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The Effect of Spirulina on Anxiety in Patients with Hypertension: A Randomized Triple-Blind Placebo-Controlled Clinical Trial

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ABSTRACT

Background: High blood pressure, coronary heart disease (CHD), and anxiety ailments entirely lead to many illness in patients and impose expenses on the health care system. Anxiety can significantly predict future CHD consequences. Spirulina is a known antioxidant that has a role in anxiety. The hypothesis was that Spirulina could alleviate anxiety and positively affect hypertension and its consequences. Nonetheless, there are scarce recently developed investigations on assessing the effect of consuming Spirulina on anxiety in human beings. **Methods:** The present study assessed the effect of Spirulina on anxiety in 48 Iranian patients with hypertension (female and male) aged 24–65 years in a randomized triple-blind, placebo-controlled clinical trial. The patients were given either 2 g Spirulina in the form of spirulina-fortified dressing or placebo. Anxiety levels were evaluated for each patient before and after eight weeks following consumption products with the Beck Anxiety Inventory. **Results:** Forty-one participants completed the intervention. At the baseline, there was no significant difference in anxiety levels between groups, and they also had the same levels of stress based on the Holmes-Rahe questionnaire. The results showed no significant difference in the level of anxiety between groups after the intervention (P = 0.93). **Conclusion:** Although no positive results were seen in this study, this novel issue has a potential for further investigations to make comprehensive decisions.

Keywords: *Spirulina; Anxiety; Beck anxiety inventory; Hypertension*

Introduction

A variety of psychosocial parameters involved in cardiovascular disease have been focused for a long time (Player and Peterson, 2011). Anxiety is a negatively perceived emotion as both psychological and somatic features. Psychological indications include worry, tension, and feelings of apprehension, and somatic indications usually arise from autonomic arousal (sweating, palpitations,

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chest pain, trembling) (Tyrer and Baldwin, 2006). The hypotheses and studies on the relationships between hypertension, CHD, and anxiety ailments have been investigated for long years. Specifically, psychosocial stress inducers accompanying anxiety ailments induce autonomic arousal through the hypothalamic-pituitary axis, thereby increasing catecholamines in the circulation. Longitudinally conducted investigations denote the risky increase in developing high blood pressure in patients suffering from anxiety (Player and Peterson, 2011).

A study by Masood (Masood *et al.*, 2008) indicated that induced oxidative stress (OS) in the hypothalamus and amygdala occurred in accompaniment by anxiety in mice. Research on humans has also revealed the relationship between total oxidant/antioxidant concentrations and anxiety ailments in children and adolescents (Guney *et al.*, 2014). A positive correlation has been observed between an increase in anxiety and rises of reactive oxygen species (ROS) in granulocytes (Bouayed *et al.*, 2007). Investigators have been persuaded by the fallouts of drugs consumed for anxiety therapy and have investigated alternate medication with less unwanted consequences (Cui *et al.*, 2013).

Spirulina, also known as athrospira, is a microscopic and filamentary cyanobacterial species that have historically been used for nutrition for a prolonged time. Spirulina consists of 50-70% protein by weight and is a plentiful resource of vitamins, particularly vitamin B12, β-carotene (provitamin A), and vitamin E. Moreover, it consists of carbohydrates, such as rhamnose, fructose, ribose, mannose, and some minerals, including Cu, Mg, zinc, K, and Fe (Soltani *et al.*, 2012). Spirulina platensis also contains phycobilisomes which are light-collecting protein-pigment complexes. Phycobilisomes include 80-85% of brightly colored polypeptides called phycobiliproteins. Phycocyanin, allophycocyanin, and phycoerythrin with the same chromophoric group are the major biliproteins in these microalgae (Sachin *et al.*, 2014). Spirulina has protective effects against OS, and C-phycocyanin, an active ingredient of Spirulina, which has significant antioxidant properties, contributes to these effects (Romay *et al.*, 2003). Thus, high blood pressure might be controlled by antioxidants which act on anxiety levels. Therefore, regarding the limitations of studies associated with the effects of Spirulina on anxiety, the present study aims to evaluate the anti-anxiety activity of Spirulina Platensis in patients with hypertension.

Materials and Methods

Study design and Participants: Forty eight patients with hypertension were enrolled in this randomized triple-blind placebo-controlled clinical trial. This study was performed at Professor Kojuri clinic, Shiraz, Iran, between January 2020 and March 2020. The inclusion criteria were having systolic blood pressure (SBP) > 130 mm Hg or diastolic blood pressure (DBP) > 80 mm Hg or both of them and age between 24-65 years. The exclusion criteria were history of cardiovascular diseases or cardiac surgery, kidney, liver, inflammatory bowel disease, thyroid disorders, diabetes, and cancer, using any supplements, and following any diet. The detailed information on method and participants properties have been previously published (Ghaem Far *et al.*, 2021)

Intervention: The intervention group (IG, n = 24) received a sachet of salad dressing containing 2 g Spirulina (in the form of spray dried powder purchased from Green Sea Company), and the placebo group (PG, n = 24) received a sachet of salad dressing once a day for eight weeks. All products were produced in Namakin Company with the same formula (with limitation of fat, sugar, salt, and calories), confirming the quality of the products by a health care professional and quality control specialist. For blinding, the study shape and prescription of the sachets were similar in both groups.

Ethical consideration: All patients were fully informed of the study protocols and were free to leave the study at any time. Informed consent was obtained from all of them who wanted to participate in this study. The study was approved

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by the Ethics Committee of Shiraz University of Medical Sciences (Registration number: 1398. 1193) and registered at the IRCT Center (https://en.irct.ir/trial/47011) with the number: IRCT20200404046940N1.

Psychological evaluation: Given the fact that anxiety and stress would contribute to the level of blood pressure, the Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988) and the Holmes–Rahe stress scale (Rahe *et al.*, 1970) were used for assessing the symptoms of anxiety and evaluating the level of stress in groups, respectively. The Holmes-Rahe Stress Questionnaire was completed at the beginning of the study, and BIA was completed twice at the beginning and end of the study by all the patients.

Dietary intake and physical activity assessment: The assessment of the dietary intake, including energy, carbohydrate, protein, fat, Na, K, Ca, and Mg was performed by dietary intake interviews (24-hour recall) at the beginning and end of the trial, and each assessment was included 3 days (2 weekdays and one weekend). The data of the dietary intake were analyzed by the Nutritionist IV software. The physical activity was also assessed using the metabolic equivalent of the task questionnaire (Ainsworth *et al.*, 2000) at the baseline and week 8.

Data analysis: All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software version 21 (SPSS Inc. Chicago, IL). The results were shown as mean ±SD. Shapiro-Wilk test was used to test the normal distribution in each group. Descriptive statistics, independent t-test, and paired sample t-test were used to analyze continuous quantitative variables. Mann-Whitney and Chi-square tests were used to analyze nominal and ordinal qualitative variables. In all statistical tests, $P < 0.05$ was considered significant.

Results

From 48 participants included in the study, 41 patients were sampled at the end of the study (**Figure 1**). The baseline characteristics in **Table 1**, shows that mean age was not significant among IG and PG (51.27 ± 1.30 vs. 50.21 ± 1.36; $P = 0.54$). The use of antihypertensive medications in the IG was higher than the PG, but differences were not significant ($P = 0.08$). The majority of participants in the IG and PG had high school, bachelor, and higher degrees (90.90% vs. 78.95%, $P = 0.54$). Physical activity changes between the two groups were not significant at baseline and end of the study ($P = 0.74$, $P = 0.21$).

The mean dietary intake was not significantly different between the two groups, except for fat at the end. Within-group analysis showed an increase in energy, protein, fat, sodium, and magnesium intake and a decrease in carbohydrate, potassium, and calcium in IG at the end of the study, but differences were not significant (**Table 2**).

The results of the Holmes-Rahe questionnaire showed that the patients in both groups were the same in terms of susceptibility to stress-induced health breakdown score, and the distribution of each group was normal ($P = 1.00$, **Table 3**).

At baseline, there was no statistically significant difference in the level of anxiety between groups based on BIA ($P = 0.05$). After the intervention, the change in percentages of the anxiety levels was not shown in the IG, but it was shown in the PG. However, the analyses showed that anxiety levels were not significantly different between the two groups at the end ($P = 0.93$, **Table 3)**.

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Table 1. General characteristics of the participants at baseline and end of the study.

Variables		Spirulina group (n=22)	Placebo group (n=19)	P-value
Age (year)		51.27 ± 1.30[c]	50.21 ± 1.36	0.54[a]
Gender				
Male		11 (50.0)[d]	8 (42.1)	0.61[b]
Female		11 (50.0)	11 (57.8)	
Smoke				
Yes		3 (13.6)	4 (21.1)	0.68[b]
No		19 (86.4)	15 (78.9)	
Antihypertensive medications				
Yes		21 (95.5)	14 (73.7)	0.08[b]
No		1 (4.5)	5 (26.3)	
Education				
Less than high school		2 (9.1)	4 (21.0)	0.54[b]
High school degree		10 (45.4)	8 (42.1)	
Bachelor degree and higher		10 (45.4)	7 (36.8)	
Physical activity				
Baseline	Low	7 (31.8)	8 (42.1)	0.74[b]
	Moderate	6 (27.3)	4 (21.1)	
	High	6 (27.3)	3 (15.7)	
	Very high	3 (13.6)	4 (21.1)	
End	Low	11 (50.0)	8 (42.1)	0.21[b]
	Moderate	6 (27.3)	2 (10.5)	
	High	4 (18.2)	4 (21.1)	
	Very high	1 (4.5)	5 (26.3)	

[a]: Mann–Whitney U test; [b]: Fisher's exact test [c]: Mean ± SD a; [d]: N (%).

Table 2. Dietary intake of the participants at baseline and end of the study.

Variables	Spirulina group (n=22)	Placebo group (n=19)	P-value
Energy (kcal/day)			
Baseline	1609.06 ± 136.38	1571.40 ± 92.78	0.69[a]
End	1572.83 ± 123.41	1655.99 ± 89.92	0.37
P-value[b]	0.68	0.21	
Carbohydrate (g/day)			
Baseline	271.35 ± 21.59	260.95 ± 18.10	1.00
End	257.91 ± 20.26	231.71 ± 14.42	0.33
P-value	0.46	0.14	
Protein (g/day)			
Baseline	60.76 ± 6.68	57.70 ± 4.98	0.81
End	66.02 ± 7.69	66.63 ± 6.43	0.69
P-value	0.80	0.27	
Fat (g/day)			
Baseline	36.60 ± 3.76	41.37 ± 2.25	0.07
End	37.76 ± 3.69	55.69 ± 6.00	0.01
P-value	0.91	0.04	
Na (mg/day)			
Baseline	1529.58 ± 140.61	1877.28 ± 177.99	0.15
End	1567.76 ± 136.23	1862.51 ± 190.96	0.23
P-value	0.75	0.87	
K (mg/day)			
Baseline	3329.51 ± 366.72	3372.84 ± 427.31	0.89
End	2954.54 ± 291.78	2703.13 ± 229.51	0.48
P-value	0.37	0.35	

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Table 2. Dietary intake of the participants at baseline and end of the study.

Variables	Spirulina group (n=22)	Placebo group (n=19)	P-value
Ca (mg/day)			
Baseline	889.25 ± 133.65	854.81 ± 101.07	0.54
End	704.62 ± 90.35	581.38 ± 60.56	0.37
P-value	0.42	0.01	
Mg (mg/day)			
Baseline	279.18 ± 28.22	296.85 ± 31.99	0.65
End	289.60 ± 23.09	253.78 ± 17.65	0.34
P-value	0.40	0.18	

[a]: Independent sample *t-test*; [b]: Paired sample *t-test*; [c]: Mean ± SD.

Table 3. Results of anxiety and stress levels at baseline and end of the study.

Variables	Spirulina group (n=22)	Placebo group (n=19)	P-value[a]
Holmes-Rahe (Baseline)			
Low Stress	9 (40.9)[b]	8 (42.1)	1.00
Moderate	9(40.9)	8 (42.1)	
High	4 (18.2)	3 (15.8)	
Beck Anxiety Inventory (BAI)			
Baseline			
No Anxiety	0 (0.0)	1 (5.3)	0.05
Moderate	13 (59.1)	5 (26.3)	
High	9 (40.9)	13 (98.4)	
End			
No Anxiety	0 (0.0)	0 (0.0)	0.93
Moderate	13 (59.1)	11 (57.9)	
High	9 (40.9)	8 (42.1)	

[a]: Fisher's exact test; [b]: N (%)

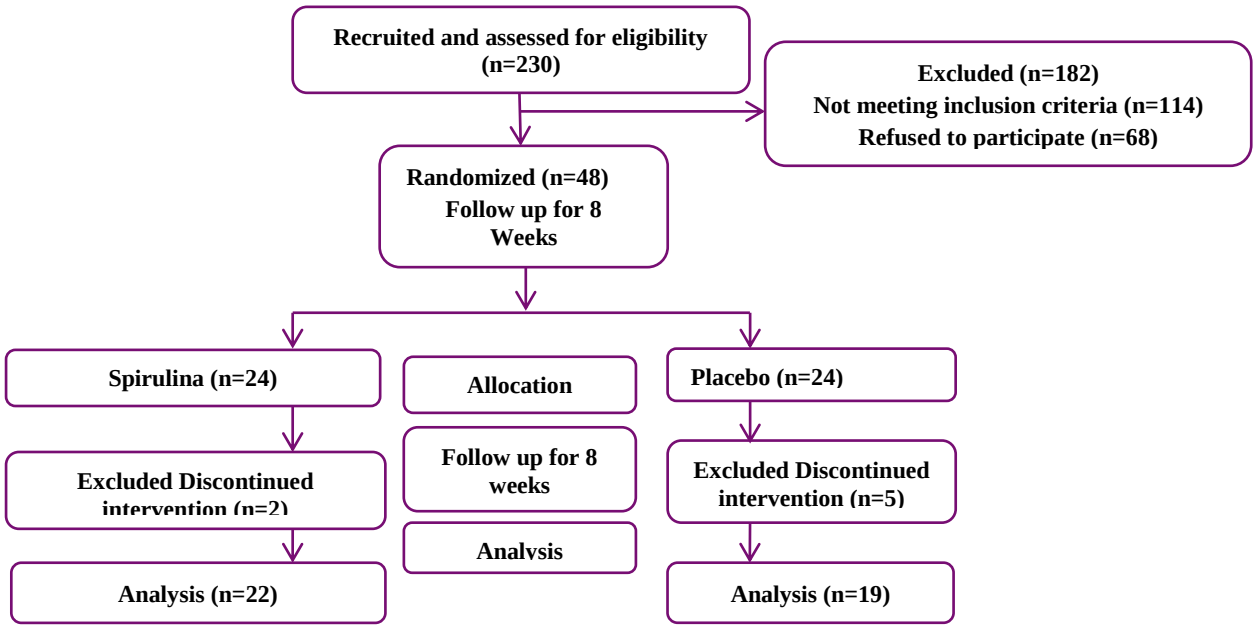

Figure 1. Flowchart of patient recruitment for the double-blind, placebo-controlled, randomized trial of Spirulina and placebo group

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Discussion

The present study evaluated the effect of Spirulina on anxiety in patients with hypertension. At the end of the study, a significant change in anxiety levels in none of the groups was observed. It is noted that according to the synchronization of the final days of the present study with the start of the COVID-19 pandemic, there is a possibility that the anxiety due to the pandemic affected the results of the study. However, due to the limitations of studies associated with the effects of Spirulina on anxiety, this has a high potential for consideration in future clinical trials.

It has been increasingly evidenced that an imbalance of OS and the antioxidant defensive system may be associated with developing neuropsychiatric disorders, including depression and anxiety. The majority of depression and anxiety are currently associated with a declined overall antioxidant status and by a stimulated OS route. Conventional antidepressants can create therapeutical outcomes different from regulating monoamines by raising the antioxidant concentrations and normalization of the injury induced by OS procedures. There is adequate evidence that antioxidants are capable of removing ROS and reactive nitrogen species (RNS). To this end, they scavenge radicals and suppress the OS route, providing more protection towards neuronal injury induced by oxidative or nitrosative stressors in the brain, expectantly leading to subsidence of depression or anxiety indications. To discover new targets for the therapy of neuropsychiatric disorders, it is necessary to functionally understand the association between OS, depression, and anxiety (Xu *et al.*, 2014).

In an investigation, it was found that supplementing with 500 g/day of vitamin C as an antioxidant for 14 days led to a significant reduction in BAI anxiety scores in high school students (Ribeiro, 2015). Elsewhere, supplementing with 1 g/day of vitamin C for 6 weeks positively affected anxiety levels, depression, and stress compared to 400 IU/day of vitamin E in type-2 diabetic patients. The authors observed significant increases in anxiety scores by the use of vitamin E. They reported that vitamin C could improve anxiety levels by alleviating oxidative injury in the brain, which caused an impaired nervous system (Mazloom *et al.*, 2013). An animal model was used to evaluate the anti-anxiety potentiality of Spirulina platensis in Swiss albino mice, in which the anti-anxiety property improved significantly by a 400 mg/kg dosage of Spirulina platensis (Sachin *et al.*, 2014).

In a study (Moradi *et al.*, 2021) that examined the effect of 8 weeks of spirulina consumption on several parameters, including quality of life in patients with ulcerative colitis, Spirulina caused significant reduction in stress score but the decrease in anxiety, depression or fatigue scores was not significant. The difference between the present study and their study was the dose of Spirulina, which was 2 grams in the present study and 1 gram in their study, but and in terms of anxiety changes, it was in line with the present study.

As reported previously, the chemical composition of Spirulina Platensis is suggestive of the presence of major biliproteins (phycocyanin, allophycocyanin, and phycoerythrin) in Spirulina, acting as a potential antioxidant factor. The mediatory mode of action for the anxiolytic activities of Spirulina is explored by the phycocyanin interplay with the GABAA receptor, possibly modulated by phycocyanin. Nonetheless, the mechanism of action for phycocyanin interplay with the Gamma-aminobutyric acid type A (GABAA) receptor is not known yet. As a result, the action of phycocyanin on anxiety occurs via its antioxidant potentiality (Sachin *et al.*, 2014). A further connection between Spirulina and anxiety may be the amino acids present therein. The nutritious quality of a protein is linked to the quality of amino acids, digestibility coefficient, and its biologic quality. Essential amino acids present in Spirulina are leucine (540 mg per 10g), valine (400mg per 10g), isoleucine (350mg per 10g), and tryptophan (90mg per 10g) (Demelash, 2018).

The synthesis of 5-hydroxytryptamine (5-HT) in the brain is increased by tryptophan, the natural

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amino acid precursor in 5-HT biosynthesis, thereby possibly stimulating 5-HT release and function. As a naturally present dietary component, tryptophan must be less toxic and cause little undesirable consequences. Owing to the aforesaid benefits, tryptophan-supplemented diets have been utilized to manage neuropsychiatric disorders, and the outcomes are variably successful (General *et al.*, 2001). Declined brain serotonin (5-HT) concentrations or functioning have been involved in diverse psychopathologic states, including anxiety (Nishizawa *et al.*, 1997). Accordingly, Spirulina is the vital creature in the world, being the paramount and cost-free accessible source that represents the preeminent candidate to enhance the nutritional elements needed for our psychological health (Demelash, 2018).

This study is the first clinical trial to assess the consumption effects of a functional product containing Spirulina on anxiety in patients with hypertension. Out of the weaknesses of the present study, the lack of analysis of OS markers and the activity of antioxidant enzymes were investigated. For a more comprehensive conclusion, it is suggested that future studies use higher dosages, larger sample size, and more duration of intervention.

Conclusion

The results indicate that adding Spirulina as a functional food to salad dressing might be a good option to promote health and reduce the risk of CVD in hypertensive patients. However, further investigations are required for a more comprehensive conclusion. The authors recommend the implementation of Spirulina in functional food for patients with hypertension in the treatment and prevention methods.

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Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contributions

Ghaem Far Z, Babajafari S and Mazloomi SM participated in propose the original idea of the study, supervise the work. Ghaem Far Z also carried out the stages of intervention, data collection, draft the article, and review. Mazloomi SM also contributed to formulation of the products, investigation of required analytical tests, quality as well as the safety of the products. Nouri N contributed to draft and revision of the article and final approval of the manuscript. Ashrafi-Dehkordi contribute to data analysis, statistical analysis, and interpretation. Kojuri J visited the patients and carry out the stages of intervention. All authors read and approved the final version of the manuscript.

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