Title: The Effectiveness of Astragalus Root Extract on Anxiety and Sleep Quality in Nurses Post COVID-19: A Randomized, Triple-Blind, Placebo-Controlled Trial

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Abstract

Background: Nurses on the front lines of COVID-19 have suffered many complications, including anxiety and sleep disorders. This study examined the effects of Astragalus root extract on nurses' anxiety and sleep quality post Covid-19.

Methods: The study was a Randomized, Triple-Blind, Placebo-Controlled trial that was conducted in Kashan, Iran, in 2023. Based on the quota of each department, the subjects were recruited and randomly allocated to either the intervention group (n=32) who received Astragalus root extract and the control group (n=32) who received placebo for one month. Demographic form, Pittsburgh Sleep Quality Index (PSQI) and Beck Anxiety Inventory (BAI) were completed by the subjects before, immediately after, and one month after the end of intervention. The data were analyzed by descriptive statistics, independent t-tests, Generalized Estimating Equations (GEE), Chi Square, one-way ANOVA and repeated measures ANOVA using SPSS version 16. The significance level was set at ($p < 0.05$). The study was conducted and reported based on CONSORT guidelines for herbal medicines.

Results: A statistically significant difference was observed in the mean sleep quality score between the intervention and control groups immediately after the intervention (p=0.001) and one month later (p=0.003). Moreover, the changes in the sleep quality score in the intervention group were significant over time (F=7.80, P<0.001). There was also a significant difference between the sleep quality of the two groups over time (F=5.32, P=0.006). The mean anxiety score between the two groups was significantly different immediately after the intervention (p= 0.02), one month later (p=0.04), and over time (F=16.69, p<0.001). Moreover, the changes in the anxiety score between the two groups showed a significant statistical difference (F=14.96, p<0.001).

Conclusion: Root extract of Astragalus can reduce anxiety among nurses, post Covid-19 and improve the quality of their sleep.

Key words: Nurses, Sleep Quality, Anxiety, Huang Qi, Astragalus Plant

Highlights

- Astragalus root extract significantly reduced nurses' anxiety post-COVID-19.
- Sleep quality and anxiety improved in the intervention group, and this effect persisted after one month.
- Compared to placebo, Astragalus root extract showed sustained effects on anxiety and sleep in nurses.
- The results of this study confirm the neuroprotective, anti-anxiety, and sleep-improving roles of the active compounds in the Astragalus root extract.

Plain Language Summary

During the COVID-19 pandemic, nurses faced not only physical strain but also significant psychological challenges, including persistent anxiety and sleep disturbances even after recovery. Although pharmacological treatments are available, they often carry undesirable side effects. Consequently, researchers have investigated natural alternatives, focusing on Astragalus—a medicinal plant widely cultivated in Iran. In a clinical study involving 64 nurses previously infected with COVID-19, participants were randomly assigned to receive either Astragalus root extract or a placebo for one month. Sleep quality and anxiety levels were systematically assessed before and immediately after the intervention, and one month later. The findings revealed that nurses who consumed Astragalus exhibited marked improvements in sleep and reductions in anxiety, with benefits persisting for at least one-month post-treatment. Importantly, no serious adverse effects were reported. These results suggest that Astragalus root extract may represent a safe and effective natural option for supporting the mental health of frontline healthcare workers.

Introduction

Nurses as the largest body of healthcare professionals played a critical role during the COVID-19 pandemic (Asadi et al., 2019; Mira et al., 2020; Salari et al., 2020). The outbreak imposed significant mental strain, including anxiety, depression, insomnia, and chronic stress (Lasalvia et al., 2021). A meta-analysis reported anxiety prevalence at 23% among health workers (Pappa et al., 2020), with nurse-specific rates ranging from 33% in Italy (Simonetti et al., 2021), 43% in China (Chen et al., 2022b), 44–73% in Iran (Sharifi et al., 2022), and nearly 54% in Portugal (De Pinho et al., 2021). Anxiety, which is defined as fear of future threats (Cohen et al., 2016), may progress to depression if persistent (Crocq, 2015).

Stressed nurses are more susceptible to mental illness, poor concentration, absenteeism, burnout, substance abuse, and weakened immunity (Amiri et al., 2021). Sleep disturbances, reported by 96% of nurses during the pandemic (Salaree et al., 2022), are widespread globally—60% in China (Qiu et al., 2020), 75% in Bahrain (Jahrami et al., 2021), and 71% in Italy (Simonetti et al., 2021). These issues have long-lasting consequences, including gastrointestinal disorders, fatigue, emotional instability, and reduced professional performance (Huang et al., 2020; Hoseinabadi, 2020). Therefore, supporting nurses' physical and psychological health is vital to sustaining healthcare delivery and minimizing the broader impact of infectious diseases.

Common treatments for anxiety and sleep problems include both pharmaceutical and herbal approaches. Serotonergic medications can relieve symptoms but often cause unwanted side effects, such as sexual dysfunction, weight gain, and drug withdrawal (Patel et al., 2016). In contrast, herbal remedies may offer safer and more culturally grounded alternatives. Clinical research on herbal medicine as Complementary and Alternative Medicine (CAM) has so far demonstrated positive outcomes (Khalafi-Kheydani et al.,2022; Maghami et al.,2023).

Astragalus membranaceus, a widely used plant in Iranian traditional medicine, shows promise in treating stress-related disorders. Known locally as radix Astragali, the root has been used to regulate heart function, sleep quality, hormonal balance, and overall health (Shahrajabian et al., 2019; Peng et al., 2022). This plant may contribute to the improvement of sleep disorders through its physiological mechanism involving oxidative stress (Davinelli, et al 2024). Iran is home to more than 850 Astragalus species, including 527 endemic varieties (Ghasemian-Yadegari et al., 2017; Aslanipour et al., 2017). As an adaptogen, Astragalus helps the body respond to stress and maintain internal balance (Liao et al., 2018; Oh et al., 2014).

Although few clinical studies exist, preclinical research shows adaptogens may reduce anxiety and improve sleep (Pawar and Shivakumar, 2012; Panossian and Wikman, 2010). Astragalus supports immune modulation, adrenal balance, inflammation reduction, and cognitive function (Peng et al., 2022; Abd Elkader et al., 2021; Jalsrai et al., 2010; Zhang et al., 2022; Bahaeddin et al., 2018). It has also shown efficacy in restoring intestinal balance, which influences sleep health (Li et al., 2023).

Given the ongoing mental health challenges faced by nurses post-COVID-19—and the paucity of studies evaluating herbal interventions—the present research investigated whether Astragalus root extract (ARE) could reduce anxiety and improve sleep among nurses. The study was guided by the hypothesis that ARE consumption would offer measurable psychological benefits in this vulnerable population.

Material and Methods

Design and setting: This study was carried out as a Randomized, Triple-Blind, Placebo-Controlled trial conducted on nurses at two educational hospitals in Kashan, Iran in 2023. The

study was conducted in a parallel design, with samples allocated one-to-one to each group. The present study was reported based on CONSORT guidelines for Herbal medicines.

Participants: The inclusion criteria included consent to participate in the study, having a history of being infected with Covid-19, at least 6 and maximum 12 months passed since the infection, working in a hospital as a nurse, not using anticoagulants, not experiencing orthostatic hypotension or allergic reactions to vegetables or beans, not being under the influence of antipsychotics or antidepressants, and not being affected by thyroid dysfunction. Exclusion criteria were unwillingness to continue participation in the study, discontinuation of medication for four consecutive days, taking anti-anxiety and sleeping pills during the study, pregnancy, occurrence of drug allergy symptoms, or experiencing hypotension reactions.

***Sample size*:** According to the research hypothesis and the parallel design of the study, the sample size was estimated using the formula for calculating the sample size in experimental studies. Based on the results of the Tingting study (2022), the sample size was calculated as 29, considering the mean difference (5.83), variance equal to 11, type I error of 0.05, and type II error of 0.2. With a probability of 10% attrition, 32 subjects were considered for each group.

$$n_1 = n_2 = {(z_{1-a/2} + z_{1-\beta})^2 \delta^2} \Big/ {d^2} \cong 29$$

***Recruitment and Randomization*:** Participants were randomly selected from the medical, surgical, emergency and critical care departments of two educational hospitals by drawing lots and based on the quota of each department and were assigned to either intervention or control group by the principal investigator using stratified random block methods. Stratified block randomization was used with a block size of four, generated by the online sealdenvelop.com software. Taking into account that gender may play a role in the outcomes, the two groups were matched in terms of this variable.

***Blinding*:** This study was conducted as a triple-blind trial. The participants, the prescribing physician, and the statistical analyst—all members of the research team—were blinded to the group assignments. Only the principal investigator, who prepared the packages and held the randomization list, was aware of the names of the intervention and control groups.

***Intervention*:** The powdered extract used in this study was obtained from the root of Astragalus. The product was processed in distilled form and prepared in 500 mg capsules by Asha Organic Company. For the placebo group, corn starch was encapsulated in capsules identical to those used in the intervention group. Participants were instructed on the proper use of the Astragalus root extract and were administered 500 mg capsules twice daily (morning and evening) for 30 days. The control group received identical capsules containing 500 mg of corn starch, also taken twice daily for 30 days.

Throughout the intervention, potential side effects were monitored by daily phone calls during the first week and weekly calls thereafter. The researcher's mobile phone number was also provided, so participants could report any side effects or concerns. No severe adverse effects were observed. A few participants in the intervention group reported mild heartburn and gastric sourness within the first hour of administration during the initial days of treatment; however, these symptoms resolved spontaneously in subsequent days. In consultation with the study's co-investigator (M.R.), it was determined that no medication was required, and participants

were simply advised to drink an additional glass of water at the time of capsule intake, which alleviated the problem.

The powder extract used in this study which was obtained from the root of the Astragalus verus species has been tested for the phytochemical constituents and as a result of this test, carbohydrates, proteins, amino acids, glycosides, saponins, volatile oils, alkaloids, sterols, and flavonoids were found (Abdallah et al, 2024). Studies have shown no signs of toxicity in rats even with a maximum dose of 2000 mg/kg of the extract during 14 days. The oral lethal dose (LD50) cut off value of the Ethanolic Extract of Astragalus membranaceus is 5000 mg/kg, as safe for use (Pathak, 2022)

Instruments

Demographic information form: The subjects were asked about their age, sex, work experience, marital status, department, number of working hours per month, number of children, level of education, and history of Covid-19.

The *Pittsburgh sleep quality index (PSQI):* This is a self-report instrument designed to evaluate sleep quality over a one-month period. It consists of 18 items grouped into seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored from 0 to 3, yielding a global score ranging from 0 to 21. A score greater than 5 indicates poor sleeper, while others are recognized as good (Buysse et al., 1989). The PSQI is widely used due to its simplicity, reliability, and validity, offering a comprehensive assessment of sleep across multiple dimensions (Bastani and Amirijavid, 2023). The original version demonstrated strong internal consistency, test–retest reliability, and validity, with diagnostic sensitivity of 89.6% and specificity of 86.5%. Cronbach's alpha values reported in different studies range from 0.78 to 0.89, confirming its reliability across populations, including Persian

adaptations. Content validity has also been established through expert review. Nasiri-Ziba examined the validity and reliability of the Persian version of the PSQI and reported a Cronbach's Alpha of 0.87(Nasiriziba et al, 2006). The reliability of the questionnaire in this study was assessed using internal consistency, yielding a Cronbach's alpha of 0.83.

The Beck Anxiety Inventory (BAI): In 1988, Aaron Beck introduced this inventory to measure the severity of clinical symptoms of anxiety. This 21-item self-assessment tool measures anxiety symptoms on a 4-point Likert scale (0=not at all, 1=mildly, 2=moderately, and 3=severely). The scores range from 0 to 63. In this scale, 0-7 indicates minimal anxiety, 8-15 shows mild anxiety, 16-25 reflects moderate anxiety, and 26-63 shows severe anxiety (Jalilvandi et al., 2025). Its internal consistency (α coefficient) was equal to 0.92 and its reliability was assessed as equal to 0.75 using the test re-test method within a one-week interval, and the correlation between the items varied from 0.30 to 0.76 (Beck et al., 1988). This questionnaire was translated into Persian in 2005 and its reliability was reported as 0.74 (Ghassemzadeh et al., 2005). In this study, the internal consistency (Cronbach α) of the scale was estimated at 0.9

Data collection: Nurses were selected from a list of names available in the nursing office and were informed of the study's objectives. Those who agreed to participate were provided with the research tools. The researcher in charge of collecting information made the arrangement with participants in advance to complete the questionnaire to their convenience. The participants were allowed to complete the questionnaires during their break time at the hospital or at home. An initial assessment was conducted prior to the administration of ARE (time 1: T1), followed by a second assessment 30 days after the administration (time 2: T2), and a third assessment 60 days afterward (time 3: T3).

***Data analysis*:** Data analysis was performed using the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the socio-demographic and clinical characteristics of each study group. The Kolmogorov-Smirnov test was used to determine normal distribution of the variables. Independent t-test, chi-square, and one-way ANOVA were used to compare demographic variables between the two groups. The repeated measures analysis of variance (ANOVA) and an independent samples t-test were used for the analysis of mean score of anxiety and sleep quality at T1, T2 and T3. Bonferroni post hoc test was also used for pairwise comparisons within groups. The Generalized Estimating Equations (GEE) test was also used to examine the effect of confounding variables on sleep quality. The level of significance for statistical tests was set at $p< 0.05$ (2-tailed). A complete-case analysis approach was used for the missing data. In this approach, participants with missing data were excluded from the analysis (Josheghani et al., 2024). The data for 29 people from the intervention group and 30 people from the control group were analyzed.

Results

During the study, three subjects in the intervention group (two persons due to tiredness and one due to hospitalization because of tibia fracture) and two subjects in the control group (one person due to tiredness and one because of forgetting to take medicine) were excluded from the study. These questionnaires were not included in the analysis and finally the data of 29 and 30 nurses from the intervention and control groups were analyzed, respectively (Figure 1).

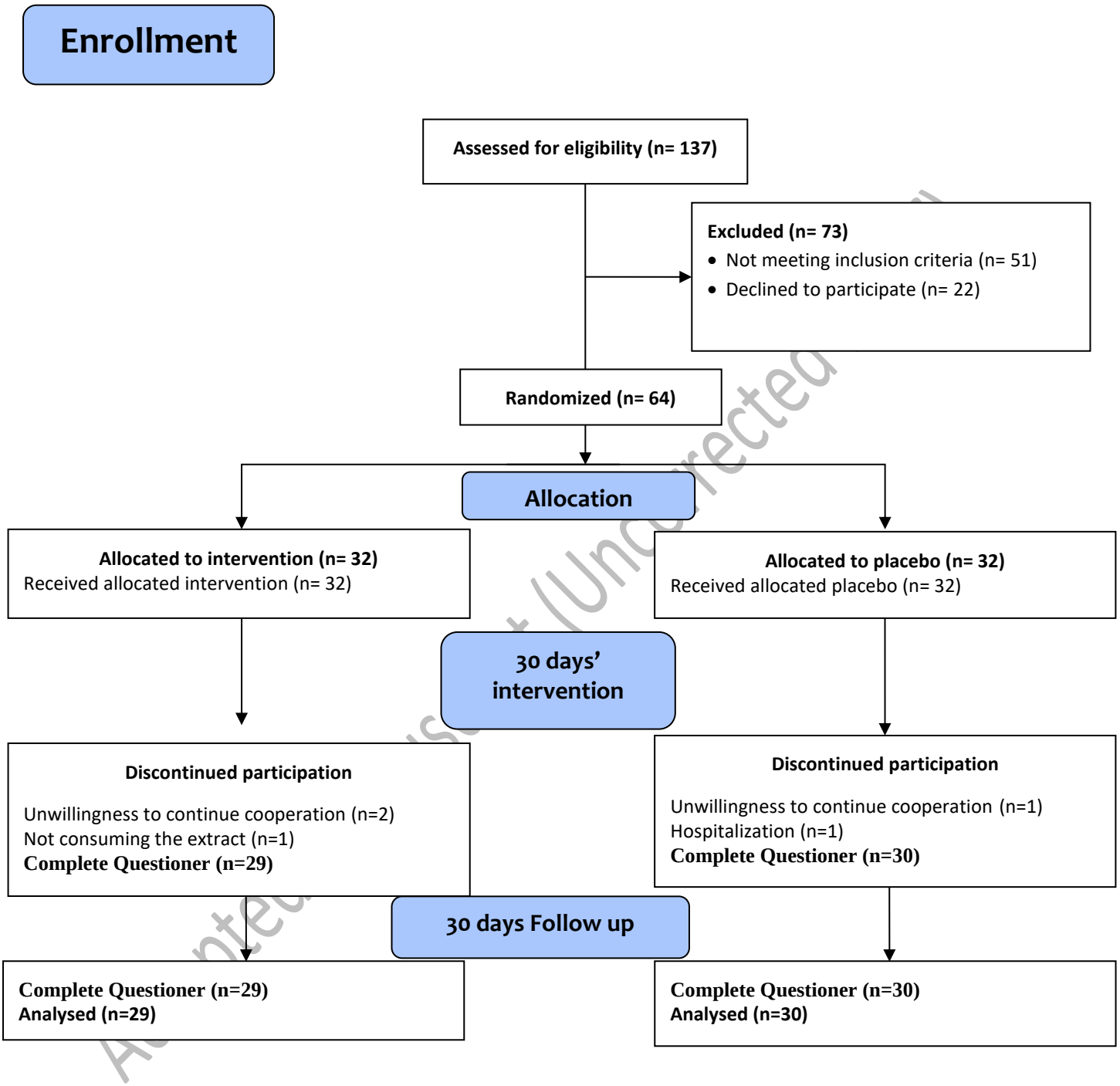

Figure 1- CONSORT flow diagram of the study process

The intervention and control groups differed significantly only in the number of children, while no significant differences were observed for the other variables (Table 1)

Table 1- Nurse's characteristics in the intervention and control group

Variable		**Intervention group**	**Control group**	**P value**
		Mean± SD	Mean± SD	
Age (year)		32.68±8.08	29.93±6.29	0.149[a]
Work experience(year)		8.65±7.18	6.76±6.26	0.286[a]
Working hours per month (hour)		179.89±53.35	175.76±50.91	0.762[a]
Infection to Covid-19 (number of times)		2.37±2.02	2.40±1.16	0.962[a]
Children (number)		1.0±1.19	0.86±0.66	0.014[a]
		N (%)	N (%)	
Sex	Female	14 (48.3%)	15 (50%)	0.89[b]
	Male	15 (51.7%)	15 (50%)	
Marital status	Single	12 (41.4%)	17 (56.7%)	0.87[b]
	Married	17 (58.6%)	13 (43.3%)	
Department	Medical	8 (27.6%)	8 (26.7%)	0.86[c]
	Surgery	7 (24.1%)	6 (20%)	
	Critical Care	8 (27.6%)	7 (23.3%)	
	Emergency	6 (20.7%)	9(30%)	
Shift work	Fixed (Morning/Night)	3 (10.3%)	4 (13.3%)	0.520[b]
	Rotation	26 (89.7%)	26 (86.7%)	
Level of education	Bachelor	24 (82.8%)	24 (80%)	0.87[b]
	Master	5 (17.2%)	6 (20%)	

SD: standard deviation; [a] independent t-test; [b] Chi Square; [c] One Way ANOVA

There were no significant differences between groups regarding sleep quality and anxiety at T1 (P>0.05). According to the results of the independent samples t-test, there was a statistically significant difference between the mean score of sleep quality in the ARE and control groups at the T2 and T3 (p<0.05). As shown by the repeated measures ANOVA, the changes in sleep quality scores in the ARE group were significant (p<0.001), and the Bonferroni post-hoc test also confirmed this significance between the T1 and the T2 as well as between the T1 and the T3. The results indicated a statistically significant difference over time between the two groups (p<0.05; Table 2).

Table 2- Comparison of the mean sleep quality score of nurses in the intervention and control groups in three measuring times

Time **Group**	**T_1**	**T_2**	**T_3**	**P value* Intergroup**	**Between Groups**	**Time*Group**	**Post hoc Bonferroni**
Intervention (n=29)	11.62±3.45	8.48±2.45	8.96±2.04	F=17.80 p<0.001 Effect size=0.38	Mauchly's Test of Sphericity: p=0.84 Sphericity Assumed	F=5.32 P=0.006 Effect size=0.085	**T_1 vs T_2: p<0.001** **T_1 vs T_3: p<0.001**
Control(n=30)	12.26±3.30	11.20±3.29	11.26±3.45	F=5.23 p=0.008 Effect size=0.15			**T_1 vs T_2: p=0.005** **T_1 vs T_3: p=0.023**
P Value**	0.46	0.001	0.003				

*Repeated measured ANOVA; T_1: time before intervention; T_2: time end of intervention; T_3: one month after end of intervention; ** independent t-test

The independent samples t-test also revealed a statistically significant difference between the mean anxiety scores of the ARE and control groups at T2 and T3 ($p<0.05$). The repeated measures ANOVA also indicated significant changes in the anxiety score of nurses in the ARE group ($p<0.001$). In addition, the Bonferroni post-hoc test showed a significant difference between the T1 and the T2, as well as the T1 and the T3. There was also a significant difference between the two groups over time ($P<0.05$; Table 3).

Table 3- Comparison of the mean anxiety score of nurses in the intervention and control groups in three measuring times

Time **Group**	**T_1**	**T_2**	**T_3**	**P value* Intergroup**	**Between Grous**	**Time * Group**	**Post hoc Bonferroni**
Intervention (n=29)	20.93±10.85	11.62±9.51	13.62±9.02	F=16.69 p<0.001 Effect size=0.37	Mauchly's Test of Sphericity: p=0.002 Greenhouse-Geisser	F=14.96 p<0.001 Effect size=0.20	T_1 vs T_2: p<0.001 T_1 vs T_3: p=0.002
Control(n=30)	17.90±9.23	16.70±6.85	18.16±8.27	F=1.07 p= 0.34 Effect size=0.03			-
P Value**	0.25	0.02	0.04				

*Repeated measured ANOVA; T_1: time before intervention; T_2: time end of intervention; T_3: one month after end of intervention; ** independent t-test

To assess the impact of confounding variables on anxiety and sleep quality, generalized estimating equations (GEE) were used, with confounders (department and history of Covid-19 infection) entered stepwise. After controlling for these variables, no significant difference in mean anxiety scores was found between the intervention and control groups ($\beta=5.60$, SE=3.02, $p=0.064$; Table 4), but the intervention group showed a significantly different trend in anxiety reduction over time ($\beta=-3.78$, SE=1.05, $p=0.0001$; Table 4).

Table 4- The results of GEE model to assess the effects of confounders on anxiety

Parameter	Beta coefficient	SD	df	P-value	95 % Wald confidence interval	
					Lower	Upper
Group (intervention)	5.60	3.02	3.44	0.064	-0.31	1.53
Time	0.13	0.44	0.08	0.76	-0.74	1.01
Group (intervention)* Time	-3.78	1.05	12.89	0.0001	-5.85	-1.72
History of Covid-19	1.28	0.56	5.24	0.02	0.18	2.38
Department (medical)	5.19	2.09	6.17	0.01	1.100	9.29
Department (surgical)	2.30	2.47	0.87	0.35	-2.54	7.15
Department (critical care)	6.33	2.58	6.03	0.01	1.27	1.39

Dependent variable: Anxiety

Nurses in medical (β=5.19, SE=2.09, p=0.01; Table 4) and critical care (β=6.33, SE=2.58, p=0.01; Table 4) departments, and those with more frequent Covid-19 infections (β=1.28, SE=0.56, p=0.02; Table 4), had higher anxiety scores compared to the emergency department. For sleep quality, no significant group difference was observed (β=-0.20, SE=1.07, p=0.84; Table 5), but the intervention group exhibited significant improvement over time (β=-0.74, SE=0.34, p=0.03; Table 5).

Table 5- The results of GEE model to assess the effects of confounders on sleep quality

Parameter	Beta coefficient	SD	df	P-value	95 % Wald confidence interval	
					Lower	Upper
Group (intervention)	-0.20	1.07	0.03	0.84	-2.32	1.91
Time	-0.49	0.17	0.08	0.76	-0.83	-0.14
Group (intervention)* Time	-0.74	0.34	4.72	0.03	-1.41	-0.07

Dependent variable: sleep quality; GEE: Generalized Estimating Equations

Discussion

The use of ARE demonstrated notable effectiveness in improving sleep quality and reducing anxiety among nurses affected by COVID-19. Over time, nurses in the ARE group showed statistically significant improvement in sleep scores, whereas the control group exhibited minimal change. This finding aligns with earlier research indicating the sleep-enhancing properties of Astragalus species (Shahrajabian et al., 2019). Li et al. (2023) reported that polysaccharides from Astragalus helped alleviate age-related sleep disorders, and Huang et al. (2019) found improvement in quality-of-life indicators including disturbed sleep. Zhang et al. (2013) found that Astragalus reduced hippocampal neuron apoptosis and oxidative markers while increasing protective enzymes like superoxide dismutase. Astragalus has also helped restore gut microbiota balance, which may support sleep regulation (Li et al., 2023).

Phytochemicals within Astragalus—including flavonoids, saponins, and polysaccharides—play a key role in its therapeutic effects (Sun et al., 2018). Saponins have been shown to extend sleep duration in animal studies (Jiang et al., 2007), while polysaccharides are linked to oxidative stress reduction and improved sleep via enhanced tricarboxylic acid cycle activity and neurotoxin elimination (Niu et al., 2018; Shao et al., 2004).

Interestingly, the control group also experienced a mild reduction in sleep disorder over time. Although no active substance was administered, psychological effects related to placebo may explain these improvements. Previous research has documented psychological influence resulting from placebo use (Lindheimer et al., 2020), and the natural passage of time could also be a contributing factor.

Beyond sleep, ARE significantly lowered anxiety levels of nurses recovering from COVID-19, with sustained effects for up to a month post-intervention. Similar anxiolytic benefits have been

observed in animal models using Astragaloside IV and Astragalus spinosus saponins (Abd Elkader et al., 2021; Oh et al., 2014). Other studies further support the neuroprotective and anti-anxiety effects of Astragalus (Jalsrai et al., 2019; Molodavkin et al., 1998; Bottles, 2022; Park et al., 2009; Yuan et al., 2024).

Anxiety is a multifaceted emotional response driven by neurotransmitter imbalance and dysfunction in key brain regions, such as the prefrontal cortex and hippocampus (Farb and Ratner, 2014). It involves altered signaling in serotonin, dopamine, and cannabinoid systems (Akter et al., 2020). Components like polysaccharides and saponins target these pathways and may relieve anxiety symptoms. Polysaccharides are recognized for their biological versatility and have shown anxiolytic activity in various models (Cui et al., 2013; Wang et al., 2018; Akter et al., 2020). Similarly, saponins and other plant-derived compounds like flavonoids and terpenes show calming effects and influence key stress-related mechanisms (Savage et al., 2018; Hosein Farzaei et al., 2016).

Stress activates the hypothalamo-pituitary-adrenal (HPA) axis, resulting in increased corticosterone and adrenocorticotropic hormone levels. Certain phytochemicals, including Astragalus polysaccharides, may modulate these responses. For instance, Ma et al. (2023) demonstrated a decrease in these hormones in rats, suggesting mood-stabilizing potential. The anxiolytic effects of ARE may also be related to interaction with GABA/benzodiazepine receptors, potentially explaining its influence on behavior and locomotor activity (Jalsrai et al., 2010).

The study yielded promising findings. However, the psychological conditions of the samples, which could be caused by forced overtime and irregular night shifts, were beyond the researchers' control and may have affected the results.

Conclusion

Using ARE can have a positive effect on the quality of sleep and reducing the anxiety of nurses suffering from Covid-19. Therefore, it can be used along with other therapies to treat sleep disorders and anxiety in this group. In order to increase the generalizability of the results, more extensive research is needed in this field to examine the effects of using this extract on the levels of hormones.

Ethical Considerations

Compliance with ethical guidelines

Ethical approval to conduct this research was obtained from Kashan university of medical sciences ethics committee (approval code: IR.KAUMS.NUHEPM.REC.1401.088) before the commencement of the study. The participants were informed that declining the invitation or withdrawing from the study at any time would not have any negative consequences. The participants provided written informed consent and were assured that their personal information would be kept confidential. The research was conducted in accordance with the Declaration of Helsinki. The research proposal for this manuscript has been registered to the Iranian registry of clinical trials (ID number: IRCT20100124003146N11) with the clinical trial registry (01 March 2023). Each listed author confirms that their research is supported by an institution that is primarily involved in education or research.

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