

Research Article

## The effect of aerobic exercise and herbal capsule (hydro-alcoholic extract of *Valeriana jatamansi* Jones ex Roxb. and *Melissa officinalis* L.) on changes in serotonin levels and headache indices in women with chronic tension-type headache

Zohreh Eskandari\*, Ghazale Mohammadi

Department of Sports Nutrition, Faculty of Social Sciences, Raja University, Qazvin, Iran

ARTICLE INFO	ABSTRACT
<p><b>Keywords:</b> Chronic tension-type headache <i>Valeriana jatamansi</i> <i>Melissa officinalis</i> Aerobic exercise Serotonin Headache indicators</p>	<p><b>Background:</b> Tension headache is the most common type of headache. <b>Objective:</b> The purpose of this study was to investigate the effect of aerobic exercise and herbal capsules on serotonin levels and headache indices in women suffering from chronic tension-type headache (CTTH). <b>Methods:</b> In this practical study, 18 adult female patients with CTTH were randomly divided into two equal groups: exercise and herbal capsule. Aerobic training was performed three sessions a week, each session lasting 75 minutes for eight week. The herbal capsule contained the hydro-alcoholic extract of <i>Valeriana jatamansi</i> and <i>Melissa officinalis</i>. Each capsule contained 280 mg of these two herbs, which the patients consumed three times a day. Serotonin levels, headache indices (intensity, duration, and frequency of headache), anxiety, depression, use of synthetic drugs, and aerobic capacity were evaluated at baseline and at the end of the study. <b>Results:</b> According to the results within the group, in both groups there was a significant increase in serotonin, aerobic capacity (only in the exercise group) and a significant decrease in anxiety, depression, headache intensity, headache frequency, headache duration (only in the exercise group) and the use of synthetic drugs. In the comparison between groups, a significant difference was observed in the intensity and frequency of headache, use of synthetic drugs, aerobic capacity and anxiety. <b>Conclusion:</b> Aerobic exercise and hydro-alcoholic extract of <i>Valeriana jatamansi</i> and <i>Melissa officinalis</i> plants can be a suitable treatment supplement for women suffering from CTTH but the effect of two plants was better in improving headache.</p>

### 1. Introduction

Tension headaches are the most common type of primary headache disorders and are often caused by stress, emotional and nervous

pressures [1]. Among its features, we can mention its bilaterality, pressing nature and a quality without throbbing. Patients with chronic tension-type headache (CTTH) have more than

**Abbreviations:** CTTH, Chronic tension-type headache; *V. jatamansi*, *Valeriana jatamansi*; *M. officinalis*, *Melissa officinalis*

\*Corresponding author: [Z.Eskandari@raja.ac.ir](mailto:Z.Eskandari@raja.ac.ir)

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15 headache days per month [2]. Researchers mentioned the sensitivity of pericranial myofascial tissues and central sensitivity (increased excitability of neurons) as the cause of CTTH [3]. Also, serotonin is one of the nerve mediators whose increase in CTTH patients helps to stop pain [4, 5]. In the study of Karakulova (2014), the amount of serotonin in CTTH patients was low and the amount of anxiety and depression was high. He concluded that there is an inverse relationship between serotonin concentration and anxiety and depression [6]. Herbal medicines and aerobic activity can be used as a supplement and even a suitable alternative for the treatment and prevention of headache due to less side effects than synthetic medicines [7, 8].

The plants of *Valeriana jatamansi* (valerian) and *Melissa officinalis* (or lemon balm) are widely used and have no side effects [7]. In several studies, their properties for treating sleep disorders, stress, depression, anxiety, muscle spasm, migraine and painful menstruation have been mentioned. In the study of Gholamreza Mirzaei et al (2013), consumption of valerian capsules (350 mg) by migraine patients for 45 days and three times a day caused a significant reduction in the number, length and intensity of migraine attacks [9]. Muller and Klement (2006) used the combination of these two plants to reduce anxiety symptoms in children under 12 years old [10]. In some other studies, the combination of these two plants reduced anxiety and sleep disorders [11, 12].

In Iranian traditional medicine, the combination of these two plants with other plants is used as a decoction to reduce pain and headache. It has been reported that valerianic acid, valeranal, and valepotriate from valerian extract derivatives can exert their sedative and analgesic effects by acting on GABA, adenosine,

and benzodiazepine receptors [13, 14]. Also, by opening potassium channels and blocking calcium channels, valerian causes muscle relaxation and antispasmodic effects [15] and on the other hand, by activating serotonin receptors, it increases serotonin and as a result has anti-anxiety and sleep-inducing effects [16-18].

Research on the effect of *Melissa officinalis* (*M. officinalis*) and the combination of these two plants on serotonin has not been done, but the anti-anxiety and calming properties of *M. officinalis* have been confirmed and attributed to the flavonoids in the plant, which strengthen this inhibitory system in the brain through the GABA mechanism [19]. Regarding the effect of *V. jatamansi* and *M. officinalis* on CTTH stimulating factors; stress, anxiety, depression, fatigue, insomnia; [8] it seems that the combination of these two herbs can help treat headaches.

Aerobic activity is one of the non-pharmacological methods whose effect on tension headache has been investigated very little. In several studies, aerobic exercise improved headache status and attributed the improvement to increased endogenous opioids and serotonin and reduced anxiety and depression induced by aerobic exercise [8, 20, 21]. Therefore, according to the few studies in this field, the aim of this study is to investigate the effect of herbal capsule (*V. jatamansi* and *M. officinalis*) and aerobic exercise as two therapeutic methods on serotonin, headache indicators, anxiety and depression in patients with CTTH.

## 2. Materials and Methods

The present research is an applied study. 50 people announced their readiness to participate in the research, which was done through

advertisements in public places of Qazvin city, including several sports clubs, several universities, social networks and a clinic. Criteria for entering the study include: signing the consent form, diagnosis of chronic tension headache according to IHS and ICHD guidelines, women between 18-45 years old, chronic tension headache with recurrence of at least 15 attacks per month.

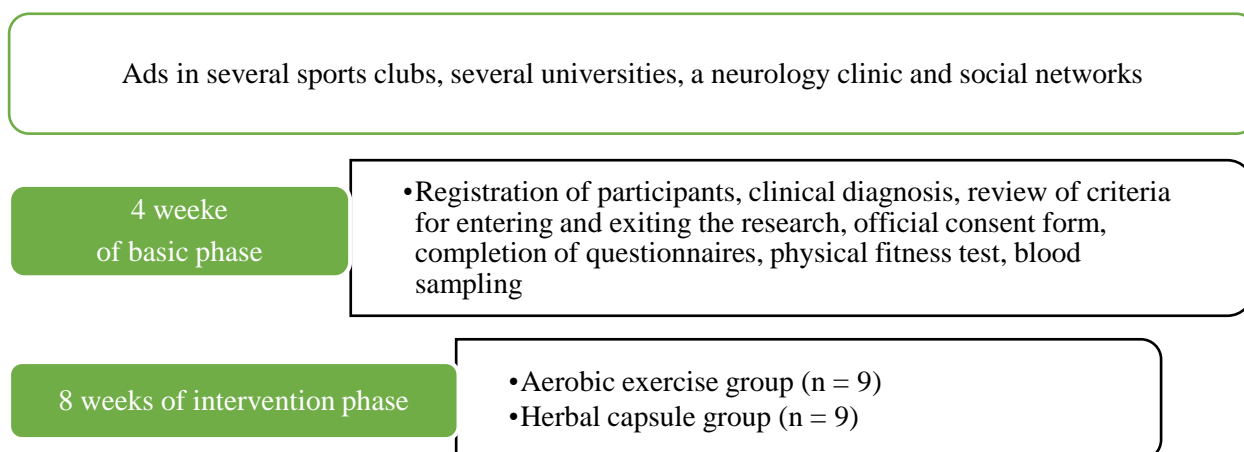
Exclusion criteria from the study include: periodic headache that cannot be distinguished from migraine and tension-type headache, pregnant women and lactating women, use of tension-type headache preventive drugs, serotonergic drugs, antidepressants, and use of sleep medications during the 12 weeks before the study, secondary headaches, Injuries to the head or neck in the last 2 years, occurrence of serious suicidal thoughts, diseases and disabilities limiting aerobic activity, smoking, Having regular aerobic exercise more than once a week during the 12 weeks before participating in the study, patients with hypothyroidism (*M. officinalis* has a negative effect on hypothyroid patients).

Finally, 18 eligible people were selected and randomly divided into two groups: 1- aerobic training (n = 9) and 2- herbal capsules (n = 9). Before entering the treatment phase, the subjects completed the daily headache questionnaire every day for a period of one month (baseline phase) so that it's content can be used as a basis for comparing the effects of the two treatment methods. At this stage, blood sampling and a modified aerobic test (Balke) were taken. The parameters evaluated in the research included serum serotonin, aerobic capacity (Vo<sub>2</sub>max), headache indices including headache frequency (days/month), headache intensity, headache duration, anxiety and depression at the baseline level and at the end of the intervention phase. To

evaluate serotonin, 5 ml of blood was taken from the left brachial vein in the fasting state in the follicular phase. Then the blood samples were placed inside the centrifuge with 2000-3000 rpm for 10 minutes. After separating the serum, the samples were immediately stored at a temperature below 24 °C. Blood samples were analyzed by ELISA method and serotonin kit (with evaluation range of 25 ng/ml-600 ng/ml and sensitivity of 12.2 ng/ml) with ZellBio brand made in Germany under the supervision of a laboratory specialist.

To complete the daily headache questionnaire, the patients were instructed to complete it every day and hand it over to the researcher at the end of the study. This questionnaire measures the intensity, duration and frequency of headache attacks, the number of painkillers used (dose, injection, nasal spray and suppository), the area and type of pain, fear of light, fear of sound and headache provoking factors.

A score of 1 to 10 was used to determine the severity of headache attacks (score 1 for a very mild headache attack that accompanies daily activities and score 10 for a severe headache attack that requires bed rest or leads to daily inactivity) becomes). Repetition of attacks was measured and calculated by calculating the total number of days of headache during a certain period and the average duration of headache by calculating the total number of hours a person had a headache during a period divided by the repetition of attacks in the same period. Patients completed the headache diary questionnaire every day for 4 weeks of the baseline phase and 8 weeks of the intervention phase. Beck anxiety and depression questionnaires were used to measure anxiety and depression. Aerobic capacity was also measured through the modified Balke test on days when subjects did not have headache.



**Fig. 1. Research process**

### 2.1. Aerobic exercise

The patients who were in the exercise group did aerobic exercise 3 times a week for 8 weeks under the supervision of the researcher in the gym. Aerobic exercise consisted of running, aerobic exercises and various ball games. In the first week, the exercise duration started with 45 minutes and in the final weeks it reached 75 minutes. Exercise intensity during training sessions averaged between 50 and 85 % of maximum heart rate. Subjects were instructed to perform the defined activity at home, public gymnasium or parks around their residence during their absence in some sessions due to headache with the same intensity and duration as aerobic exercise in the gym. Also, videos of exercises similar to the movements performed in the gym were sent to them through virtual networks. Subjects who did not perform aerobic exercises more than 3 times a month or did not deliver the questionnaires were excluded from the study.

### 2.2. Herbal capsule group

Patients in the herbal capsule group take 2 capsules daily in the first month; one number in the day shift and one number in the night shift; and in the second month, 3 numbers; two capsules during the day and one during the night; consumed. Subjects who did not consume the

capsules regularly or at all and did not complete the questionnaires were excluded from the study.

### 2.3. Preparation method of powdered extract

To prepare the extract, the root and rhizome of the *V. jatamansi* plant and the leaves and branches of the *M. officinalis* plant were purchased from a reputable perfumer in Qazvin city. Then they were identified and confirmed by medicinal plant specialists. After confirming the species of the plants, the extract process was carried out in the Research Institute of Medicinal Plants located in Karaj city. The steps of extraction were as follows. The plants were crushed and turned into powder by an electric mill. The powder was passed through a 16 mesh sieve and then the homogenized powder was mixed with hydro-alcoholic solvent (70 % ethanol and 30 % water).

The ratio of plant to solvent was chosen as 1 to 10, that is, 10 liters of solvent were used for each kilogram of plant powder. The soaked mixture was placed at 55 °C for 8 hours. The extracted mixture was filtered. The solution obtained from the filtration was transferred to a rotary device to remove the excess solvent and concentrate, and at a temperature of 50 °C, some alcohol was separated from the extract and

evaporated. But still about 15 % alcohol remained in the extract. At the end, the concentrated extract was made into a dried powder by a spray dryer (Spray dryer machine made in Iran, by rotating the atomizer disk 20000, 50 liters of evaporation per hour, nominal capacity, inlet temperature 180 °C, outlet temperature 75 °C). In fact, the spray dryer atomizes the liquid (turning the material into small particles), which causes more contact of the hot air with the atomized droplets. Then the hot air of the spray dryer removes their moisture

and causes the liquid to dry quickly and turn it into a solid powder. The extraction of two plants was done separately but with the same recipe. The extract powder was poured into 500 mg capsules by a capsule filling machine (Manual capsule filling machine made in Iran, for 500 mg capsules). Each capsule contained 200 mg of *V. jatamansi* extract, 80 mg of *M. officinalis* extract and some maltodextrin as a filler. The selected dose was exactly based on the studies of Müller & Klement (2006) and Taavoni & Haghani (2013) [10, 12].



Fig. 2. *Valeriana jatamansi* plant



Fig. 3. *Melissa officinalis* plant



Fig. 4. Herbal capsule

### 2.4. Statistical Analysis

First, the characteristics of the subjects and research data were summarized in a table using descriptive statistics. The tests used in inferential statistics included the Kolmogorov-Smirnov test to determine the normality of the data, the paired-sample t-test to examine intragroup comparisons in each group, and the independent t-test to compare two groups. Statistical calculations were performed using SPSS software, version 19 at a significance level of  $P < 0.05$ .

### 3. Results

The results of the Kolmogorov-Smirnov test indicated that the variables were normal. In Table 1, the descriptive characteristics of the subjects and in Table 2, the values of the research variables in the two groups of aerobic exercise and herbal capsule are presented in the pre-test and post-test stages. Also, the results of paired-Sample and independent t-test are given.

**Table 1.** Characteristics of subjects in two groups of aerobic exercise and herbal capsule

Variable	Aerobic exercise group	Herbal capsule group
age (years)	32.80 ± 5.60	33.67 ± 6.49
height (cm)	163.60 ± 5.70	162.34 ± 4.20
weight (kg)	60.30 ± 5.22	64.86 ± 6.68

**Table 2.** Paired-sample t-test and independent t-test for intragroup and intergroup comparison

Variable	Group	Pretest	Posttest	Paired-sample t-test		Independent t-test	
				t	p	t	p
Serotonin (ng/ml)	Aerobic Exercise	162.88 ± 11.28	199.66 ± 10.59	-6.27	0.000	-0.37	0.71
	Herbal capsule	161.55 ± 9.09	193.77 ± 13.06	-7.28	0.000		
Headache intensity (1-10)	Aerobic Exercise	6.53 ± 0.81	3.48 ± 0.58	14.63	0.000	3.69	0.002
	Herbal capsule	6.79 ± 0.91	2.63 ± 0.36	13.21	0.000		
Headache frequency (day of the month)	Aerobic Exercise	20 ± 3.16	7.66 ± 3.17	6.81	0.000	3.84	0.001
	Herbal capsule	20.33 ± 3.31	3.11 ± 1.61	18.04	0.000		
Headache duration (hours/rep)	Aerobic Exercise	8.88 ± 1.90	7.22 ± 1.98	3.53	0.008	-0.61	0.54
	Herbal capsule	9.55 ± 2.12	7.77 ± 1.85	2.23	0.05		
Synthetic drugs used (Number per month)	Aerobic Exercise	8.44 ± 3.43	4.44 ± 2.06	7.23	0.000	2.91	0.01
	Herbal capsule	8.66 ± 3.87	2.22 ± 0.97	6.34	0.000		
Vo <sub>2</sub> max (ml/kg/min)	Aerobic Exercise	30.85 ± 1.52	37.16 ± 4.46	-4.74	0.001	3.79	0.002
	Herbal capsule	30.76 ± 1.90	31.28 ± 1.30	-1.24	0.25		
Anxiety (0-63)	Aerobic Exercise	18.55 ± 5.63	11.33 ± 3.46	6.62	0.000	4.03	0.001
	Herbal capsule	18.33 ± 5.19	6 ± 1.93	7.84	0.000		
Depression (0-63)	Aerobic Exercise	19.22 ± 6.18	12 ± 3.12	5.65	0.000	0.06	0.94
	Herbal capsule	19 ± 5.61	11.88 ± 3.65	5.39	0.001		

Paired-sample t-test was used to examine intra-group differences from pre-test to post-test. The research results showed that in the aerobic training group, eight weeks of activity caused a significant increase in serotonin levels ( $P = 0.000$ ) and  $VO_{2max}$  ( $P = 0.001$ ). Anxiety level ( $P = 0.000$ ), depression ( $t_8 = 5.65$ ,  $P = 0.000$ ), headache intensity ( $P = 0.000$ ), number of headache days/headache frequency ( $P = 0.000$ ), the duration of headache ( $P = 0.008$ ), the amount of synthetic drugs used ( $P = 0.000$ ) decreased significantly compared to the pre-test. In the herbal capsule group, consumption of eight of them caused a significant increase in serotonin levels ( $P = 0.000$ ).  $VO_{2max}$  ( $P = 0.25$ ) and headache duration ( $P = 0.05$ ) did not change, but anxiety ( $P = 0.000$ ), depression ( $P = 0.001$ ), headache intensity ( $P = 0.000$ ), the number of headache days/ headache frequency ( $P = 0.000$ ), the amount of synthetic drugs used ( $P = 0.000$ ) decreased significantly compared to the pre-test. Independent t-test was used to compare between groups. The results of the test showed that there was no significant difference in the amount of serotonin ( $P = 0.71$ ), duration of headache ( $P = 0.54$ ) and depression ( $P = 0.94$ ) between the two groups. However, the variables of headache intensity ( $P = 0.002$ ), headache frequency ( $P = 0.001$ ), the amount of synthetic drugs consumed ( $P = 0.01$ ), and anxiety ( $P = 0.001$ ) in the herbal capsule group were significantly reduced compared to the aerobic group.  $VO_{2max}$  increased more in aerobic exercise group ( $P = 0.002$ ).

#### 4. Discussion

The aim of the present study was to investigate aerobic exercise and herbal capsules on headache status, serotonin level, anxiety and

depression and aerobic capacity in patients with CTTH.

In the present study, aerobic exercise increased blood serotonin, which is analogous with the results of Valim et al (2013), Sharifi et al (2018) [22, 23]. Researchers have attributed the cause of the increase in serotonin due to aerobic exercise due to the increase in plasma free tryptophan; only about ten percent of tryptophan in plasma is free, and the rest is bound to albumin, and on the other hand, it is only free tryptophan that can enter the brain. Aerobic exercises increase free fatty acids in the blood, and then there is a competition between fatty acids and tryptophan amino acid for binding to plasma albumin, which increases free tryptophan in plasma. As a result, more tryptophan can enter the brain, which is converted into serotonin in the brain [24].

Unfortunately, there is little research on the effect of aerobic exercise on serotonin levels in people with headaches. In a theoretical discussion, Darling (1991) acknowledged that increasing serotonin levels due to aerobic exercise helps improve migraine headaches [25]. Because serotonin has analgesic properties, so that its decrease facilitates the pain process and its increase causes pain reduction and cessation [26, 27]. According to research, the level of serotonin in people with CTTH is low. Anthony and Lance (1989) and Karakulova et al (2014) noted that the level of serum serotonin in people with CTTH depends on the severity of pain, depression and anxiety, and the increase of these variables causes a decrease in serum serotonin [6, 28].

On the other hand, the use of serotonergic drugs in the prevention and treatment of headache has side effects, and many patients refuse to use serotonergic drugs due to their side

effects. Therefore, aerobic exercises are a low-cost and uncomplicated treatment method that can help treat headaches by increasing serotonin. In this study, blood samples were taken at the follicular stage. Serotonin levels are changed by estrogen (direct effect). In the early follicular phase, due to the sharp drop in estrogen, the level of serotonin is less fluctuating and more stable [29]. Due to the different menstrual cycles of the subjects, the duration of the blood sampling procedure lasted two weeks. But serotonin levels were still high a few days after the study was completed, indicating adaptation. Serotonin increased by 17 % in patients with CTTH.

In this study, consumption of herbal capsules caused a significant increase in patients' serotonin levels (20 %). The effect of the combination of these two plants on serotonin has not been investigated yet. However, the effect of valerian on the amount of serotonin was investigated in a number of studies conducted on laboratory animals, which showed an increase in the amount of serotonin in the brain [16-18]. Also, a number of researchers stated that *M. officinalis* plays a role in improving depression through increasing serotonin and other neurotransmitters [30, 31].

One of the possible reasons for the increase in serotonin caused by the consumption of this herbal capsule can be their constituent compounds. Also, the calming effects of these two plants can increase serotonin. Acute stress temporarily increases serotonin levels, but chronic stress depletes serotonin stores. On the other hand, with the increase of depression and anxiety, the level of serotonin decreases [6]. Patients with CTTH usually have high stress, anxiety and depression [6, 8, 32], which can cause a decrease in their serotonin. In the present study, the sedative properties of these two plants

reduced anxiety and depression in patients, which subsequently increased serotonin.

In the present study, eight weeks of aerobic training significantly reduced anxiety and depression in patients with CTTH. In Canady's (2002) study, aerobic exercise reduced anxiety in patients with TTH [20]. Also, in the article of Menon et al (2013), yoga exercises reduced anxiety and depression in patients with CTTH [33]. The researchers attributed the improvement of depression and anxiety as a result of exercise to the following: increasing beta-endorphin levels, increasing neurotransmitters such as serotonin and GABA, reducing norepinephrine and cortisol levels [34].

The level of anxiety in the herbal capsule group was significantly reduced. In the study of Muller and Klement (2006) and Kennedy et al (2006), the combination of these two plants reduced restlessness and had an anti-anxiety effect [10, 11]. Researchers have attributed the sedative and anti-anxiety properties of valerian to valerenic acid, valeranal and valepotriate, which are its active ingredients. These effective substances exert their sedative properties by acting on GABA receptors. Also, valerenic acid inhibits the enzyme GABA transaminase, which causes the breakdown and reduction of GABA in the nervous system, and increases GABA levels in the brain [14, 35]

Glutamine, one of the other components of the extract, can easily cross the blood-brain barrier and is absorbed by nerve terminals and converted into GABA [36]. Increasing the concentration of GABA in the brain reduces the activity of different brain nuclei and causes sedative effects [37]. On the other hand, the activation of adenosine and serotonin receptors by valerian extract and its compounds have been reported as other mechanisms of its anti-anxiety, hypnotic



and sedative effects [16]. Researchers have mentioned the cause of the anti-anxiety properties of *M. officinalis* because of the active ingredients in the plant, such as citronellal, which bind to GABA receptors [38]. Awad et al (2007) and Ibarra et al (2010) showed in their research that *M. officinalis* extract, which includes rosmarinic acid, oleanolic acid, and ursolic acid, inhibits the activity of GABA-T enzyme and increases the amount of GABA in the brain, thereby reducing anxiety [38, 39].

In the present study, consumption of herbal capsules for eight weeks significantly reduced the level of anxiety in the group of patients with CTTH (67 %). According to researches, the anti-anxiety and calming effect of valerian and *M. officinalis* is moderate and they are ineffective in extreme stressful situations. Because they increase GABA in the brain in a small amount [12, 39]. On the other hand, the combination of two plants intensify each other's effect [12]. In the present study, the subjects had moderate anxiety in the basic stage, and the herbal capsule was able to have a significant effect on anxiety.

In the present study, consumption of herbal capsules reduced the level of depression in patients with CTTH (37 %). In several studies, consumption of valerian extract by laboratory animals increased serotonin [17, 18]. Considering the role of serotonin in depression, therefore increasing it can help reduce depression. Taiwo et al. (2012) investigated the anti-depressant and anti-anxiety effects of *M. officinalis*. The result of their study showed that aqueous and ethanol extracts of *M. officinalis* have an inhibitory effect on monoamine oxidase. Monoamine oxidase enzyme plays a role in breaking down serotonin, dopamine and other catecholamines inside the synapses. Therefore, its inhibition increases these mediators in

synapses and increases the amount of serotonin in these spaces. Increasing serotonin reduces depression [30]. Also, it seems that the main factor of depression in headache patients is the number of headache attacks/number of headache days, not its severity. Therefore, the sedative, analgesic and antispasmodic properties of these two plants can help reduce headache attacks and thus reduce depression symptoms.

VO<sub>2</sub>max increased significantly only in the aerobic exercise group. The optimal protocol for taking advantage of the positive results of aerobic exercise and increasing cardiovascular fitness is exercises with an intensity of 70-85 % HR<sub>max</sub>, 3 to 5 d/w and 20 to 30 minutes per session. The current study protocol was designed based on the mentioned protocol. People with headaches tend to be sedentary and have low physical fitness, and it has also been reported that there is a linear relationship between less physical activity and more headache recurrence [19]. Therefore, in addition to improving their headache, aerobic exercise can be beneficial for them in improving their health and preventing diseases. Also, no change in VO<sub>2</sub>max in the herbal capsule group was due to their lack of physical activity.

In the present study, aerobic exercise significantly reduced pain intensity (46 %), headache frequency (61 %) and headache duration (19 %) in patients. In the study of Canady's (2002) and Sertel et al. (2017), the frequency and intensity of headache and in the study of Soderberg et al (2006) the number of headache days in patients with tension headache were significantly reduced due to a period of aerobic exercise [8, 20, 21]. Researchers attributed the improvement of headache indices in patients due to a period of aerobic training as a result of endorphin production, reduction of negative conditions such as fatigue, depression

and anxiety and improvement of sleep quality [8]. In the present study, aerobic exercise decreased anxiety and depression and increased Vo<sub>2</sub>max and serotonin in patients. Considering the role of these factors in tension headaches, their improvement helped the status of headache indicators.

In the present study, consumption of herbal capsules caused a significant reduction in headache intensity (61 %) and headache frequency (85 %) in patients, but the decrease in headache duration (18 %) was not statistically significant. The analgesic effect of valerian and *M. officinalis* has been shown in several studies. In Gholamreza Mirzaei's study, taking *Valerian* capsules reduced the intensity, duration and number of migraine attacks [9].

There are no studies that have directly investigated the combined effect of these two herbs on tension headache. But a number of studies have confirmed the positive effect of valerian and *M. officinalis* separately on sleep disorders, stress, depression, anxiety and muscle spasms [40]. The results of the patients' daily headache questionnaire showed that stress, insomnia, fatigue, depression, and anxiety had the greatest effect on the onset of their TTH attacks. Considering the effectiveness of these two herbs on the headache-inciting factors, it is likely that the improvement of CTTH indicators in the present study is related to the increase of serotonin, reduction of anxiety and depression, and other effects of these two herbs that were not investigated in this study, such as improving sleep and analgesic effect.

The use of synthetic drugs (non-serotonergic drugs) in the present study decreased in both groups, but this decrease was similar between the two groups. In the study of Sertel et al (2017) and Kennedy (2002), aerobic exercise significantly

reduced the use of acute medications in patients with tension-type headache [11, 21]. The reduction in the number of synthetic drugs used in the two study groups can be related to the improvement of the patients' headache condition.

The results of the comparison of the two groups showed that the changes in the amount of serotonin, duration of headache and depression were similar in the two groups. Vo<sub>2</sub>max increased more in aerobic exercise group (20.40 % exercise vs 1.69 % capsule). Also, headache intensity (61 % capsule vs 46 % exercise), headache frequency (85 % capsule vs 61 % exercise), anxiety (67 % capsule vs 39 % exercise) and the amount of synthetic drugs used (74 % capsule vs 47 % exercise) in the herbal capsule group were reduced more compared to the aerobic exercise group.

The better improvement of the headache condition in the herbal capsule group compared to the aerobic exercise group can be argued that these two herbs have antispasmodic and sedative properties and directly affect and reduce the spasm of the muscles related to the brain of the patients. While aerobic exercise directly does not have this capability. On the other hand, improving headache status can reduce anxiety in patients who suffer from chronic headaches. Anxiety decreased in both groups, but the decrease was greater in the herbal capsule group because the improvement in headache status was better.

Although aerobic exercise and these two plants directly affect anxiety. Reducing the use of synthetic drugs in both groups is related to the improvement of the headache condition. In the herbal capsule group, the use of synthetic drugs decreased more because the improvement of the headache condition was better. Vo<sub>2</sub>max was significantly increased in the aerobic exercise

group compared to the herbal capsule group. The lack of increase in Vo<sub>2</sub>max in the herbal capsule group is related to their lack of exercise.

## 5. Conclusions

The results of the present study showed that in both the aerobic exercise and herbal capsule groups, the level of serotonin increased, but the level of anxiety, depression, and headache indicators decreased. The condition of headache improved more in the herbal capsule group. Patients with CTTH can use both methods to improve their headache condition.

## Author contributions

ZS: Conceptualization, methodology, editing and finalization. GH M: analysis

## References

1. Kumar S and Raje A. Effect of progressive muscular relaxation exercises versus transcutaneous electrical nerve stimulation on tension headache: A comparative study. *Hong Kong Physiotherapy Journal* 2014; 32(2): 86-91. doi: 10.1016/j.hkpj.2014.06.002.
2. Ghadiri-Sani M and Silver N. Headache (chronic tension-type). *BMJ Clin. Evid.* 2016; 2016: 1205.
3. Ashina S, Bendtsen L and Ashina M. Pathophysiology of migraine and tension-type headache. *Techniques in Regional Anesthesia and Pain Management.* 2012; 16(1): 14-8. doi: 10.1053/j.trap.2012.11.002.
4. Ashina M. Neurobiology of chronic tension-type headache. *Cephalalgia* 2004; 24(3): 161-72. doi: 10.1111/j.1468-2982.2003.00644.x.
5. Gupta R, Ahmed T, Banerjee B and Bhatia M. Plasma calcitonin gene-related peptide concentration is comparable to control group among migraineurs and tension type headache

## Conflict of Interests

There was no conflict of interest in this study.

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## Ethical Approval

The research project has been reviewed in the Research Ethics Committee of Sport Sciences Research Institute and was approved according to compliance with Ethical Standards in Research of the Ministry of Science, Research and Technology, with the code IR.SSRI.REC.1396. 160.

- subjects during inter-ictal period. *J. Headache Pain.* 2009; 10(3): 161-6. doi: 10.1007/s10194-009-0110-x.
6. Karakulova I. EHMTI-0299. Serotonin as biomarker of ache intensity in chronic tension headache. *J. Headache Pain.* 2014; 15(Suppl. 1): C27. doi: 10.1186/1129-2377-15-S1-C27.
7. Cass H. Herbs for the nervous system: Ginkgo, kava, valerian, passionflower. *Seminars in Integrative Medicine* 2004; 2(2): 82-88. doi: 10.1016/j.sigm.2004.07.001.
8. Söderberg E, Carlsson J and Stener-Victorin E. Chronic tension-type headache treated with acupuncture, physical training and relaxation training. Between-group differences. *Cephalalgia* 2006; 26(11): 1320-9. doi: 10.1111/j.1468-2982.2006.01209.x.
9. Mirzaee MGh, Kheiri S and Bahrami M. Effect of valerian capsules in patients with migraine attacks treated with sodium valproate: a

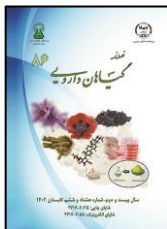
- randomized clinical trial. *J. Shahrekord Univ. Med. Sci.* 2015; 16(6): 119-26.
- 10.** Müller SF and Klement S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. *Phytomedicine* 2006; 13(6): 383-7. doi: 10.1016/j.phymed.2006.01.013.
- 11.** Kennedy DO, Little W, Haskell CF and Scholey AB. Anxiolytic effects of a combination of *Melissa officinalis* and *Valeriana officinalis* during laboratory induced stress. *Phytotherapy Res.* 2006; 20(2): 96-102. doi: 10.1002/ptr.1787.
- 12.** Taavoni S, Naxem Ekbatani N and Haghani H. Valerian/lemon balm use for sleep disorders during menopause. *Complement Ther. Clin. Pract.* 2013; 19(4): 193-6. doi: 10.1016/j.ctcp.2013.07.002.
- 13.** Murphy K, Kubin ZJ, Shepherd JN, Ettinger R. *Valeriana officinalis* root extracts have potent anxiolytic effects in laboratory rats. *Phytomedicine.* 2010; 17(8-9): 674-8. doi: 10.1016/j.phymed.2009.10.020.
- 14.** Benke D, Barberis A, Kopp S, Altmann K-H, Schubiger M, Vogt KE, Rudolph U and Mohler H. GABAA receptors as in vivo substrate for the anxiolytic action of valerianic acid, a major constituent of valerian root extracts. *Neuropharmacol.* 2009; 56(1): 174-81. doi: 10.1016/j.neuropharm.2008.06.013.
- 15.** Gilani AH, Khan A-u, Jabeen Q, Subhan F and Ghafar R. Antispasmodic and blood pressure lowering effects of *Valeriana wallichii* are mediated through K<sup>+</sup> channel activation. *J. Ethnopharmacol.* 2005; 100(3): 347-52. doi: 10.1016/j.jep.2005.05.010.
- 16.** Dietz BM, Mahady GB, Pauli GF and Farnsworth NR. Valerian extract and valerianic acid are partial agonists of the 5-HT<sub>5a</sub> receptor *in vitro*. *Brain. Res. Mol. Brain. Res.* 2005; 138(2): 191-7. doi: 10.1016/j.molbrainres.2005.04.009.
- 17.** Tang J, Zeng Y, Chen Q, Qin Y, Chen S, Zhong Z. Effects of valerian on the level of 5-hydroxytryptamine, cell proliferation and neurons in cerebral hippocampus of rats with depression induced by chronic mild stress. *J. Chine. Integr. Med.* 2008; 6(3): 283-8. doi: 10.3736/jcim20080313.
- 18.** Yan X, Hong Y, Shi J, Qin Y, Zhang J, Lin Q, Chen Zh, Zhao R, Cui X and Gao X. Influence of iridoid from *Valeriana jatamansi* on 5-HT and 5-HIAA in rats with irritable bowel syndrome. *Zhongguo Zhong Yao Za Zhi.* 2011; 36(9): 1235-8. doi: 10.4268/CJCM20110927.
- 19.** Irby MB, Bond DS, Lipton RB, Nicklas B, Houle TT and Penzien DB. Aerobic exercise for reducing migraine burden: mechanisms, markers, and models of change processes. *Headache.* 2016; 56(2): 357-69. doi: 10.1111/head.12738.
- 20.** Canady BE. The effects of regular aerobic exercise on tension headache: Marshall University; 2002.
- 21.** Sertel M, Bakar Y and Şimşek TT. The effect of body awareness therapy and aerobic exercises on pain and quality of life in the patients with tension type headache. *Afr. J. Tradit. Complement Altern. Med.* 2017; 14(2): 288-310. doi: 10.21010/ajtcam.v14i2.31.
- 22.** Valim V, Natour J, Xiao Y, Pereira AFA, da Cunha Lopes BB, Pollak DF, Zandonade E and Russell IJ. Effects of physical exercise on serum levels of serotonin and its metabolite in fibromyalgia: a randomized pilot study. *Rev. Bras. Reumatol.* 2013; 53(6): 538-41. doi: 10.1016/j.rbr.2013.02.001.
- 23.** Sharifi M, Hamedinia MR and Hosseini-Kakhak SA. The effect of an exhaustive aerobic, anaerobic and resistance exercise on serotonin, beta-endorphin and BDNF in students. *Physical Education of Students* 2018; 22(5): 272-7. doi: 10.15561/20755279.2018.0507.

- 24.** Melancon MO, Lorrain D and Dionne JJ. Exercise and sleep in aging: emphasis on serotonin. *Pathol. Biol.* 2014; 62(5): 276-83. doi: 10.1016/j.patbio.2014.07.004.
- 25.** Darling M. Exercise and migraine. A critical review. *J. Sports Med. Phys. Fitness* 1991; 31(2): 294-302.
- 26.** Hamel E and Currents H. Serotonin and migraine: biology and clinical implications. *Cephalalgia* 2007; 27(11): 1293-300. doi: 10.1111/j.1468-2982.2007.01476.x.
- 27.** Sokolov AY, Lyubashina O and Panteleev S. The role of serotonin receptors in migraine headaches. *Neurochemical J.* 2011; 5(2): 92-9. doi: 10.1134/S1819712411020085.
- 28.** Anthony M and Lance JW. Plasma serotonin in patients with chronic tension headaches. *J. Neurol. Neurosurg. Psychiatry.* 1989; 52(2): 182-4. doi: 10.1136/jnnp.52.2.182.
- 29.** Aggarwal M, Puri V and Puri S. Serotonin and CGRP in migraine. *Ann. Neurosci.* 2012; 19(2): 88-94. doi: 10.5214/ans.0972.7531.12190210.
- 30.** Taiwo AE, Leite FB, Lucena GM, Barros M, Silveira D, Silva MV and Ferreira VM. Anxiolytic and antidepressant-like effects of *Melissa officinalis* (Lemon balm) extract in rats: Influence of administration and gender. *Indian J. Pharmacol.* 2012; 44(2): 189-92. doi: 10.4103/0253-7613.93846.
- 31.** Ghazizadeh J, Sadigh-Eteghad S, Marx W, Fakhari A, Hamedeyazdan S, Torbati M, Taheri-Tarighi S, Araj-khodaei M and Mojgan Mirghafourvand M. The effects of *Lemon balm* (*Melissa officinalis* L.) on depression and anxiety in clinical trials: A systematic review and meta-analysis. *Phytother. Res.* 2021; 35(12): 6690-705. doi: 10.1002/ptr.7252.
- 32.** Gupta SN, Gupta VS and Borad G. Preictal symptomatology in migraines: diagnostic and therapeutic significance. *J. Headache Pain Manag.* 2016; 1(1): 1-9. doi: 10.4172/2472-1913.100007.
- 33.** Menon B, Satyanand V and Karishma PH. Effects of yoga on tension headache. *Journal of Dr NTR University of Health Sciences* 2013; 2(3): 167. doi: 10.4103/2277-8632.117181.
- 34.** Hatami K, Shokrollahi B and Haidari N. The effect of aerobic activities on depression and anxiety symptoms and sleep disturbances of female students. *Middle-East J. Scientific Res.* 2013; 14(2): 284-287. doi: 10.5829/idosi.mejsr.2013.14.2.7242.
- 35.** Del Valle-Mojica LM, Ayala-Marín YM, Ortiz-Sanchez CM, Torres-Hernández BA, Abdalla-Mukhaimer S and Ortiz JG. Selective interactions of *Valeriana officinalis* extracts and valerianic acid with [<sup>3</sup>H] glutamate binding to rat synaptic membranes. *Evidence-Based Complementary and Alternative Medicine* 2011; 2011: 1-7. doi: 10.1155/2011/403591.
- 36.** Santos MS, Ferreira F, Faro C, Pires E, Carvalho AP, Cunha AP and Macedo T. The amount of GABA present in aqueous extracts of valerian is sufficient to account for [<sup>3</sup>H] GABA release in synaptosomes. *Planta Med.* 1994; 60(5): 475-6. doi: 10.1055/s-2006-959538.
- 37.** Möhler H. The GABA system in anxiety and depression and its therapeutic potential. *Neuropharmacol.* 2012; 62(1): 42-53. doi: 10.1016/j.neuropharm.2011.08.040.
- 38.** Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL and Arnason JT. Effects of traditionally used anxiolytic botanicals on enzymes of the  $\gamma$ -aminobutyric acid (GABA) system. *Can. J. Physiol. Pharmacol.* 2007; 85(9): 933-42. doi: 10.1139/Y07-083.

39. Ibarra A, Feuillere N, Roller M, Lesburgere E and Beracochea D. Effects of chronic administration of *Melissa officinalis* L. extract on anxiety-like reactivity and on circadian and exploratory activities in mice. *Phytomedicine* 2010; 17(6): 397-403. doi: 10.1016/j.phymed.2010.01.012.

40. Kenda M, Kočevar Glavač N, Nagy M and Sollner Dolenc M. Medicinal plants used for anxiety, depression, or stress treatment: An update. *Molecules* 2022; 27(18): 6021. doi: 10.3390/molecules27186021.

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## تأثیر تمرین هوازی و کپسول گیاهی (عصاره هیدروالکلی سنبل الطیب هندی و بادرنجبویه) بر تغییرات سطوح سروتونین و شاخص‌های سردرد در زنان مبتلا به سردرد مزمن تنشی

زهره اسکندری\*، غزاله محمدی

گروه تربیت بدنی، دانشکده علوم اجتماعی، دانشگاه غیرانتفاعی رجاء، قزوین، ایران

### چکیده

### اطلاعات مقاله

مقدمه: سردرد تنشی شایع‌ترین نوع سردرد می‌باشد. هدف: هدف از پژوهش حاضر بررسی تأثیر تمرین هوازی و کپسول گیاهی بر سطوح سروتونین و شاخص‌های سردرد در زنان مبتلا به سردرد تنشی مزمن (CTTH) بود. روش بررسی: در این مطالعه کاربردی، ۱۸ بیمار زن بزرگسال مبتلا به سردرد تنشی مزمن به صورت تصادفی در دو گروه مساوی: تمرین و کپسول گیاهی قرار گرفتند. تمرین هوازی سه جلسه در هفته، هر جلسه ۷۵ دقیقه برای هشت هفته اجرا شد. کپسول گیاهی شامل عصاره هیدروالکلی سنبل الطیب هندی و بادرنجبویه بود. دوز هر کپسول شامل ۲۸۰ میلی‌گرم از هر دو گیاه بود که سه بار در روز مصرف شد. سطوح سروتونین، شاخص‌های سردرد (شدت، مدت و تکرار سردرد)، اضطراب، افسردگی، مصرف داروهای سنتتیک و توان هوازی در مرحله پایه و پایان مطالعه ارزیابی شد. نتایج: طبق نتایج درون گروهی، در هر دو گروه افزایش معنی‌دار در سروتونین، توان هوازی (فقط گروه تمرین) و کاهش معنی‌داری در اضطراب، افسردگی، شدت سردرد، تکرار سردرد، مدت سردرد (فقط در گروه تمرین) و میزان داروهای سنتتیک مصرف شده مشاهده شد. در مقایسه بین گروهی تفاوت معنی‌داری در شدت و تکرار سردرد، مصرف داروهای سنتتیک، توان هوازی و اضطراب مشاهده شد. نتیجه‌گیری: تمرین هوازی و عصاره هیدروالکلی گیاه سنبل الطیب هندی و بادرنجبویه می‌توانند مکمل درمانی مناسبی برای زنان مبتلا به CTTH باشد اما تأثیر دو گیاه در بهبود سردرد بهتر بود.	گل‌واژگان: سردرد تنشی مزمن سنبل الطیب هندی بادرنجبویه تمرین هوازی سروتونین شاخص‌های سردرد
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مخفف‌ها: CTTH، سردرد تنشی مزمن؛ *V. jatamansi*، سنبل الطیب هندی؛ *M. officinalis*، بادرنجبویه

\* نویسنده مسؤول: [Z.Eskandari@raja.ac.ir](mailto:Z.Eskandari@raja.ac.ir)

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