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# Articulo Original / Original Article Association between neuropsychological parameters and serum melatonin levels in individuals with tension-type headache treated with Qianyang Anshen formula

[Asociación entre parámetros neuropsicológicos y niveles séricos de melatonina en individuos con cefalea tensional tratados con la fórmula Qianyang Anshen]

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Lu L, Huang XY, Yuan GH, Peng HP. Association between neuropsychological parameters and serum melatonin levels in individuals with tension-type headache treated with Qianyang Anshen formula **Bol Latinoam Caribe Plant Med Aromat** 24 (5): 843 - 852 (2025) https://doi.org/10.37360/blacpma.25.24.5.58 **Abstract:** This study aimed to explore the relationship between neuropsychological parameters and serum melatonin levels in individuals with tension-type headache (TTH) treated with the Qianyang Anshen Formula, compared to Western medicine treatment with flunarizine. A total of 60 patients diagnosed with TTH were randomly assigned to receive either the Qianyang Anshen Formula (n=30) or flunarizine (n=30) for a 4-week treatment period. The Qianyang Anshen Formula group received one daily dose of the TCM formula, while the flunarizine group received 5 mg of flunarizine daily. After 4 weeks of treatment, the Qianyang Anshen Formula group demonstrated a total effective rate of 90%, significantly higher than the flunarizine group (73.3%, p<0.01). The Qianyang Anshen Formula outperformed flunarizine in improving neuropsychological outcomes and melatonin levels in TTH patients, suggesting it may alleviate TTH symptoms and related anxiety/sleep issues via melatonin regulation.

Keywords: Anxiety; Insomnia; Qianyang Anshen Formula; Serum melatonin; Tension-type headache.

**Resumen:** Este estudio tuvo como objetivo explorar la relación entre parámetros neuropsicológicos y niveles séricos de melatonina en individuos con cefalea tensional (CT) tratados con la fórmula Qianyang Anshen, en comparación con el tratamiento con medicina occidental mediante flunarizina. Un total de 60 pacientes diagnosticados con CT fueron asignados aleatoriamente para recibir la fórmula Qianyang Anshen (n=30) o flunarizina (n=30) para un período de tratamiento de 4 semanas. El grupo tratado con la fórmula Qianyang Anshen (n=30) o flunarizina (n=30) para un período de tratamiento de 4 semanas. El grupo tratado con la fórmula Qianyang Anshen (n=30) de flunarizina de la fórmula de medicina tradicional china, mientras que el grupo de flunarizina recibió 5 mg diarios de este medicamento. Después de 4 semanas de tratamiento, el grupo de la fórmula Qianyang Anshen mostró una tasa total de efectividad del 90%, significativamente mayor que el grupo de flunarizina (73.3%, p < 0.01). La fórmula Qianyang Anshen superó a la flunarizina en la mejora de los resultados neuropsicológicos y los niveles de melatonina en pacientes con CT, sugiriendo que puede aliviar los síntomas de la CT y los problemas relacionados de ansiedad y sueño mediante la regulación de la melatonina.

Palabras clave: Ansiedad; Insomnio; Fórmula Qianyang Anshen; Melatonina sérica; Cefalea tensional

## INTRODUCTION

Headaches are among the leading causes of disability worldwide, with severe or frequent episodes imposing a significant burden on individuals, families, and society (Leonardi et al., 1998; Vos et al., 2012). Tension-type headache (TTH) is the most common form of headache and the second most prevalent disease globally, following dental caries (Martelleti et al., 2013). Compared to migraines. TTH has been relatively underexplored (Jensen, 2018). TTH has become a major public health issue, leading to widespread health losses, impaired quality of life, and productivity decline (Stovner et al., 2007; Steiner et al., 2015; Stovner et al., 2018). In China, the increase in TTH cases and the years lived with disability present ongoing health challenges (Yao et al., 2019). Studies demonstrate that individuals with TTH experience reduced sleep duration, decreased sleep efficiency, prolonged sleep onset latency, frequent awakenings, and significantly reduced slow-wave sleep (Drake et al., 1990). Research by Houle et al. diary-based records has using demonstrated correlations between stress, sleep duration, and headache severity. Qianyang Anshen Formula (QYAF) exerts its therapeutic effects through a synergistic mechanism, wherein MT-enhancing herbs elevate melatonin levels, while anxiolytic components alleviate anxiety, collectively improving TTH and associated neuropsychological symptoms outcomes (Houle et al., 2012; Auld et al., 2017).

The TCM diagnostic criteria for TTH, particularly liver yang hyperactivity syndrome, integrate physical symptoms (e.g., headache, constipation), emotional distress (anxiety, irritability), and clinical signs (red tongue with yellow coating, thready and wiry pulse), effectively reflecting the biopsychosocial profile of TTH. In TCM research, challenges such as herbal standardization and placebo effects must be addressed. Variations in herbal composition can affect treatment efficacy, while placebo responses may complicate outcome assessments, highlighting the need for rigorous methodologies and quality control.

Melatonin (MT) regulates biological rhythms, promotes sleep, and possesses analgesic, sedative, antioxidant, free radical-scavenging, and immuneenhancing properties (Xiao *et al.*, 2014). Research indicates that individuals experiencing headaches often exhibit reduced MT levels, disrupted secretion rhythms, and are prone to neuropsychological conditions such as sleep disorders and anxiety (Tao *et al.*, 2019). This study examined the effects of Qianyang Anshen Formula on neuropsychological parameters and serum MT levels in patients with TTH. Changes in clinical scores and biochemical parameters were observed, and the correlation between neuropsychological factors and serum MT levels were analyzed.

The Qianyang Anshen Formula innovates by integrating MT-enhancing herbs with anxiolytic components, offering a novel therapeutic approach that addresses both physical symptoms and neuropsychological comorbidities of TTH. Moreover, QYAF has been shown to improve headache symptoms in clinical use without causing side effects, distinguishing it from existing TCM or MT-based therapies.

# MATERIAL NAD METHODS

#### Clinical study

#### Participants and methods

A total of 60 patients diagnosed with TTH who visited the outpatient department of this hospital between January and December 2023 were enrolled in the study. Participants were randomly assigned to two groups using a random number table: 30 patients in the Qianyang Anshen Formula group and 30 in the Flunarizine group. An additional 30 healthy individuals undergoing routine physical examinations at the hospital during the same period were assigned to the healthy control group. Participants in the Qianyang Anshen Formula group received treatment with the formula for 4 weeks. Neuropsychological assessments were conducted using the Hamilton Anxiety Scale (HAMA) and Pittsburgh Sleep Quality Index (PSQI), while serum MT levels were measured using ELISA. The study aimed to evaluate the association between neuropsychological parameters and serum MT levels in individuals with TTH following treatment with Qianyang Anshen Formula. Data were recorded and subjected to statistical analysis to determine the relationship between neuropsychological outcomes and serum MT levels. A technical roadmap summarizing the study design is presented in Figure No. 1.

## Diagnostic criteria

## Western medicine diagnostic criteria

The diagnosis of TTH was established based on the standards outlined in the International Classification of Headache Disorders (3<sup>rd</sup> edition). The criteria are as follows (Ettlin, 2013):

(1) The duration of the headache ranges from 30 minutes to one week.

(2) The headache is characterized by at least two of the following criteria: (1) bilateral; (2) non-pulsating, described as pressing or tight; (3) mild to moderate in intensity; (4) not aggravated by routine activities.

(3) Presence of phonophobia or photophobia, without accompanying nausea or vomiting.

(4) Other headache disorders must be excluded.

# Traditional Chinese medicine (TCM) diagnostic criteria

The diagnostic framework adhered to the diagnostic and efficacy evaluation criteria for head wind, as well as the Syndrome Section of the Terminology for Traditional Chinese Medicine Clinical Diagnosis and Treatment (Criteria for Diagnosis *et al.*, 1993; Shanghai University *et al.*, 2021): The primary symptom is distension pain on both sides of the head.

Secondary symptoms include dry mouth, bitter taste, flushed face, red eyes, irritability, insomnia with vivid dreams, distension pain in the bilateral hypochondria, menstrual irregularities in women, and constipation. Tongue appearing red with a yellow coating, and thready and wiry pulse.

The diagnosis of headache with liver yang hyperactivity syndrome was confirmed when the primary symptom was observed along with two or more secondary symptoms and corresponding tongue and pulse characteristics.

#### Inclusion criteria

(1) Diagnosed with TTH according to the Western medicine diagnostic criteria.

(2) Diagnosed with headache with liver yang hyperactivity syndrome according to the TCM diagnostic criteria.

(3) No abnormalities detected on head CT or MRI.

(4) No history of other medication use within the past six months.

(5) Voluntary participation, with signed informed consent provided.

Approval for the study was obtained from the medical ethics committee.

## Exclusion criteria

(1) Non-compliance with the inclusion criteria.

(2) Individuals older than 65 years of age.

(3) Diagnosed with other primary headache disorders, excluding TTH.

(4) Required analgesics or other related medications.

(5) Diagnosed with severe organic diseases that may affect the study's assessments.

(6) Had communication difficulties or unable to

perform self-care.

#### Withdrawal and dropout criteria

(1) Research participants who demonstrated noncompliance with study requirements or actively requested withdrawal from the study.

(2) Deviated from the prescribed treatment protocol.

(3) Failed to attend visits consistently, did not complete the treatment course, or had inadequate follow-up.

(4) Experienced severe adverse drug reactions during treatment.

(5) Initiated the use of medications that could interfere with the study treatment.

Participants meeting any of the above conditions were excluded from further participation, and their involvement in the study was terminated.

#### Treatment methods General information

A total of 90 subjects who met the inclusion criteria were included in this study and were divided into three groups using the random number table method: the observation group, the control group, and the healthy group, with 30 cases in each group (Table No. S1). There was no statistically significant difference in basic information such as gender and age among the three groups (p>0.05), indicating that the study met the requirements. Specifically, the age of the subjects ranged from 19 to 64 years, and the age distribution met the study requirements (p>0.05). In terms of gender, in the traditional Chinese medicine group (observation group), there were 14 males (46.7%) and 16 females (53.3%); in the Western medicine group (control group), there were 18 males (60%) and 12 females (40%); in the healthy group, there were 14 males (46.7%) and 16 females (53.3%). and the gender distribution met the study requirements (p>0.05). In addition, the disease duration of patients with tension - type headache ranged from 1 month to 36 months, and the disease duration distribution also met the study requirements (*p*>0.05).

## Qianyang Anshen Formula group

The Qianyang Anshen Formula is derived from the modified version of Gastrodiae Uncariae Decoction, as documented in the book *New Theories and Practices on the Treatment of Internal Medicine Diseases in Traditional Chinese Medicine*.

The Qianyang Anshen Formula group received the TCM formula Qianyang Anshen Formula, which consisted of the following

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components: 10 g of Gastrodiae Rhizoma, 30 g of *Uncariae ramulus* cum Uncis (added later), 30 g of *Haliotidis concha* (added first), 10 g of *Gardeniae* fructus, 10 g of *Scutellariae* radix, 15 g of *Achyranthis bidentatae* Radix, 10 g of *Eucommiae* cortex, 15 g of *Taxilli* herba, 15 g of *Polygoni multiflori caulis*, and 30 g of *Sclerotium* poriae pararadicis. A daily dose of 400 ml was decocted, divided into two 200 ml doses, administered in the morning and evening. The treatment was provided for 4 weeks, completing one course of therapy.

# Flunarizine group

The Flunarizine group received flunarizine capsules (5 mg, manufacturer: Xi'an Janssen Pharmaceutical Ltd., specification: 5 mg  $\times$  20 capsules/box). The prescribed dosage was 1 capsule taken once daily, 1 hour before bedtime. The treatment regimen lasted 4 weeks, completing one course of therapy.

## Efficacy observation

## **Observation indicators**

The headache index, TCM syndrome score, HAMA score, PSQI score, and serum MT levels of the participants were recorded.

## Blood sample collection and processing

Peripheral venous blood samples (2 mL) were collected from participants prior to 9:00 a.m. The samples were centrifuged at 1,000 g for 20 minutes (Xie *et al.*, 2019). The supernatant was then collected. Serum MT concentration in peripheral blood was measured using the ELISA kit (brand: Elabscience; instrument: Tecan fully automated enzyme immunoassay analyzer) in accordance with the manufacturer's instructions.

## Safety indicators

Safety monitoring included the following assessments: Complete blood count (CBC), urinalysis, liver function tests, renal function tests, and electrocardiogram (ECG).

## Statistical analysis

The monitoring database was established using EpiData 3.0 software, and statistical analysis was conducted with SPSS 16.0 software. Following an assessment of normality and homogeneity of variance, continuous variables with a normal distribution were

expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). Intergroup comparisons were made using independent sample t-tests, paired t-tests, and analysis of variance (ANOVA). Non-normally distributed data were expressed as median and interquartile range (M, P25-P75), with inter-group comparisons performed using the rank-sum test (Kruskal-Wallis test). Categorical data were expressed as rates or percentages, with inter-group comparisons conducted using the chisquared ( $\chi^2$ ) test. Statistical significance was set at  $\alpha$ = 0.05.

## **Research findings**

# Comparison of pre-treatment HAMA scores

Prior to treatment, the HAMA scores in both the Qianyang Anshen Formula group and the Flunarizine group were significantly higher than those in the healthy control group (p<0.01). However, no significant difference was observed between the Qianyang Anshen Formula medicine and Flunarizine groups (p>0.05), indicating comparability (see Table No. 1).

# Comparison of pre-treatment PSQI scores

Before treatment, the PSQI scores in both the Qianyang Anshen Formula group and the Flunarizine group were significantly higher than those in the healthy control group (p<0.01). No significant difference was observed between the Qianyang Anshen Formula and Flunarizine groups (p>0.05), indicating comparability (see Table No. 1).

# 2.3 Comparison of pre-treatment serum MT levels

Prior to treatment, the serum MT levels in both the Qianyang Anshen Formula group and the Flunarizine group were significantly lower than those in the healthy control group (p<0.01). No significant difference was observed between the Qianyang Anshen Formula and Flunarizine groups (p>0.05), indicating comparability (Table No. 1).

# Comparison of Visual Analogue Scale (VAS) scores before and after treatment

**Intra-group comparison**: A statistically significant difference in VAS scores before and after treatment was observed within both, the Qianyang Anshen Formula and Flunarizine groups (p<0.01). **Inter-group comparison**: No significant difference in VAS scores was found between the two groups during the same period (p>0.05) (Table No. 2).

#### Efficacy analysis: Comparison of headache duration scores before and after treatment

Intra-group comparison: Headache duration scores significantly decreased in both groups after 4 weeks of treatment compared to baseline, with a statistically significant difference observed (p<0.01). Inter-group comparison: No significant difference in headache duration scores was found between the the Oianvang Anshen Formula and Flunarizine groups after 4 weeks of treatment (p>0.05) (Table No. 3).

Table No. 1   Comparison of HAMA scores, PSQI scores, and serum MT levels before treatment					
Group	n	HAMA score ( $\bar{x} \pm s$ , point)	<b>PSQI score</b> $(\bar{x} \pm s, point)$	Serum MT level (Pg/mL)	
Qianyang Anshen Formula group group	30	15.57±4.02°	13.20 ±3.199°	22.83±4.53°	
Flunarizine group	30	$14.97\pm3.34^{\circ}$	11.71 ± 3.914°	$24.94\pm5.70^{\circ}$	
Control group	30	$3.80 \pm 1.80^{ab}$	$4.27\pm1.706^{ab}$	$31.59\pm6.67^{ab}$	
F		129.21	71.89	19.245	
<i>p</i> -value		< 0.01	< 0.01	< 0.01	

Note: Under the same index,  ${}^{a}p<0.05$  vs. Qianyang Anshen Formula group, <sup>b</sup>p<0.05 vs. Flunarizine group, <sup>c</sup>p<0.05 vs. control group

Table No. 2 Comparison of VAS scores before and after treatment ( $\bar{x} \pm s$ , point)							
Group	n		VAS score	Intra-group <i>p</i> -value pre-			
		Pre-treatment	Post-treatment	and post-treatment			
Qianyang Anshen Formula group	30	$3.90 \pm 1.58$	$2.00\pm1.08$	<0.01			
Flunarizine group	30	$4.30 \pm 1.69$	$1.60 \pm 1.38$	<0.01			
t		1.013	1.249				
<i>p</i> -value		0.274	0.217				

Table No. 2
Comparison of VAS scores before and after treatment ( $\bar{x} \pm s$ , point)

Table No. 3Comparison of headache duration score and headache index before and after treatment ( $\bar{x} \pm s$ , point)						
Group	H	leadache duration score	Headache index			
	<b>Pre-treatment</b>	Post-treatment	Pre-treatment	Post-treatment		
Qianyang Anshen Formula group	$2.77 \pm 1.073$	$0.97 \pm 0.718^*$	$10.67 \pm 6.35$	2.27 ± 2.10*		
Flunarizine group <i>p</i> -value	$3.07 \pm 1.081 \\ 0.316^{\Delta}$	$1.03 \pm 0.85^{**}$ $0.744^{\Delta\Delta}$	$\begin{array}{c} 13.60 \pm 6.11 \\ 0.109^{\Delta} \end{array}$	$2.67 \pm 2.56^{**}$ $0.915^{\Delta\Delta}$		

# Comparison of headache index before and after treatment

Intra-group comparison: The headache index significantly decreased in both, the Qianyang Anshen Formula and Flunarizine groups, after 4 weeks of treatment compared to baseline, with a statistically significant difference (*p*<0.01). Inter-group comparison: No significant difference in the headache index was observed between the groups after 4 weeks of treatment (p>0.05) (Table No. 3).

## Comparison of TCM syndrome scores before and after treatment

Intra-group comparison: TCM syndrome scores significantly decreased in both, the Qianyang Anshen Formula and Flunarizine groups after 4 weeks of

treatment compared to baseline, with a statistically significant difference observed (*p*<0.01). Inter-group comparison: Statistical analysis of the TCM syndrome scores at the same time point revealed a statistically significant difference between the groups after 4 weeks of treatment ( $\Delta\Delta p < 0.05$ ) (Table No. 4).

#### Comparison of HAMA scores before and after treatment

Intra-group comparison: Both, the Qianyang Anshen Formula group and the Flunarizine group demonstrated a significant decrease in HAMA scores after treatment, with the difference being statistically significant (p<0.01). Inter-group comparison: After treatment, the HAMA score in the Qianyang Anshen Formula group was significantly lower than that in the Flunarizine group, with the difference being statistically significant (p < 0.01) (Table No. 5).

#### Comparison of PSQI scores before and after treatment

Intra-group comparison: Both the Qianyang Anshen Formula group and the Flunarizine group demonstrated a significant decrease in PSOI scores after treatment, with the difference being statistically significant (p<0.01). Inter-group comparison: The Qianyang Anshen Formula group exhibited a larger decrease in PSOI scores compared to the Flunarizine group, with the difference being statistically significant (p < 0.01) (Table No. 5).

Table No. 4Comparison of TCM syndrome scores before and after treatment ( $\bar{x} \pm s$ , point)						
TCM syndrome score						
Pre-treatment	Post-treatment					
$23.33 \pm 3.66$	$9.17 \pm 1.60*$					
$23.60\pm3.31$	10.33 ± 2.33**					
0.769 <sup>Δ</sup>	0.493					
	Table No. 4 ores before and after treatment ( $$ TCM sync Pre-treatment $23.33 \pm 3.66$ $23.60 \pm 3.31$ $0.769^{\Delta}$					

Note: p<0.01, \*\*p < 0.01 vs. before treatment. p>0.05, ap>0.05 vs. inter-group comparison during the same time period

[ score
l score
-
Difference - before and tment after treatment
3±1.62 <sup>Δ</sup> 10.10±2.928
±1.85 <sup>ΔΔ</sup> 7.47±4.158
1.99 2.836
< 0.01 < 0.01

# Table No. 5

## Comparison of serum MT levels before and after treatment

Intra-group comparison: Following treatment, the serum MT levels in both the Qianyang Anshen Formula group and the Flunarizine group significantly increased, with the difference being statistically significant (*p*<0.01). Inter-group comparison: The difference in serum MT levels between the Qianyang Anshen Formula and Flunarizine groups was statistically significant, with the Qianyang Anshen Formula group showing a greater increase than the Flunarizine group (\*p < 0.05). There was no significant difference between the Qianyang Anshen Formula/Flunarizine groups and

the healthy control group (p>0.05) (Table No. 6).

# Comparison of overall clinical efficacy after treatment

After treatment, a significant difference in overall clinical efficacy was observed between the Qianyang

Anshen Formula and Flunarizine groups (p<0.01). The total effective rate was 90.00% in the Qianyang Anshen Formula group and 73.3% in the Flunarizine group. The efficacy of the Qianyang Anshen Formula group was superior to that of the Flunarizine group (Table No. 7).

Table No. 6					
Comparison of serum MT level (pg/mL)					

		MT level					
Item	n	Pre-treatment	Post-treatment	Difference before and alfter treatment	Intra-group p-value before and after treatment		
Qianyang Anshen	30	$22.83 \pm 4.53$	$34.82\pm5.03$	$13.01\pm4.42$	< 0.01		
Formula group							
Flunarizine group	30	$24.94 \pm 5.70$	$28.83 \pm 8.23$	$6.82 \pm 8.21$	< 0.01		
Т		0.871	1.326	4.740			
<i>p</i> -value		0.25	0.005	<0.01			

Table No. 7

Comparison of overall clinical efficacy between the two groups after treatment

Item	n	Clinical	Markedl	Effective	Ineffective	Z	<i>p</i> -value
		cured					
Qianyang Anshen	30	7	10	10	3	2.64	< 0.01
Formula group							
Flunarizine group	30	3	5	14	8		

Note: After the rank sum test of two samples, *p*<0.01 denotes statistically significant difference

#### DISCUSSION

In this study, efficacy was assessed through clinical cure rates, marked effectiveness, and overall symptom improvement, with the Qianyang Anshen Formula group showing superior outcomes compared to the Flunarizine group. The significant increase in serum melatonin levels in the QYAF group suggests a potential mechanistic link between MT regulation and symptom relief in tension-type headache. Given that MT is known for its sleep-enhancing and analgesic properties, the observed improvements in anxiety, sleep quality, and headache indices may be attributed to the MT-elevating effects of QYAF. Prior to treatment, the HAMA and PSQI scores in patients with TTH were significantly higher than those in the healthy control group, indicating that patients with TTH frequently experience anxiety and poor sleep. Kim et al. found that insomnia is common among patients with TTH, and insomnia, TTH, and anxiety often co-occur (Kim et al., 2017). Insomnia can exacerbate both headache and anxiety symptoms in patients with TTH, which aligns with the findings of this study.

Anxiety leads to chronic contraction of head and neck muscles, which intensifies the severity of TTH. Additionally, poor sleep quality, which constitutes a significant portion of an individual's life, adversely affects work productivity, quality of life, and overall health. Mayer et al. suggested that the comorbidity of headaches, anxiety, and insomnia is related to neurodegenerative, traumatic, ischemic, and inflammatory changes in the brainstem and hypothalamic nuclei, as well as alterations in neurotransmitter systems (Mayer *et al.*, 2021). They proposed that patients may benefit from treatments aimed at regulating MT levels, mood-enhancing medications, and cognitive-behavioral therapy.

The relationship between TTH and emotional anxiety can be summarized as follows: The brain's pain processing system involves primary structures such as the lateral cortex and insular cortex, as well as internal systems involved in emotional responses, including the cingulate gyrus and hippocampus. Although cranial imaging techniques such as CT

scans typically reveal no abnormalities in patients with TTH, advancements in neuroimaging have identified reductions in gray matter volume in individuals with chronic TTH. Research suggests that the abnormal mechanisms underlying pain and anxiety in TTH are both linked to changes in the occipital lobe (Frick *et al.*, 2014).

The relationship between TTH and sleep disorders is also significant. Luigi et al. indicated that both sleep deprivation or excessive sleep, forms of sleep disorder, are often reported as triggers for acute TTH episodes (Ferini-Strambi et al., 2019). Studies suggest that headaches and sleep disorders may manifest as dysfunctions in the same system. Patients with TTH and poor sleep experience more frequent headache attacks, creating a vicious cycle between TTH and sleep disorders. Therefore, addressing both symptoms and underlying causes when managing anxiety and sleep disorders coexisting with TTH is essential. Effective diagnosis and treatment of these conditions not only improve treatment outcomes but also improve the patient's overall quality of life. Koreshkina suggested that the use of  $\beta$ -phenyl- $\gamma$ aminobutyric acid (Noofen) could improve sleep, cognitive impairment, and relieve headaches (Koreshkina, 2021).

In the treatment of TTH with TCM, the Qianyang Anshen formula demonstrated significant efficacy in alleviating anxiety and improving sleep disorders. This formula demonstrated superior outcomes compared to the Flunarizine group. The observed benefits may be attributed to the sedative and sleep-promoting properties of key ingredients in the Qianyang Anshen formula, including Gastrodiae Rhizoma, Uncariae Ramulus cum Uncis, Polygoni Multiflori Caulis, and Sclerotium Poriae Pararadicis. Contemporary pharmacological studies suggest that these TCM herbs target both the symptoms and underlying causes of the condition.

Prior to treatment, the serum MT levels in patients with TTH were significantly lower than those in the healthy control group. Following treatment with the Qianyang Anshen Formula, serum MT levels in patients with TTH increased significantly, nearing levels observed in healthy individuals. This suggests that the therapeutic mechanism of the Qianyang Anshen method in treating TTH may involve the regulation of serum MT levels. The Qianyang Anshen method appears effective in elevating MT levels in patients with TTH.

MT is naturally present in several TCM ingredients, including *Scutellariae Radix* (7,110 ng/g), *Cicadae Periostracum, Uncariae Ramulus cum Uncis, Mori Folium, Epimedii Folium, Taxilli Herba*, Poria, *Eucommiae Cortex, Ziziphi Spinosae Semen, Leonuri Herba* and *Polygoni Multiflori Caulis* (143 ng/g). Many of these herbs are characterized as cold in nature and bitter in taste, suggesting that their yang-subduing and mind-tranquilizing effects may resemble those of MT. It is plausible that they may contain MT or compounds with similar effects, exerting sedative, sleep-enhancing, and analgesic effects.

This study demonstrated that the use of TCM with the Qianyang Anshen formula effectively reduced HAMA and PSQI scores in patients with TTH, while also increasing serum MT levels. These findings suggest that the Qianyang Anshen method exerts sedative, sleep-enhancing, and analgesic effects. Consequently, this treatment may provide significant benefits for patients with TTH, addressing both physical symptoms of the condition and associated anxiety and sleep disturbances.

In summary, our study lies in elucidating the multifaceted role of melatonin in TTH management. By demonstrating significant improvements in both neuropsychological outcomes and serum MT levels with the Qianyang Anshen Formula, this research highlights MT's potential as a biomarker and therapeutic target. These findings challenge existing paradigms, suggesting that integrating MT regulation into TTH treatment could enhance clinical efficacy and patient quality of life. This work paves the way for future mechanistic studies and the development of novel, MT-focused interventions.

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