorse only short-term use for insomnia.

Therefore, the search for new therapeutic agents continues. The interests in alternative medicine and plant-derived functional food to conquer insomnia and promote relaxation have increased recently (Jeon et al., 2015).The latest study reported that enzyme-treated asparagus extract possessed neuroprotective effect and attenuates cognitive impairment in senescence-accelerated mice (Sakurai et al., 2013).In a search to identify novel botanical marerials to improve sleep status, we discovered asparagus (*Asparagus officinalis L.*) as a likely candidate. Asparagus is a typical agricultural product in China, Japan and other countries.

Asparagus officinalis L., a well-known nutritious and healthy vegetable, was applied widely in the traditional Chinese medicine clinic practice, as a tonic, heat-clearing, antitussive, and diuretic agent. In recent years, various healthful effects of the asparagus have been scientifically verified (Ito et al., 2013; Krishnamurthy et al., 2013). In early 2013, the Chinese government authorized the aqueous extract of asparagus (AEA) as a natural functional food and beverage ingredient. The present study investigated the potentials ofanti-sleep disturbance andanti-insomnia of AEA oninsomnia patients. Meanwhile, the safety of AEA was evaluated.

2. MATERIALS AND METHODS

2.1.Plant Material.

Asparagus officinalis L. was collected from cultivation in Hangu administration zone of Tangshan, a vegetation zone that belongs to Qinhuangdao Changsheng Agricultural Technology Development Co., Ltd. Botanical samples were identified by botany expert of Hebei Normal University of Science and Technology, Qinhuangdao, China.

2.2. Aqueous Extracts of Asparagus Preparation.

Aqueous Extracts of Asparagus (AEA) from the stemof *Asparagus officinalis L.* was provided by QinhuangdaoChangsheng Agricultural TechnologyDevelopmentCo., Ltd.,Hebei Province, China. To obtain the aqueous extract fromthe woody stem of asparagus, fresh plant material (60.0 kg)was cleaned, crushed, and then extracted with drinking water(ratio ofplant and water 1 : 8 w/v; water temperature: 85 ± 5℃) bydynamic maceration for 5 h. After filtering, the solution ofasparagus stem was treated with spray drying to dryness,yielding extract powder (aqueous extract of Asparaguspowder).

2.3. Procedures.

The patients were selected from the persons with sleep disturbance, includingthe troubles of difficulty falling asleep, multiple awakening at night, difficulty falling asleep again after waking up or felling fatigue after waking up. According to the Pittsburgh Chef`s Table(Miguel et al., 2006), the sleep quality of patients was evaluated, and recorded the sleep quality evaluation system, and then analyzed the sleep status automatically. The datawere collected, and the experimental persons were selected according to the results of Pittsburgh evaluation. Under a stable and same condition, the participants conducted the test.The levelsof blood ALT, AST and HLT of the participants were determined. The tested persons were grouped on the basis of test results, and filled out the consent inform in line with the ethical standards. The participants ate 25 g AEA at 3~5pm daily for 60 days. The changes of tested persons on sleepquality were compared and evaluated after 60 days, and evaluated the efficacy of the asparagus extracts on improving sleepquality. After the test, the above blood indexes of the participants were determined again to analyze the safety of AEA.

3. RESULTS

3.1. Changes of sleep time on the pre- treated and post-treated AEA

After treated with asparagus extract orally for 60 days, the sleep time of participants were evaluated and analyzed, as shown on Figure 1. The results indicated that the sleep time of the participants was obviously improved, and the average sleep time has been prolonged from 5.1 hours to 6.08 hours, which was increased 18.7%. There was significant difference on pre- and post-using asparagus extract. Among them, 73.3% of the participants had obviously increase on the sleep time.

3.2. Changes of falling sleep time on pre- treated and post-treated AEA

After treated with asparagus extract orally for 60 days, the time to fall asleep of participants were evaluated and analyzed, as shown on Figure 2. The results indicated that the time to fall asleep of the participants was obviously reduced, and the average time for fall asleep has been decreased from 50.41 mins to 25.33 mins, which was reduced about 49.75%. Among participants, the 42.86% of people with more than 120 mins to fall asleep could fall asleep within 15 mins after eating the asparagus extract, 57.14% participants could fall asleep within 30 mins. And the results showed that the participants with sleep difficulties, their time to fall asleep all reduce in different degrees after eating the asparagus extract. Therefore, the asparagus extract could obviously shorten falling asleep time, especially for the persons with obvious difficulty falling asleep.

3.2. Changes of night awaking times at after the consumption of asparagus extract

After consumption of asparagus extract orally for 60 days, the awaking times at night of the participants were evaluated and analyzed, as shown on Figure 3. The results indicated that the night wake times of the participants were obviously reduced by 16.13%. Among the participants with night awaking three times or more, 57.14% persons significantly reduced on the night awaking times. In addition, the 42.86% of people with falling asleep for more than 120 mins could sleep within 15 mins after eating the asparagus extract, meanwhile, 57.14% participants could sleep within 30 mins. The participants with sleep difficulties, their time to go into sleep all reduced in different degrees after eating the asparagus extract. The study showed that asparagus extract could obviously shorten falling asleep time, especially for the persons with obvious difficulty on falling asleep.

3.4. Time changes of awaking then falling sleep again pre-therapy and post-therapy using AEA

Some patients often wake up, after waking cannot sleep again.The results indicated that the participants reduced the time of fall asleep again after awaking from 46.52 to19.47 mins on average after treated with asparagus extract 60days, which decreased 58.15%. Among them, the participants needing more than 120 minutes, there were 41.52% of persons falling asleep again within 15 mins after consumption of the extract, and 58.13% of persons could fall asleep again within 30 mins. Among the patients with 60-90 mins falling asleep again, there were 33.3% of people in 15 mins to fall asleep again, and 11.12% of people can fall asleep again using 30 minutes.

3.5. Changes of sleep quality pre-therapy and post-treatment using asparagus extract

The participants' sleep quality was evaluated pre-therapy and post-treatment using asparagus extract for 60 days. According to the quality of sleep, including: ① fair (1 score); ② poor (2 score); ③very bad (3 score), the patients marked for the sleep quality. The lower score means the better sleep quality. The grade according to 30 participants, the sleep quality scored an average of the results before and after the consumption of the extract as shown in figure 5. The results indicated that the sleep quality of 93.33% of people improved significantly, the sleep quality satisfaction of participants was higher under the extract treatment.

The participates in evaluation personnel commonly used reflect improving sleep quality during sleep disorders produce adverse reactions, such as dizziness, head, head bilges, drowsiness, fatigue, etc. were obviously improved. the 30 patients, 93% of people sleep quality improved significantly, the satisfaction of participants for sleep quality is higher after the extract treatment, more than 77% of the participates were satisfied with the extract effect, the patients considered that this extract can effectively improve sleep problems.

3.6. Safety evaluation of asparagus extract

After 30 cases of participators were treated using AEA for 60 days, the levels of glutamic - pyruvic transaminase (ALT), glutamic oxalacetic transaminase (AST), lactic dehydrogenase (LDH) in the blood were determined, the results are shown in table 1. Comparing with pre-therapy, there were not significant changes, which suggested that AEA was healthy and non-toxic side effects for liver.Urine routine indexes were examined for theparticipants before and after taking the drug,there were not abnormal changes on urine, and the urea nitrogen values were within the normal range.The normal routine urine examination showed that the drug was non-toxic side effects for kidney.After 3 cases of abnormal liver function participants treated with the drug for 60 days, the results were shown in table 2, the levels of ALT, AST and LDH were declined in varying degrees, but there was no significant change ($P > 0.05$). So AEA had not non-toxic side effects for the abnormal liver function patients.

4. DISCUSSION

Asparagus is a perennial and herbaceous plant, which has been used as a vegetable and medicine, owing to its delicate flavour, diuretic properties, and more. Asparagus is low in calories and is very low in sodium. It is a good source ofvitamin B_6, calcium, magnesium, and zinc, and a very good source of dietary fibre, protein, beta-carotene, vitamin C, vitamin E, vitamin K, thiamin, riboflavin, rutin, niacin, folic acid, iron, phosphorus, potassium, copper, manganese and selenium (Waldron et al., 2006).Antioxidant activity of asparagus was evaluated using 2,2'-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) and P-carotene bleaching assays. Asparagus showed greater antioxidant activity. Methanol and acetone extracts of asparagus had significantly greater antioxidant activity than their water extracts. The antioxidant activity of asparagus extracts demonstrated a linear relationship with their flavonoid content (Sun et al., 2007).This study showed that AEA treatment is feasible in non-sleepy, sleepy difficulty patients.93% our participants showed good evaluationfor the therapy. Compared with pre-therapy, AEA significantly decreased the time spending on falling sleep and increased the sleep time on the above persons. To our knowledge this is the first systematic study of AEAon the treatment of chronic adult insomnia.The literature survey revealed that the steroidal saponinswere the main biologically active constituents of Asparagus (Dawid et al., 2014). In the previous pentobarbital-induced sleep test, linear regression analysis showed a correlation between asparagus saponin intake and increased sleeping time. Reports suggest that sarsasapogenin from*Anemarrhenaasphodeloides*Bunge (Liliaceae) exiledantidepressant activity by mediation of the central monoaminergic neurotransmitter systems (Kang et al., 2010; Wang et al., 2014). The content of AEA was quantified by determination of sarsasapogenin, as an index of active constituents of asparagus. So the use of rasayana drugs is not only for alleviating diseases, but also to improve the quality of life in general. Hence, more appropriately, these may also be considered as functional foods. The physiological concept of these drugs is based on regulation of neuroendocrine axis and immunological system for maintenance of homeostasis for general well-being.

In the search for new sources of health-promoting ingredients in vegetables, we focused on an asparagus extract, which has recently been observed to enhance the expression of heat shock protein 70 that is thought to help protect the body from various stresses (Ito et al., 2014).A single oral dose study was conducted to assess the potential toxicity and LD50 value of ETAS. Based on the results of the study, the LD50 value was considered to be greater than 2000 mg/kg body weight in female rats. This value corresponds to a single dose of 120 g for a 60-kg human in a simple conversion or 20 g for a 60-kg human in surface-area-guided dosing. A 90-day repeated oral dose toxicity study was performed at the doses of 0, 500, 1000 and 2000 mg/kg body weight. Most parameters assessed showed no differences between the control and any of the three test doses. However, a significant increase in urinary protein excretion was observed in male and female rats in the 2000 mg/kg group. These observations were supposed to be attributable to the treatment with ETAS, whereas no histopathological renal changes were detected in any of the animals in both groups. Thus, the elevation of urinary protein excretion was not considered toxicologically significant. Since it is known that urinary protein excretion becomes temporarily positive after taking a hot bath, it cannot be denied entirely

Goto group research indicated that enzyme-treated asparagus has been developed as a novel anti-stress functional food ingredient that is produced from asparagus.Two human intervention trials with ETAS were conducted in healthy adult male volunteers. The persons treated with enzyme-treated asparagus extract showed a tendency to enhance HSP70 mRNA expression level, and the asparagus extract intake was effective to modulate the sleep state among those with low sleep efficiency or excess sleep time (Ito et al., 2014). The safety of enzyme-treated asparagus extract (ETAS) developed as a novel anti-stress functional material was assessed in acute and subchronic studies and genotoxicity assays. The 50% lethal dose (LD50) of ETAS was determined to be greater than 2000 mg/kg. The 90-day subchronic study (500, 1000 and 2000 mg/kg body weight, delivered by gavage) in rats reported no significant adverse effects in food consumption, body weight, mortality, urinalysis, hematology, biochemistry, necropsy, organ weight and histopathology. The potential of ETAS to induce gene mutation was tested, and the extract was not mutagenic to the test strains (Ito et al., 2014).

In conclusion, these findings indicated that the aqueous extract of asparagus exhibited a strong anti-insomnia effect at dose of 25 grams per day for the insomnia patient for 60 days, So AEA therapy may be considered an alternative approach for the management of insomnia.

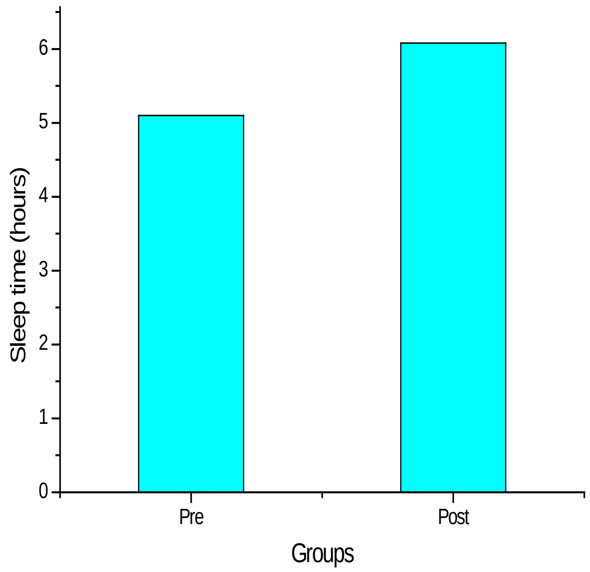

Figure 1Sleep time of the participants on the pre-treated and post-treated AEA

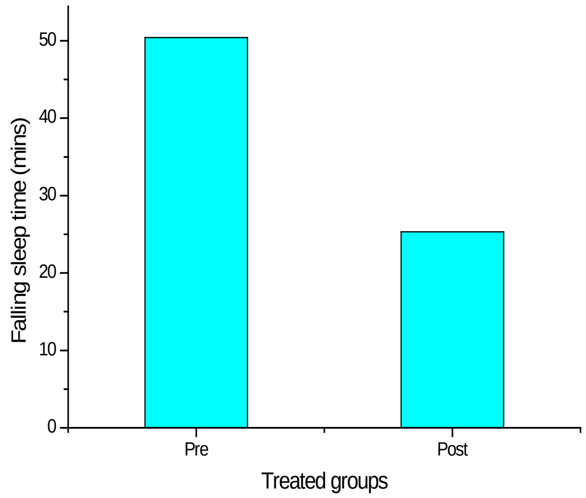

Figure2 Fallingasleep time of the participants on pre-treated and post-treated AEA

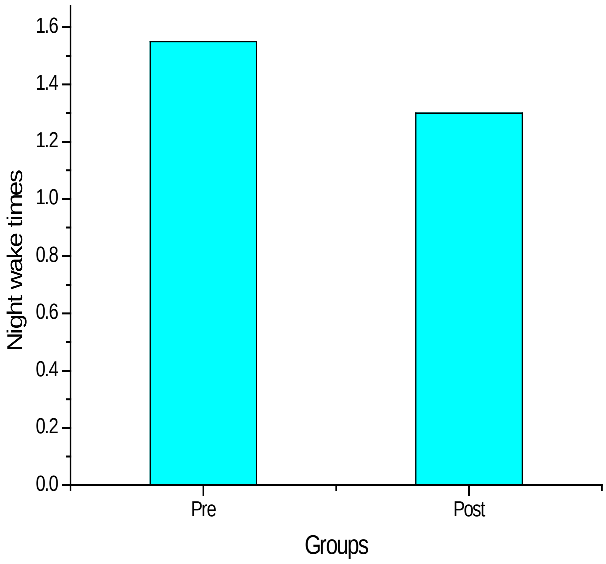

Figure3 Night waking times of the participants on pre-treated and post-treated AEA

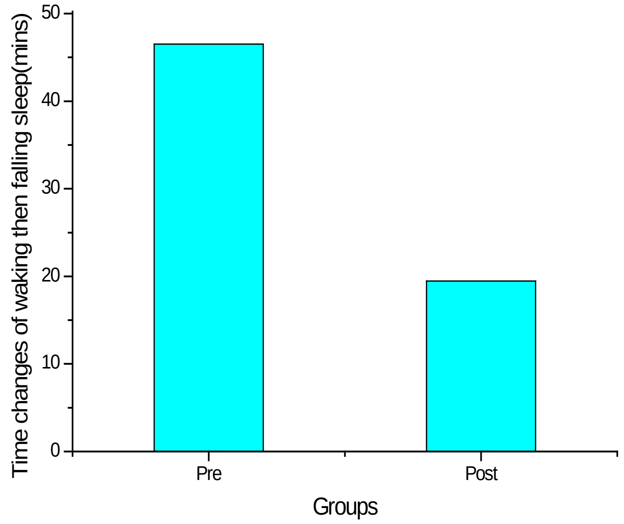

Figure 4 Time of waking then falling sleep of the participants on pre-treated and post-treated using AEA

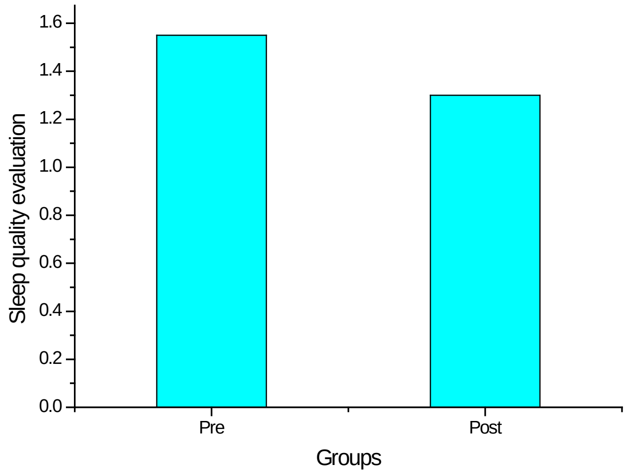

Figure 5 Sleep quality evaluations of the participants on pre-treated and post-treated using AEA

Table 1 Effects of AEA on levels of ALT, AST and LDH for participants with normal hepatic function

Indexs	n	Pre-therapy	Post-therapy	P values
ALT（U)	25	18.0±7.8	18.1±11.7	>0.05
AST（U)	25	18.8±3.7	17.7±5.1	>0.05
LDH（U)	25	171±27.3	181±25.8	>0.05

Table 2 Effects of AEA on levels of ALT, AST and LDH for participants with abnormal hepatic function

Indexs	n	Pre-therapy	Post-therapy	P value
ALT（U)	3	30.3±11.3	39.3±8.3	>0.05
AST（U)	3	23±5.7	25.3±3.4	>0.05
LDH（U)	3	153±12.3	177±5.7	>0.05

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