Spirulina (Arthrospira)

Subjects: Nutrition & Dietetics

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Spirulina (*Arthrospira*) is a cyanobacteria considered to be a blue-green microalga that has historically been consumed by North Africans and Mexicans because of its nutritional value, containing 60–70% protein by dry weight and bioactive compounds (Neyrinck, Taminiau et al. 2017). The currently preferred name for the genus *Spirulina* is *Arthrospira*, while spirulina is referring generically to biomass preparations of the microalga. *Arthrospira* species are abundant in tropical and subtropical areas with carbonate and bicarbonate-rich alkaline water bodies (Richmond and Hu 2013). They contain high concentrations of antioxidants (β-carotene and phycocyanin), minerals (K, Na, Ca, Mg, Fe, Zn), vitamins (tocopherols), eight essential amino acids, PUFAs (especially γ-linolenic acid (ALA, 18:3 n-6)), and phenolic compounds (Neyrinck, Taminiau et al. 2017). Nowadays, spirulina is used as a nutritional dietary supplement, mainly due to its anti-inflammatory activity, and its intake is recommended for individuals with pathologies and conditions such as arterial hypertension, IR and diabetes among others.

Arthrospira algae microalgae obesity diabetes dietary fiber Unsaturated Fatty Acids Polyphenols Phycobilins

1. Spirulina (*Arthrospira*) and Metabolic Alterations

In vivo studies indicate that *Arthrospira maxima* and *platensis*, as well as other microalgae, exert their anti-obesity effects via the reduction of both adipogenesis in white adipose tissue (WAT) and lipogenesis in WAT and brown adipose tissue (BAT). They increase lipolysis in WAT, lipid oxidation in WAT and skeletal muscle, and also thermogenesis and mitochondriogenesis in WAT, BAT, and skeletal muscle [1]. An ethanolic extract of *A. maxima* (150 or 450 mg/kg/day) reduced body weight, both subcutaneous and visceral adipose tissue, blood fasting glucose and lipid concentrations in mice fed a high-fat (HF) diet [2]. These changes were associated with lower protein expression of factors related to adipogenesis and higher expression of proteins related to adenosine 5′-monophosphate-activated protein kinase-α (AMPKα)-induced adipose browning [2]. In rats, the administration of dried *A. maxima* (62.5, 125, or 250 mg/kg) also reduced weight gain and the elevated WAT index induced by an HF diet, and it attenuated the changes related to metabolic alterations, including serum adiponectin, leptin, tumor necrosis factor α (TNF-α), glucose, insulin, and the lipid profile. These effects of *A. maxima* appear to be associated with activation of the AMPK pathway and sirtuin 1 (SIRT1) in mesenteric adipose tissue and skeletal muscle, leading to the suppression of lipid synthesis [3].

Another species, *A. platensis*, modulates dysbiosis, intestinal inflammation, and gut permeability in rats fed an HF diet. When administered as 3% of feed, it counteracted the dysbiotic changes triggered by the HF diet, namely the

increased populations of Proteobacteria and Firmicutes. *A. platensis* also decreased inflammatory cytokines and the expression of myeloid differentiation factor 88 (MyD88), toll-like receptor 4 (TLR4), and NF-κB p65, as well as that of tight junction proteins in the intestinal mucosa (ZO-1, Occludin, and Claudin-1) [4]. A recent meta-analysis of 12 clinical trials analyzed the effect of spirulina supplementation on anthropometric indexes [5]. Spirulina was found to reduce body weight and waist circumference as well as body mass index when supplementation lasted for more than 12 weeks. The authors therefore suggest that spirulina may be used as an adjuvant treatment for obesity [5].

Spirulina biomass as well as the different extracts obtained from it have shown potential as antidiabetic agents. While studies that focus on the prevention of diabetes are scarce, a recent review summarized studies in which spirulina was tested in humans presenting different MS factors [6]. In one study, ingestion of 2–6 g of spirulina per day resulted in an improvement in insulin sensitivity and a reduction in glycated hemoglobin (HbA1c), although other studies did not show any detectable effect [6]. Studies in animal models have also shown an effect of spirulina on metabolic risk factors. *A. platensis* was found to counteract hyperglycemia and hyperlipidemia induced by alloxan in mouse [7] and rat [8][9] models of T1DM [10]. Moreover, *A. platensis* (5% in the diet) counteracted renal injury and oxidative stress in alloxan-induced diabetic rats [11]. *A. platensis* also showed antidiabetic effects in streptozotocin (STZ)-injected rats [12][13][14]; animals injected with STZ are also models of T1DM [10]. *A. platensis* (500 mg/kg body weight, 2 months) significantly decreased serum glucose, HbA1c, and malondialdehyde (MDA) levels and significantly increased the serum insulin concentration and the activity of antioxidant enzymes, as well as normalizing their mRNA gene expression and inducing upregulation of the gluconeogenic enzyme pyruvate carboxylase (PC), the pro-apoptotic factor Bax and caspase-3 (CASP-3), and TNF-α gene expression [13]. The authors suggested that the antioxidant, anti-inflammatory, and anti-apoptotic properties of spirulina might be due to its polyphenolic components. In an HF diet/low-dose STZ (HFD/STZ) rat model of diabetes, oral doses of *A. platensis* (250, 500 or 750 mg/kg body weight) for 30 days were shown to ameliorate levels of fasting blood glucose, insulin, and hepatic enzymes [14]. *A. platensis* also influenced the serum lipid profile and exhibited an anti-inflammatory effect via TNF-α and adiponectin modulation, in turn, probably mediated by the sterol regulatory element-binding transcription factor-1c (SREBP-1c) [14].

Arthrospyra contains a variety of bioactive components that may contribute to its beneficial effects on diabetes-associated alterations (hyperglycemia, hyperlipidemia, inflammation, and oxidative stress) acting through different mechanisms. The biomass of a typical industrial preparation of spirulina contains 71.7 g protein, 8.5 g fat, 3.0 g fiber, 16.2 g phycocyanin, and 477.0 mg carotenoids per 100 g dry weight [15]. It has been suggested that the dietary fiber and bioactive peptides are primarily responsible for the protection against IR it provides [16].

2.1. Dietary Fiber from Spirulina

Dietary fiber is believed to prevent IR through maintaining balanced gut microbiota (prebiotic effect) and its direct action on epithelial and immune cells that regulate the intestinal barrier and immune function [17] Spirulina (*A. platensis)* biomass has been shown to promote the growth of putatively beneficial microorganisms (e.g., *Lactobacillus casei*, *L. acidophilus*, *Saccharomyces thermophilus*, and *Bifidobacterium* spp.) and to reduce the populations of putatively harmful bacteria in vitro [18][19][20]. In healthy male mice, spirulina (1.5–3.0 g of spray-dried

A. platensis powder/kg body weight daily for 24 days) was found to modify the cecal populations of microbiota at the genus level (*Clostridium* XIVa, *Desulfovibrio*, *Eubacterium*, *Barnesiella*, *Bacteroides*, and *Flavonifractor*). These changes correlated with markers of oxidative stress and with blood lipid levels [21][22]. A polysaccharide isolated from spirulina was effective at lowering blood glucose and increasing superoxide dismutase (SOD) in STZ-induced diabetic Sprague-Dawley rats (100–200 mg/kg body weight by intragastric administration for 8 weeks) [23]. Whether the effects of spirulina are partially mediated by its fiber components (e.g., oligo and polysaccharides) remains to be clarified.

2.2. Peptides and Enzymes from Spirulina

Hydrolysates from seaweeds and microalgae contain bioactive peptides with putative applications in the food industry [24][25][26]. Peptides from spirulina biomass may make a decisive contribution to its antidiabetic effects. Proteins in *A. platensis* mainly consist of two phycobiliproteins (PBP): C-phycocyanin (C-PC) and allophycocyanin (APC) [27]. Tripsin hydrolysates of PBP yield fragments with dipeptidyl peptidase-IV (DPP-IV) inhibitory activity [28]. DPP-IV is a serine exopeptidase that is considered a promising target for the management of T2DM, because it plays a key role in glucose metabolism via N-terminal truncation and subsequent inactivation of the incretins glucagon-like peptide 1 (GLP-1) and gastrointestinal insulinotropic peptide (GIP), which are responsible for most postprandial insulin secretion [29]. The peptide Leu-Arg-Ser-Glu-Leu-Ala-Ala-Trp-Ser-Arg obtained from *A. platensis* by ultrasound treatment and subcritical water extraction exhibited inhibition of DPP-IV (IC_{50} 167.3 µg/mL). This peptide also showed further activity that would contribute to the protective effects of *A. platensis* against hyperglycemia: inhibition of α-amylase (IC_{50} 313.6 µg/mL) and α-glucosidase (IC_{50} 134.2 µg/mL) [30]. These two activities are important because they delay the digestion of starch and, consequently, lower post-prandial glycaemia [31]. While the potency of this decapeptide against these three enzymes is modest, the combined effect of these and other activities (e.g., the prebiotic effects of dietary fiber) may result in an efficient overall effect for the whole biomass. Enzymatic hydrolysates of spirulina biomass also contain angiotensin I-converting enzyme (ACE-I) inhibitors [32]. ACE-I is a dipeptidyl carboxypeptidase that catalyzes the conversion of angiotensin I to angiotensin II, a process that increases blood pressure. ACE-I inhibitors reduce the concentration of angiotensin II and consequently lower blood pressure [33]. This antihypertensive effect of peptidic fractions (200 mg/kg body weight) in spontaneously hypertensive rats has been attributed to the active peptides in *A. platensis*: Ile-Ala-Glu (IC_{50} 34.7 µM), Phe-Ala-Leu, Ala-Glu-Leu, Ile-Ala-Pro-Gly (11.4 µM), and Val-Ala-Phe (35.8 µM) [34]. Furthermore, the decapeptide Gly-Ile-Val-Ala-Gly-Asp-Val-Thr-Pro-Ile from *A. platensis* has been found to exert direct endothelium-dependent vasodilation ex vivo via a PI3K (phosphoinositide-3-kinase)/AKT (serine/threonine kinase Akt) pathway, resulting in NO release [35].

2.3. Unsaturated Fatty Acids from Spirulina

The ethanolic (95% ethanol) fraction of *A. platensis* biomass contains a mixture of unsaturated fatty acids that have a hypolipidemic effect in Wistar rats fed an HF diet [36]. This effect is mediated via upregulation of the AMPK-α pathway and downregulation of the SREBP-1c and the 3-hydroxy-3-methyl glutaryl coenzyme A reductase, acetyl CoA (HMG-CoA) pathways in the liver. The extract was found to increase the populations of putatively beneficial

bacteria, such as *Prevotella*, *Alloprevotella*, *Porphyromonadaceae*, *Barnesiella*, and *Paraprevotella*, while reducing the populations of *Turicibacter*, *Romboutsia*, *Phascolarctobacterium*, *Olsenella*, and *Clostridium* XVIII, which correlated positively with serum TAG, total cholesterol (TC), and low-density lipoprotein cholesterol levels, but negatively with serum high-density-lipoprotein TC levels [36]. The ethanolic (55% ethanol) fraction (SP55) extracted from *A. platensis* showed antihyperglycemic activity in male rats fed an HF diet, as assessed by the oral glucose tolerance test (OGTT) [37]. The extract contained both saturated and unsaturated fatty acids. Other active components, such as polyphenols and peptides, may also have been extracted under the conditions used. The SP55 fraction appears to increase the gut populations of *Oscillibacter*, *Parasutterella*, and *Alloprevotella* and to decrease the abundance of *Turicibacter* [37].

2.4. Polyphenols from Spirulina

Phlorotannins (phloroglucinol-based polyphenols) and bromophenols (brominated phenolic derivatives) are both families of polyphenols that are abundant in algae [25]. Algal polyphenols have shown small-to-medium positive effects on fasting blood glucose, TC, and low-density lipoprotein (LDL) cholesterol levels in humans [25]. Little is known about the possible role of polyphenolic components in *Arthrospyra* in its antidiabetic effect. A polyphenol-rich butanol extract was found to have quite potent α-glucosidase inhibitory activity (IC_{50} 23 µg/mL) [38]. Inhibitors of intestinal α-glucosidases are instrumental in the management of diabetes, because they lower postprandial blood glucose levels. The total phenolic and flavonoid contents were estimated to be 121 mg gallic acid equivalents/100 g and 27 mg rutin equivalents/100 g *A. platensis* biomass, respectively, but no more information was provided on the structure of the putative phenolics [38]. Another ethanolic extract of spirulina biomass obtained after hydrolysis showed α-amylase inhibitory activity [39]. Although the possible structures of the active polyphenols were not revealed, the authors showed evidence that chlorogenic acid is a major component in the extract.

2.5. Pigments from Spirulina

Phycobilins are secondary pigments in microalgae that capture light energy while protecting microalgae from harmful radiation [40]. Phycocyanin, a blue pigment biosynthesized by *Arthrospyra*, was found to protect insulin-producing pancreatic islets from alloxan injury in mice at doses of 100 and 200 mg/kg body weight [41]. It also reduced fasting blood glucose and glycosylated serum protein (GSP) levels, maintained the total antioxidative capacity, reduced TC levels and TAG levels in the serum and liver, increased the level of hepatic glycogen, and maintained glucokinase (GK) expression in the liver. The authors suggested that inhibition of the p53 pathway could be one of the mechanisms responsible for the protection provided by phycocyanin, as it decreased p53 expression in the pancreas at the mRNA level [41]. Phycocyanin may also exert its antidiabetic effect via the inhibition of both α-amylase and α-glucosidase, as suggested by molecular docking and in vitro testing [42]. Moreover, phycocyanin from *A. platensis* reduced plasma TC and LDL cholesterol as well as oxidative stress and NADPH oxidase expression induced by an atherogenic diet in hamsters, particularly when administered together with selenium [43]. The authors suggested that phycocyanin might prevent atherosclerosis.

β-Carotene extract obtained from *A. platensis* biomass presented antihyperglycemic activity in STZ-induced diabetic mice when given at a dose of 100 mg/kg body weight after 10 days of treatment [44].

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