Effect of Spirulina Supplementation

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Contributor: Piotr Machowiec

Spirulina is a microalga that presents various important pro-health properties, for instance lowering blood pressure in the research. The study aims to appraise the efficacy of Spirulina administration on systolic (SBP) and diastolic blood pressure (DBP). Randomized controlled trials (RCTs) were retrieved by a systematic search of PubMed, Web of Science, and the Cochrane Library databases from inception to June 2021 according to a standardized protocol. The effect size of each study was counted from mean and standard deviation before and after the intervention and shown as Un-standardized mean difference and 95% confidence interval. Sensitivity analyses were performed. Meta-analysis on 5 RCTs with 230 subjects was eligible. The amount of Spirulina ranged from 1 to 8 g per day, and intervention durations ranged from 2 to 12 weeks. Data analysis indicated that Spirulina supplementation led to a significant lowering of SBP (Mean Difference (MD): −4.59 mmHg, 95% Confidence Interval (CI): −8.20 to −0.99, I square statistic (I2) = 65%) and significant lowering of DBP (MD: −7.02 mmHg, CI: −8.86 to −5.18, I2 = 11%), particularly in a subgroup of hypertensive patients. Spirulina administration might have a supportive effect on the prevention and treatment of hypertension. More exact randomized controlled trials are needed to clarify the effect of Spirulina supplementation on blood pressure.

Keywords: Spirulina ; diastolic blood pressure ; systolic blood pressure ; hypertension

1. Introduction

Arterial hypertension is the crucial independent risk factor in cardiovascular diseases for developed countries, characterized by an increasing prevalence in recent years [1][2]. Despite significant advancement in perception, diagnosis, and therapy of hypertension, it is underlined that blood pressure control is insufficient in less than half of the hypertensive patients and it poses a challenge for further patients' management [2]. The most common method of treatment of hypertension is drug therapy. Nevertheless, one of the difficulties with decreasing blood pressure values is that monotherapy is often inadequate and that is why combination therapy may be considered in some cases [3][4], especially in elderly patients. Alternatively, natural medical products are frequently used as adjunctive therapy to improve long-term outcomes in patients with arterial hypertension and to reduce the number of antihypertensive drugs that are taken. Thus, it may potentially exclude the side effects concerned with combination therapy use [5].

The intake of microalgae has been popularized for centuries and for the sake of their nutritional value and properties, its intake is recommended by organizations, such as WHO (World Health Organization) and FAO (The Food and Agriculture Organization) [6][7]. Microalgae contain a variety of biologically valuable substances including proteins, polyunsaturated fatty acids, amino acids, antioxidants, pigments, minerals, and vitamins [7]. *Spirulina*, a microscopic and filamentous cyanobacterium is considered a sustainable and eco-friendly microalga, playing an increasing role in alternative medicine [8].

Spirulina presents various important pro-health properties according to experimental studies and human research. Antioxidant, anti-inflammatory, and immunomodulatory activities of *Spirulina* were investigated in experimental studies on animals [9][10][11][12]. Hypoglycemic and hypolipidemic activities were described in human research [9][13]. According to clinical studies, the antioxidant activity of *Spirulina* might be a potential treatment for chronic obstructive pulmonary disease and might improve motor development among infants [10][14].

The effect of *Spirulina* intake on blood pressure is considered in some human randomized clinical trials. However, the results are not completely decisive and they should be deepened. A few studies indicated that *Spirulina* significantly changes (lowers) only the systolic blood pressure (SBP) [15][16] or only the diastolic blood pressure (DBP) [17]. Two studies reported that there were no statistically significant differences between the experimental and control group regarding systolic and diastolic blood pressure [18][19]. In this meta-analysis, we evaluated the effectiveness of *Spirulina* supplementation on systolic and diastolic blood pressure to elucidate the subject. According to the PICOS (Participants, Intervention, Comparison, Outcomes, Study design) statement, our meta-analysis aims to find an answer to the question

does the oral use of *Spirulina* in a daily dose from 1 to 8 g and more for 2, 8, or 12 weeks in adult patients with co-existing diseases reduce systolic and diastolic blood pressure.

2. Current Research on *Spirulina*

Arterial hypertension is one of the most common health problems in developed countries and is a risk factor for cardiovascular diseases. Numerous studies have shown the positive effect of certain nutrients and dietary interventions on high blood pressure levels [20]. Diet with natural fruits and vegetables containing antioxidants has a blood pressure-lowering effect [20]. According to recent studies, lycopene-carotenoid from tomatoes or such nutraceuticals as flavonoids contained in cacao, beetroot with nitrates, garlic, and fish oil, being a source of unsaturated fats, have the potential to improve blood pressure [20][21].

In this paper, we present the results of a systematic review and meta-analysis which indicated *Spirulina* supplementation significant reduction of systolic and diastolic blood pressure. Our meta-analysis focuses on SBP and DBP parameters and not all components of metabolic syndrome, which makes the study comprehensible. *Spirulina* is a functional food that might have a beneficial effect on decreasing blood pressure. However, individual RCTs showed some different results regarding blood pressure values between themselves. Martínez-Sámano et al. showed a statistically significant decrease in systolic blood pressure after 12 weeks of *Spirulina* supplementation in a dose of 4.5 g per day ($p < 0.05$) and no statistically significant changes regarding the diastolic blood pressure [15]. Miczke et al. confirmed a hypotensive effect of *Spirulina*. Significant decreases in SBP and DBP were observed in the *Spirulina* group after three months of treatment with 2 g [16]. Administration of 8 g per day of *Spirulina* for 12 weeks showed a significant lowering effect on DBP ($p < 0.021$) and no significant effect on SBP in the study by Lee et al. [17]. Results of the study by Jensen et al. indicated that with a dose of 2.3 g there were no statistically significant differences between *Spirulina* and placebo groups regarding SBP and DBP at baseline or after 2 weeks. However, the consumption was associated with a mild reduction in DBP [18]. In contrast, Moradi et al. claimed that *Spirulina* taken 1 g per day by ulcerative colitis patients did not influence blood pressure values ($p > 0.05$) [19].

Discrepancies require further in-depth analyzes. Some other possible confounding factors in assessing the impact of *Spirulina* on SBP and DBP, for example, physical activity, diet, and smoking should be taken into consideration. These conflicting outcomes of the studies can depend on the supplementation of different doses of *Spirulina* in different periods of time. The fact that no significant hypotensive effect was seen after administration of 1 g of *Spirulina* might suggest the role of the appropriate dosage of the supplement to decrease blood pressure. It is worth mentioning that no significant changes in blood pressure parameters were noted in studies, in which the duration of *Spirulina* supplementation was below 12 weeks: 2 or 8 weeks, respectively [18][19]. Studies of 12 weeks of *Spirulina* administration showed a significant decrease in at least one component of blood pressure [15][16][17]. However, our subgroup analysis based on a dose of supplementation indicated that there was no significant difference between dose ≤2 g or >2 g, and subgroup analysis based on “≥12 weeks” or “<12 weeks” duration of *Spirulina* intake did not show any difference between subgroups. Meta-analysis results are evidence of greater importance than analysis of particular studies. It is worth highlighting that *Spirulina* supplementation resulted in greater SBP lowering in a subgroup of hypertensive patients compared with those with normal blood pressure. It suggests that patients with hypertension might reap greater benefits with *Spirulina* supplementation. Both dosage and the duration of supplementation require further studies.

Other non-randomized controlled studies assessing a relationship between *Spirulina* intake and blood pressure values showed that 4.5 g per day for 6 weeks had the positive effect on SBP and DBP reduction in a sample of overweight patients [22]. On the contrary, Mazopakis et al. found no significant changes in SBP and DBP after the intervention of 1 g of *Spirulina* per day for 12 weeks in a Cretan population [23][24].

The mechanism of lowering blood pressure by *Spirulina* is partially understood. It was supposed that the high content of potassium in *Spirulina* might have a lowering effect on blood pressure [17]. Phycocyanin, a blue pigment with antioxidant activity from *Spirulina*, decreases parameters of blood pressure by strenghtening the expression of endothelial nitric oxide synthase in the aorta after the stimulation of adiponectin [19][25]. Oxidative stress connected to endothelial damage, contributing to a decrease in nitric oxide synthase (NOs), and decreased vasoconstriction has been reported in hypertension [15]. In mice, the decameric peptide of *Spirulina platensis* decreases blood pressure levels through a PI3K (phosphoinositide-3-kinase)/AKT (serine/threonine kinase Akt)/eNOS (endothelial NO synthase) -dependent mechanism [26]. Martínez-Sámano et al. proved the antioxidative properties of *Spirulina* in SBP—they observed an increase in glutathione peroxidase (GPx) activity and oxidized glutathione (GSSG) concentrations ($p < 0.05$) [15]. Additionally, sVCAM-1, sE-selectin, and endothelin-1 levels—considered as markers of endothelial dysfunction were reduced [15]. *Spirulina* improves endothelial function by reducing arterial stiffness index (SI) [27]. Moreover, *Spirulina* contains natural angiotensin

I converting enzyme inhibitor (ACEi) peptide. ACEi suppresses the synthesis of angiotensin II that induces the vasoconstriction of blood vessels and the release of aldosterone, resulting in blood pressure increase [27][28][29]. More studies should be performed to confirm these hypotheses and evaluate the exact mechanism of antihypertensive properties of the substance in humans.

Due to many complications of hypertension, intake of *Spirulina* with antioxidant and hypotensive activity might reduce blood pressure, which potentially reduces cardiovascular risk and prevents serious effects such as stroke or heart attack. Moreover, hypertension is frequently associated with diabetes mellitus and metabolic syndrome. Some studies revealed that *Spirulina* intake improved glucose and lipid metabolism, reduced oxidative stress, modulated appetite, so it can be considered as a therapeutic nutraceutical not only by reducing blood pressure [13][25]. According to our analysis, *Spirulina* may potentially reduce blood pressure among hypertensive patients. Supplementation of *Spirulina* products promoted as “superfoods” is more and more popular due to its health benefits, but recent studies revealed contamination of toxic substances—cyanotoxins, heavy metals, or polycyclic aromatic hydrocarbons (PAHs) [30][31]. Further research is needed, which doses and forms are the most effective and safe for patients. It is necessary to assess the safety profile of combination therapy consisting of *Spirulina* and pharmacotherapy.

The limitations of this meta-analysis were the small number of analyzed RCTs and the lack of possibility to assess publication bias. However, the greatest strength of this paper is the inclusion of two novel studies from 2018 and 2021 [15][19]. The studies were first included in a meta-analysis that broadened the analysis compared with the previous meta-analysis assessing the influence of *Spirulina* supplementation on a decrease of blood pressure. In the meta-analysis by Huang H. et al. *Spirulina* supplements significantly lowered DBP (weighted mean differences = −7.17 mmHg; 95% CI: −8.57 to −5.78; $p = 0.0001$; $I^2 = 0\%$), but not SBP (weighted mean differences = −3.49 mmHg; 95% CI: −7.19 to 0.21; $p = 0.06$; $I^2 = 50\%$) [32]. Differences in included studies might be a reason for different results for SBP compared with our meta-analysis. Yousefi et al. in a systematic review came to similar conclusions to our meta-analysis that additional studies with greater sample sizes and extended durations are needed to establish the hypotensive effect of *Spirulina* [33].

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