The Efficacy of *Spirulina* Supplementation on Diabetes

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As a result of rising mortality rates due to cardiovascular diseases (CVDs), there has been a growing urgency to find alternative approaches to conventional pharmaceutical treatment to prevent the onset of chronic diseases. *Arthrospira platensis*, commonly known as *Spirulina*, is a blue-green cyanobacterium, classified as a “superfood”, used worldwide as a nutraceutical food supplement due to its remarkable nutritional value, lack of toxicity, and therapeutic effects. Many research studies have demonstrated that *Spirulina* has therapeutic functions such as antioxidant, anti-inflammatory, hypolipidemic, antidiabetic, and brain-protective properties.

Spirulina supplementation diabetes blood glucose level antioxidant metformin

1. Introduction

Arthrospira platensis is a photosynthetic, microscopic filamentous blue-green microalga classified as a cyanobacterium belonging to the Microcoleaceae family [1]. *A. maxima* and *A. platensis*, commonly known as “*Spirulina*”, are the two most studied species for their considerable nutritional and therapeutic properties. *Spirulina* inhabits tropical regions, particularly alkaline lakes with a pH 11 and a high concentration of carbonate and bicarbonate salts. Additionally, these algae can survive in extreme environments, such as the frozen lakes of Antarctica [2][3]. These microorganisms were first discovered in Lake Texcoco in Mexico. The Aztecs were among the first to incorporate this microalga into their diet, particularly in the creation of a blue-green cake known as “tecuitlatl”, as unearthed by the Spanish army during their conquest of Mexico [4]. Since ancient times, *Spirulina* has been utilized for its beneficial characteristics. Today, *Spirulina* is still used in a wide range of applications. In recent decades, it has garnered the classification of a “superfood” because of its copious protein content (60–70% by dry weight) as well as its abundance of carbohydrates, essential fatty acids, vitamins, minerals, and pigments like carotenes, chlorophyll a, and phycocyanin [5]. Because of its impressive nutritional value, is widely utilized in both the food and pharmaceutical fields. In the food industry, *Spirulina* is used as a nutraceutical food supplement, added to foods such as baked goods, beverages, dairy products, sports supplements, and baby food [6]. On the other hand, the pharmaceutical sector has produced tablets, dehydrated powders or encapsulated forms, which are marketed as “nutraceuticals” [7].

As a consequence of the considerable market demand for *Spirulina* products, *S. platensis* has been classified as generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) [8]. Many research studies have demonstrated that *Spirulina* has therapeutic functions such as antioxidant, anti-inflammatory, hypolipidemic,

antidiabetic, and brain-protective properties [9][10][11]. Remarkably, the abundant presence of natural pigments endows *Spirulina* with antioxidant potential, notably carotenoids and C-phycocyanin [12][13]. Several research investigations indicated that β-carotene, diadinoxanthin, diatoxanthin, and C-phycocyanin exhibited very high scavenging activity [14][15]. Thanks to its antioxidant properties, this microalga is considered beneficial in preventing cardiovascular diseases [11]. Today, CVDs are the main cause of death globally [16]. Therefore, drug therapies used today to prevent certain predisposing disorders such as diabetes, hypertension, and dyslipidemia display many benefits and, at the same time, some adverse effects. For this reason, the use of nutraceuticals, such as *Spirulina*, has been shown promising results as a support therapy for the maintenance of cardiovascular health and the reduction in cardiovascular risk [17][18]. This renewed focus on functional-food-based therapy is now seen as a new strategy to achieve a healthy generation. In the 21st century, it is essential to follow the ideologies established by Hippocrates (460–377 B.C.), who claimed “Let food be your medicine” [19].

In the last decade, there has been a gradual increase in individuals afflicted with type 2 diabetes [20]. Diabetes mellitus (DM) represents a complex disease marked by elevated glucose levels and an increased basal metabolic rate because of a defect in insulin signaling.

In these conditions, hyperglycemia adversely affects the integrity of cellular membranes, leading to insulin resistance in both the liver and peripheral tissues and producing reactive oxygen species (ROS) [21].

Moreover, type 2 diabetes accounts for approximately 90% of all diagnosed cases of diabetes and is considered a risk factor for the development of CVDs, including myocardial infarction, peripheral vascular disease (PVD), heart failure, stroke, retinopathy, and neuropathy, as a result of microvascular and macrovascular complications due to hyperglycemia [22].

One of the proposed pharmacological approaches to treat hyperglycemia in diabetes is the utilization of metformin [23]. Generally, metformin has no impact on lipid profiles in subjects diagnosed with type 2 diabetes [24].

However, it is important to note that before considering the use of metformin, which can induce side effects of similar to those of digestive disorders, such as diarrhea and nausea [25], there are preventive measures that can be taken to avoid the development of diabetes. Pre-diabetes is a condition that occurs before the onset of diabetes, where blood sugar levels are higher than the normal range but not high enough to be considered type 2 diabetes.

Although it is often not possible to avoid the onset of the disease, exercise and food supplements can delay or improve the management of the disease because of improvements insulin sensitivity [26]. Furthermore, the bioactive ingredients contained in some food supplements, such as polyphenols, polysaccharides, and others, can affect the modulation of glucose metabolism [27].

Considerable research has focused on studying natural compounds with antihyperglycemic properties, such as *Spirulina*. Furthermore, unlike metformin, *S. platensis* not only reduces circulating glucose levels but can also

influence lipoprotein metabolism, high levels of which are associated with diabetes. This would represent a possible cardiovascular benefit in diabetic patients [28].

Spirulina has gained attention as a functional food due to its potential to lower blood glucose levels, control cholesterol, and provide antioxidant benefits.

2. Clinical Studies

A recent randomized, double-blind, placebo-controlled study included 60 patients under usual treatment with metformin for type 2 diabetes [29]. The results suggest that 2 g of *Spirulina platensis* given as four capsules before meals, in addition to metformin therapy, markedly improved glycemic parameters, including glycosylated hemoglobin (HbA1c) ($p < 0.001$) and fasting blood glucose levels (FBS) ($p < 0.001$), compared to the placebo group under metformin treatment only. Hence, the supplementation of 2 g/day of *S. platensis* for 3 months is considered safe and free of side effects, making it an effective treatment option for the management of type 2 diabetes and its associated complications [29]. In line with this evidence, Alam et al. [30] evaluated that the administration of 7 g twice daily of *Spirulina* powder in patients with no pharmacological treatment can reduce FBS ($p < 0.01$) and postprandial glycemia (PPBS) similarly to the control group who received two capsules of 500 mg metformin before meals for 45 days. The authors observed no statistically significant differences in HbA1C levels induced by *Spirulina* treatment. As stated by the authors, this scenario could probably be due to the short duration of treatment and the small sample size. Further studies are needed to evaluate its pharmacological effect and its usefulness as a reliable alternative to classic antidiabetic agents [30]. Sowjanya and colleagues [31] divided diabetic patients into two groups. The first group (EG-1) was given 2 g of *Spirulina* contained in two snack bars (25 g each) in the mid-morning and evening. The second group (EG-2) was given two *Spirulina* capsules in the morning and evening, while the control group was given no supplementation. In both the EG-1 and EG-2 groups, their FBS, PPBS and HbA1c levels were significantly more reduced from the baseline to the endpoint both in males ($p < 0.01$) than in females ($p < 0.05$). In the EG-1 group, the reduction in FBS and PPBS levels was greater than in the EG-2 group, possibly due to the synergistic effects of other nutritional ingredients. In addition, the reduction in FBS and PPBS in females is lower than that in males [31]. Another clinical study showed that 2 g/day of *Spirulina* capsules, taken during lunch and dinner for 2 months, led to a reduction in FBS, PPBS, and HbA1c ($p < 0.05$) from the baseline to the endpoint [32]. A similar effect was induced by a dosage of 8 g of *Spirulina* administered daily for 3 months in tablet form to 50 patients with type 2 diabetes treated with their usual antidiabetic therapy, but the reduction in HbA1c levels was not significant. It is possible that *Spirulina* can lower serum glucose levels in the short term, but it may require a longer treatment period to affect hemoglobin A1C levels [33]. The reduction in the HbA1c level highlighted suggests an improvement in the regulation of long-term glucose management.

Moreover, in Cretan patients with non-alcoholic fatty liver disease (NAFLD), 6 g/day *Spirulina* (Greek production) supplementation for six months led to a significant reduction in the HOMA-IR index, a measure representing an enhancement in insulin sensitivity [34]. The main characteristics at the baseline and after *Spirulina* supplementation of the included studies are shown in **Table 1**.

Table 1. Detailed characteristics of the included studies on diabetic patients.

References	Patients' Cohort	Dose of *Spirulina*	Duration Treatment (Weeks/Months)	Outcomes in *Spirulina* Group; (*p*-Value)	Outcomes in Control Group; (*p*-Value)	*p*-Value
				HbA1c (mg/dL)	**HbA1c (mg/dL)**	
				Baseline 8.87 ± 0.29	Baseline 8.47 ± 0.21	0.65
				End 7.44 ± 0.20	End 8.15 ± 0.17	NA
Karizi et al., 2022 [29]	*Spirulina* + Metformin group;	2 g/day	3 months	*p* = 0.001	*p* = 0.016	
	Placebo + Metformin group			**FBS (mg/dL)**	**FBS (mg/dL)**	
				Baseline 167.30 ± 4.34	Baseline 227.60 ± 67.85	0.47
				End 136.33 ± 4.42	End 165.47 ± 3.37	NA
				p = 0.001	*p* = 0.99	
				HbA1c (mg/dL)	**HbA1c (mg/dL)**	
				Baseline 9.73 ± 1.92	Baseline 9.61 ± 1.49	0.862
				End 9.95 ± 2.11	End 9.15 ± 2.03	0.303
				p = 0.525	*p* = 0.459	
				FBS (mg/dL)	**FBS (mg/dL)**	
Alam et al., 2016 [30]	*Spirulina* group;	7 g/day	45 days	Baseline 245.53 ± 78.95	Baseline 227.60 ± 67.85	0.525
	Placebo + Metformin			End 204.87 ± 78.15	End 191.80 ± 78.91	0.65

References	Patients' Cohort	Dose of *Spirulina*	Duration Treatment (Weeks/Months)	Outcomes in *Spirulina* Group; (*p*-Value)	Outcomes in Control Group; (*p*-Value)	*p*-Value
	group					
				$p = 0.003$	$p = 0.212$	
				PPBS (mg/dL)	**PPBS (mg/dL)**	
				Baseline 345.73 ± 98.33	Baseline 329.60 ± 72.92	NA
				End 303.67 ± 96.16	End 282.80 ± 99.90	NA
				NA	NA	
				HbA1c (mg/dL)	**HbA1c (mg/dL)**	
				Baseline EG-I M 9.19 ± 0.88; W 8.88 ± 0.70 EG-II M 7.33 ± 0.54; W 7.20 ± 0.33	Baseline M 8.00 ± 1.05; W 8.64 ± 0.79	NA
				End EG-I M 7.11 ± 0.64; W 7.64 ± 0.48 EG-II M 6.48 ± 0.36; W 6.58 ± 0.35	End M 7.98 ± 1.03; W 8.62 ± 0.74	NA
				EG-I M $p < 0.01$; W $p < 0.01$ EG-II M $p < 0.01$ W $p < 0.01$	M n.s; W n.s	
	EG1 group;			**FBS (mg/dL)**	**FBS (mg/dL)**	

References	Patients' Cohort	Dose of *Spirulina*	Duration Treatment (Weeks/Months)	Outcomes in *Spirulina* Group; (*p*-Value)	Outcomes in Control Group; (*p*-Value)	*p*-Value
Sowjanya et al., 2022 [31]	EG2 group	2 g/day	3 months	Baseline EG-I M 138.00 ± 18.39; W 128.08 ± 11.76 EG-II M 135.02 ± 18.22; W 132.33 ± 10.89	Baseline M 146.10 ± 25.29; W 135.12 ± 10.27	NA
	Control group			End EG-I M 122.21 ± 14.48; W 111.00 ± 14.48 EG-II M 119.31 ± 14.33; W 123.12 ± 9.81	End M 141.43 ± 20.84; W 130.12 ± 9.76	
				EG-I M $p < 0.01$; W $p < 0.01$ EG-II M $p < 0.01$; W $p < 0.05$	M n.s; W n.s	NA
				PPBS (mg/dL)	**PPBS (mg/dL)**	
				Baseline EG-I M 210.33 ± 28.99; W 212.12 ± 39.45 EG-II M 197.45 ± 23.31 W 190.03 ± 14.86	Baseline M 206.17 ± 22.83; W 179.24 ± 17.82	NA
				End EG-I M	End M 202.37 ±	NA

References	Patients' Cohort	Dose of *Spirulina*	Duration Treatment (Weeks/Months)	Outcomes in *Spirulina* Group; (*p*-Value)	Outcomes in Control Group; (*p*-Value)	*p*-Value
				165.56 ± 25.35; W 175.58 ± 32.11 EG-II M 171.28 ± 24.77 W 175.50 ± 18.38	22.76; W 172.09 ± 15.49	
				EG-I M $p < 0.01$; W $p < 0.01$ EG-II M $p < 0.01$; W $p < 0.05$	M n.s; W n.s	
				HbA1c (mg/dL)	**HbA1c (mg/dL)**	
				Baseline 9.0 ± 2.3	Baseline 8.7 ± 1.5	NA
				End 8.0 ± 1.3	End 8.7 ± 1.3	NA
				$p < 0.05$	n.s	
				FBS (mg/dL)	**FBS (mg/dL)**	
				Baseline 161.7 ± 48.6	Baseline 164.3 ± 59.4	NA
Parikh et al., 2001 [32]	*Spirulina* group;	2 g/day	2 months	End 142.4 ± 27.4	End 165.1 ± 44.3	NA
	Control group			NA	NA	
				PPBS (mg/dL)	**PPBS (mg/dL)**	
				Baseline 264.9 6 65.2	Baseline 215.2 6 67.3	NA
				End 248.8 6 68.9	End 212.3 6 57.6	NA
				NA	NA	

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References	Patients' Cohort	Dose of *Spirulina*	Duration Treatment (Weeks/Months)	Outcomes in *Spirulina* Group; (*p*-Value)	Outcomes in Control Group; (*p*-Value)	*p*-Value
				FBS (mg/dL)		
Beihaghi et al., 2017 [33]	*Spirulina* group;	8 g/day	3 months	Baseline 158.1 ± 44.2	NA	
	Control group			End 127.8 ± 36.7		
				NA		

Abbreviations: HbA1c, glycosylated hemoglobin; FBS, fasting blood glucose levels; PPBS, post-prandial blood glucose; EG1, Experimental group-1 who received *Spirulina* snack bar; EG2, Experimental group-2 who received *Spirulina* capsules; NA, not available. n.s, not significant.

Overall, *Spirulina* supplementation has been shown to be an effective agent for hyperglycemia; however, it is necessary to increase the number of studies and the duration of the treatment to confirm its effect on the regulation of HbA1c levels, indicative of long-term glucose management. These studies pave the way for future research on the use of nutraceuticals as an adjunct to basic therapy in managing diabetes mellitus.

3. Animal Studies

Similar research on the hypoglycemic property of *Spirulina* has been conducted in animal models. *Spirulina* oral supplementation in different concentrations (5, 10, and 15 mg/kg body weight) in streptozotocin-diabetic rats led to a decrease in FBS levels and, on the other hand, elevated plasma insulin and serum C-peptide concentrations ($p < 0.05$). Moreover, the researchers observed an increase in total hemoglobin levels in the *Spirulina*-treated group, which may be indirectly proportional to HbA1c formation, due to its ability to lower circulating glucose levels and its high iron content which is crucial for the metabolism of hemoglobin [34].

Further, the oral administration of *Spirulina* in albino diabetic rat models, at 10, 20, and 30 mg/kg body weight diluted in distilled water, resulted in a significant dose-dependent reduction in FBS compared to the diabetic control group ($p < 0.01$) [35].

Also, El-Sayed and colleagues [37] demonstrated that phenolic compounds and phycocyanin contained in *Spirulina* are responsible for the hypoglycemic effect. The four groups of diabetic rats treated for 30 days with oral *Spirulina* biomass suspension (50 mg/kg body weight), phycocyanin (50 mg/kg body weight), phycocyanobilin (982 µg/kg body weight), and phycopeptide (49 mg/kg body weight), respectively, showed a reduction in fasting blood glucose level and in the HOMA-IR score, which highlights insulin resistance, compared to the control and glibenclamide groups ($p \leq 0.05$). In addition, a histopathological analysis revealed that diabetic rats treated with *Spirulina*,

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4. Mechanism of Action

Although the mechanisms are not fully understood, *Spirulina* could be involved in pancreatic insulin secretion by islet β-cells or facilitate glucose transport from the blood to peripheral tissues [35].

The insulin-releasing impact of *S. platensis* occurs through a multitude of pathways, such as the adenylate cyclase/cAMP or phosphatidylinositol pathway or through direct influence on membrane depolarization [38].

Proteins extracted from *Spirulina* have been found to improve glucose entry into liver cells and promote glycogen synthesis by increasing the activities of hexokinase (HK) and pyruvate kinase (PK), which ultimately leads to lower blood glucose levels and improves insulin resistance.

Additionally, three peptides extracted from *Spirulina platensis* inhibit α-amylase, α-glucosidase, and dipeptidyl peptidase-4 (DPP-IV), which are critical enzymes involved in glycemic control. This makes them useful targets in treating type 2 diabetes [39].

The high fiber content of *Spirulina* may hinder glucose absorption, leading to a glucose-lowering effect [40].

According to Hozayen et al. [41], *Spirulina* could have a positive impact in diabetic rats, enhancing serum adiponectin and decreasing TNF-α levels. High levels of adiponectin are commonly known to improve insulin sensitivity, while low levels of a pro-inflammatory cytokine TNF-α enhance glucose production in the liver and the ability of insulin to stimulate glucose uptake in peripheral tissues. Furthermore, the antioxidant capacity caused by *Spirulina* supplementation has been shown to increase GSH levels and SOD and GPx activity. As a result, it protects against oxidative-stress-induced cell damage associated with diabetes [41].

Some authors believe that the antioxidant capacity of *Spirulina* is attributed to phycocyanin, selenium-bound phycocyanin, phenolic acids, and flavonoids, which are known for their antioxidant action in preventing diabetes-induced pancreatic cell damage, while chromium-bound phycocyanin activates insulin receptors [37].

As a consequence of increased antioxidant enzymes, malondialdehyde (MDA) levels are decreased following *Spirulina* supplementation [42].

Lastly, Sadek et al. [43] provided evidence that *Spirulina* exerts its antidiabetic effect by attenuating the upregulation of gluconeogenic enzyme pyruvate carboxylase (PC) and pro-apoptotic Bax and caspase-3 (CASP-3) gene expression in diabetic rats, thereby resulting from its antioxidant activity. Furthermore, *Spirulina* has been shown to possess anti-apoptotic properties by mitigating the expression of pro-apoptotic MAPK pathways, consequently leading to the attenuation of apoptotic pathways induced by diabetes [43].

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