The mechanism of action of Spirulina as antidiabetic: a narrative review

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ABSTRACT

Spirulina happens to be a special type of blue-green algae that originally emerged 3.5 billion years ago and was used as a source of nutrition. Spirulina gets its name from the filaments' spiral or helical structure, but its true name is taxonomically Genus *Arthrospira* which encompasses several species. The most common species are *S. fusiformis*, *S. maxima*, and *S. platensis*. It is rich in various nutrients and chemical components including protein, carbohydrates, lipids, vitamins, minerals, pigments, chlorophyll, and enzymes. Spirulina's active molecules and rich nutrients make it have several pharmacological activities and uses including antioxidant, anti-inflammatory, immunomodulatory, immune system booster, anticancer, antiviral activity, and neuroprotective properties. It is also utilized as a nutritional supplement and for weight loss. Moreover, several studies confirm that Spirulina improves insulin sensitivity and reduces blood glucose levels in rat models as well as diabetic patients. The reason behind this unique behavior could be credited to the presence of several active components in it, but the action's fundamental mechanism is still a matter of debate. Several studies have suggested different mechanisms including anti-inflammatory activity, increased insulin sensitivity, inhibition of gluconeogenesis, antioxidant activity, modulating gut microbiota composition, improved glucose homeostasis, and insulin receptor activation. Therefore, it became clear that Spirulina is a mine of active substances used as a nutritional supplement and reduces blood glucose levels or used in conjunction with other treatments to tackle type 2 diabetes. Further exploration is required to fully explain its effects on human physiology and determine optimal dosages for treatment.

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Introduction

A significant global health issue is diabetes mellitus. Globally, 537 million individuals living in the world have diabetes, according to the International Diabetes Federation. If appropriate preventive measures are not adopted, this figure will eventually rise to as many as 643 million individuals by the year 2030.[1] Chronic disease diabetes is characterized by the pancreas not producing enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar levels. Diabetes is classified into four general categories: The first type (happens with autoimmune beta-cell destruction); the second type (attributable to a non-autoimmune gradual loss of sufficient-cell insulin

production); the 3rd category is a specific type of diabetes due to other cases, such as monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced (glucocorticoid, organ transplantation treatment or AIDS treatment) diabetes; in addition, the 4th category of diabetes is gestational diabetes which occurs during pregnancy.[2] Managing diabetes can be challenging, but with appropriate treatment and self-care, diabetes individuals are able to live a healthy and fulfilling life. The course of treatment may involve weight management, focused glycemic control, preventing and treating comorbid conditions, and avoiding consequences including hypoglycemia.[3,4] Cyanobacteria is thought to have emerged 3.5 billion years ago. Spirulina gets its name from the filaments' spiral or helical structure.[5] Filamentous floating microalgae called Spirulina develop in water bodies that are alkaline. Spirulina was consumed as food by the Kanembu, Toltecs, and Mayas around the time of the Aztec civilization in Mexico about 400 years ago. In addition, it has been proposed as a sustainable, environmentally benign microalga for CO_2 fixation, nitrification, and bioremediation.[5,6] It is highly protein-rich and is high in vitamins, minerals, and antioxidant contents. Spirulina has been shown to have many benefits for health, including antidiabetic properties.[7] Many studies have recently looked at Spirulina's functional and nutritional potentials as an antioxidant, anti-hyperlipidemic, and anti-hyperglycemic. Therefore, this study will review the characteristics of *Spirulina* antidiabetic bioactive peptides. Consequently, this study aims to provide a comprehensive review of the characteristics of bioactive peptides in Spirulina with antidiabetic properties.

What is Spirulina?

Cyanobacteria, the earliest bacterial class to acquire the ability to convert atmospheric CO_2 into organic carbon compounds while generating oxygen, plays a crucial role in this process. The name "Spirulina" is derived from the helical or spiral structure of its cyanobacteria filaments. Spirulina, previously known as Arthrospira, represents a group of cyanobacteria (microscopic filamentous) that engage in photosynthesis and have a longstanding utilization in the past as a food source.[8]

Among the commercially significant microalgae, certain species belonging to the cyanobacterial genus Arthrospira hold notable prominence. Despite their taxonomic inaccuracy, they are commonly referred to as "Spirulina". The infra-generic classification of this genus remains uncertain.[9] The classification of Spirulina (T'ah'lab) falls within the Cyanobacteria phylum, Cyanophyceae class, and Oscillatoriales order. The genus Spirulina comprises various species, including *S. maxima*, *S. fusiformis*, and *S. platensis*. These three species are widely used as dietary supplements due to their high nutritional value.[10]

Spirulina possesses a prokaryotic gram-negative bacterial cell structure devoid of membrane-bound organelles. The cell wall of Spirulina consists primarily of peptidoglycan and lipopolysaccharides, forming a thin, multilayered envelope. Additionally, the thylakoid membranes of Spirulina cells contain carboxysomes, ribosomes, phycobilisomes, DNA fibrils, gas vacuoles, and granules containing cyanophycin, polyphosphate, and poly-glycan.[8]

Optimally thriving in warm conditions (with an ideal temperature range of 35-38°C), Spirulina grows in alkaline water with a pH range of 8-11.5, abundant CO_2, and ample nutrients (nitrogen, phosphorus, potassium, and other trace minerals). Adequate illumination is necessary for photosynthesis to occur. Overall, Spirulina is a relatively adaptable alga capable of flourishing in diverse environments as long as its fundamental requirements are met. After cultivating Spirulina biomass commercially, the subsequent steps involve harvesting, drying, and packaging.[8]

Chemical components

Spirulina is renowned for its abundance of diverse nutrients and chemical constituents. It contains significant amounts of protein, carbohydrates, lipids, vitamins, minerals, pigments, polysaccharides, trace elements, chlorophyll, and enzymes. Notably, Spirulina is particularly rich in glycolipids, carotenoids, phycocyanin, sulfolipids, superoxide dismutase, DNA, and RNA.[11,12]

As a protein source, Spirulina stands out, comprising approximately 60-70% protein by weight. The protein it provides is highly digestible and contains all essential amino acids. The alga also contains various carbohydrates, including glucose, fructose, and polysaccharides. While its lipid content is relatively low, Spirulina does contain essential fatty acids, primarily ω-6 fatty acids such as linoleic acid including γ-linolenic acid. Moreover, Spirulina is an affluent source of vitamins A, C, and E, as well as thiamine, riboflavin, pyridoxine, niacin, and folic acid.[13,14] It also provides an array of minerals, including magnesium, potassium, iron, calcium, sodium, phosphorus, copper, zinc, and selenium. Spirulina's pigment profile encompasses chlorophyll-a, phycocyanin (a blue pigment), carotenoids (including beta-carotene), and xanthophylls. The alga's antioxidant properties are attributed to compounds such as phycocyanin and beta-carotene, which help safeguard cells against oxidative damage. Spirulina further contains various polysaccharides known for their immune-enhancing properties (Figure 1). *S. platensis* offers numerous phytonutrients that are often lacking in typical human

diets, setting it apart from other dietary options due to its distinctive nutrient.[15]

To provide a tangible comparison, 3 grams of Spirulina exhibit greater anti-inflammatory and antioxidant activity than five servings of fruits and vegetables, containing 5100% greater iron than spinach, 3100% greater β-carotene than carrots, and 180% more calcium than whole milk.[16] Turkish Spirulina, specifically, has been found to possess a high antioxidant capacity. Among the phenolic compounds discovered in Spirulina, pinocembrin (41.28%) and acacetin (53.62%) represent the major components. These phenolic compounds exhibit a bio-accessibility value of approximately 60%. Polyunsaturated fatty acids play a crucial role in preventing lipid peroxidation, thereby functioning as essential antioxidant molecules.[7] The alcoholic extract of Spirulina, analyzed by GC-MS, revealed several bioactive constituents, including 1-monolinoleoylglycerol trimethylsilyl ether, phytol, 2-methylene- (3β,5α), fatty acids, and cholestan-3-ol.[17]

Uses and pharmacological activities

Spirulina has been found to have various pharmacological activities and uses including the following: i) antioxidant activity: Spirulina contains phycocyanin, which is a potent antioxidant. It scavenges free radicals and prevents oxidative damage to cells; ii) anti-inflammatory activity: Spirulina has anti-inflammatory properties due to the presence of phycocyanin and other compounds including polysaccharides and fatty acids. It reduces inflammation by inhibiting the production of pro-inflammatory cytokines;[5] iii) immune system booster: Spirulina has been shown to improve immune function by increasing the production of antibodies and white blood cells; iv) immunomodulatory activity: Spirulina enhances the immune system by increasing the production of antibodies, cytokines, and natural killer cells; v) anticancer activity: Spirulina has been found to have anticancer properties due to its ability to inhibit tumor growth and encourage apoptosis (programmed cell death) in cancer cells; vi) neuroprotective activity: Spirulina protects neurons from oxidative stress and inflammation, which are connected to neurodegenerative illnesses like Parkinson's and Alzheimer's; vii) antidiabetic: Spirulina has been shown to reduce blood sugar levels in animal studies by enhancing insulin sensitivity; viii) cardiovascular health: Spirulina may help lower blood pressure and reduce cholesterol levels, which can improve cardiovascular health; ix) neuroprotective: some studies suggest that Spirulina may have neuroprotective properties due to its ability to reduce inflammation and oxidative stress in the brain.[18-21]

Spirulina is utilized as a dietary supplement for weight loss, diabetes management, cardiovascular health, and skin health. It is used for several purposes including the following: i) nutritional supplement, Spirulina is a valuable origin of vitamins, protein, and minerals. It is used as a nutritional supplement to improve overall health and prevent nutrient deficiencies; ii) weight loss, Spirulina is effective in reducing body weight by suppressing appetite and increasing metab-

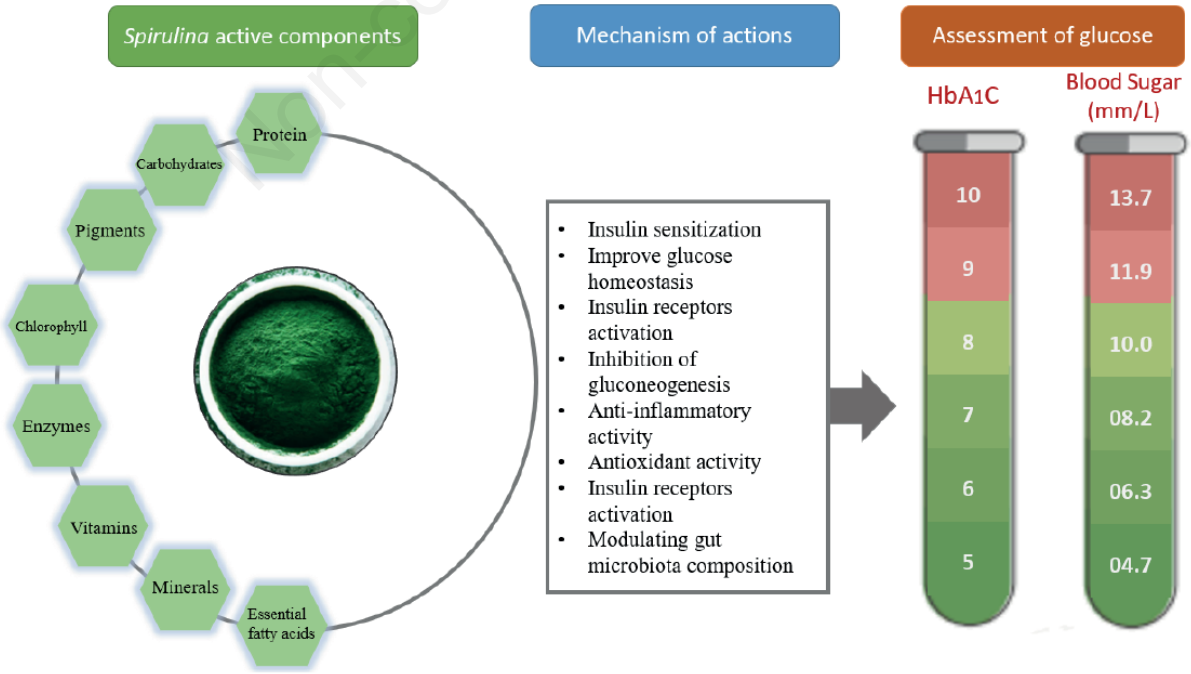

Figure 1. Spirulina active components and antidiabetic mechanism of action.

olism; iii) cardiovascular health, Spirulina reduces cholesterol levels, triglycerides, and blood pressure, and improves endothelial function, which is beneficial for cardiovascular health; iv) skin health, Spirulina has been found to improve skin health by reducing inflammation, oxidative stress, and improving collagen production; v) in diabetes management, Spirulina has been found to enhance insulin sensitivity and decrease blood sugar levels in diabetic patients.[14,22]

Under diabetes conditions, oxidative stress may be generated, and it is probably implicated in the development of pancreatic-cell dysfunction. Additionally, when the system is experiencing oxidative stress, pancreatic cells may be prone to attacks from the reactivity of the oxygen because of the comparatively low manufacturing of antioxidant enzymes like superoxide dismutase and catalase.[23] Similar to this, excessive quantities of free radicals brought on by an insufficient antioxidant defense system can impair cellular function, damage membranes through oxidation, and make them more vulnerable to lipid peroxidation.[24]

Streptozotocin-induced rat studies have demonstrated that dietary treatment with natural antioxidants for instance flavonoids, vitamin E, melatonin, and vitamin C, several of them present in Spirulina, which reduced oxidative stress and diabetic condition.[13,14]

S. platensis has several beneficial qualities, but its antioxidant capacity is one of the most significant. Antioxidants are chemicals that counteract the free radicals produced as a result of oxidative stress. Free radicals may wreak havoc inside the body in addition to being bothersome molecules in the surroundings. They are the unstable byproducts of typical cell operations.[25]

The oxygen molecule's unpaired electron renders it unstable and electrically charged, which is the cause of its destructive effects. Only when it connects with the closest other molecules accessible, this unstable molecule become stable. These molecules can be anything from fats, carbohydrates, and proteins to DNA. It has been demonstrated that the effects of these free radicals might range from cell death to harm to the affected cell. *S. platensis*' essential amino acids and fatty acids, highly rich protein content, carotenoids, vitamins, minerals, and other antioxidant-active elements, which support growth and preserve health, may be the cause of its antioxidant benefits.[12]

Vitamins in the form of pills are preferable to naturally occurring meals high in these antioxidants. It is an excellent source of natural antioxidants in addition to having a high protein content because it contains extremely high levels of tocopherol, beta-carotene, and these antioxidants in combination. Spirulina can be used to make a variety of enzymes, including antioxidant enzymes. Superoxide dismutase, a crucial enzyme for scavenging free radicals, is highly present in it. As aging is thought to be a result of oxidative stress, this enzyme can be utilized therapeutically to treat a variety of disorders linked to oxidative stress or as a component in anti-wrinkle skin creams and face masks. The essential amino acids, high protein, vitamins, minerals, essential unsaturated fatty acids, carotenoids, phenolic compounds, and other antioxidant active elements of *S. platensis* may be the cause of its antioxidant activities, which support growth and health.[14,26,27] The chemoprotective and radioprotective properties of *S. platensis* polysaccharide make it potentially useful as an addition to cancer treatment. In the mouth, submucous fibrosis is lessened by beta-carotene. *S. platensis* safeguarding cells against radiation-induced damage. Following post-radiation, phycocyanin dramatically reduced the dehydrogenase activity in rat models.[28,29]

S. platensis generates calcium spirulan is a unique sulfated polysaccharide product and it acts as an antiviral action by preventing enveloped viruses' entry mechanism, for instance, Measles, Cytomegaloviruses, Varicella zoster, and Herpes simplex (HSV-1&2) entry into the host cell. By blocking the adsorption of the virions, sulfated polysaccharide from the red alga Porphyridium.[30]

Additionally, Spirulina possesses neuroprotective properties that greatly reduce cerebral mantle (cortex) damage and animals' enhanced locomotor activity following stroke. Long-term administration of Spirulina helped prevent ischemic brain damage and showed the nervous system to be on the defense against oxidative stress brought on by fluoride exposure in the offspring of pregnant animals exposed to fluoride-induced oxidative stress.[12,31] *S. platensis* extracts demonstrated antioxidant activity utilizing the 2,2-Diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl (DPPH) free radical scavenging and reducing power, as well as overall antioxidant capacity activity. The methanolic extract of *S. platensis* had the greatest antioxidant activity across all test tests and the greatest inhibitory effects on the diabetes enzymes α-amylase (96.46%) and α-glucosidase (97.42%).[17]

A rats' *in vivo* study of *S. platensis* showed that it has antioxidant, hypoglycemic, and hypolipidemic activity.[31,32] Both diabetic and controlled rats given *S. platensis* showed a strong antinociceptive effect. *S. platensis* was given orally to a painful diabetic neuropathic rat model for a month to determine its diabetic status and antinociceptive effects.[32]

Spirulina is a viable supplement for diabetes patients since it can lower the lipid, kidney, and liver disease indicators in animals that have been given streptozocin to develop these diseases. Spirulina has a very high potential as a natural treatment and management option for the difficulties of the liver and kidney caused by diabetes.[33]

Hypoglycemic property (activity)

Diabetes is a chronic condition that interferes with the body's ability to process blood sugar. Diabetes comes in two primary forms: type 1 and 2. The immune system of the body targets and destroys pancreatic cells that make insulin in type 1 diabetes, a long-term autoimmune condition that stops your pancreas from producing insulin which is a hormone controlling blood glucose. To control their blood glucose levels, type 1 diabetics must administer insulin via injections or an insulin pump, while a metabolic disorder known as second-type diabetes occurs when the body develops insulin resistance or produces insufficient amounts of insulin to control blood glucose levels. Therefore, the second type of diabetes can be controlled by changing lifestyle, for instance by doing exercise and modifying diet but some individuals may also need medication or insulin therapy. Other types of diabetes include gestational diabetes, which occurs during pregnancy, and prediabetes, in which blood glucose levels are higher than the normal average but not high enough to be classified as second-type diabetes. Chronic hyperglycemia is a hallmark of the metabolic disease diabetes mellitus. It results from either insulin receptor sensitivity issues or poor insulin secretion. Oxidative stress levels rise in association with diabetes mellitus and its consequences. Increases in the degree of oxidative stress are frequently linked to diabetes mellitus and its consequences.[34]

Hyperglycemia, a feature of diabetes mellitus, is frequently followed by several problems, including hypertension, obesity, atherosclerosis, hyperlipidemia, and even cardiovascular disease.[35]

Spirulina lowered triglyceride, glycemia, and values of total cholesterol in alloxan-induced diabetic animals. The outcomes demonstrated that *S. platensis*'s antidiabetic impact was already apparent after a 5-day course of treatment.[36]

In streptozotocin-induced diabetic male rats, *S. maxima* reacts as a hypoglycemic agent. Hippocampal tissue homogenates from obese rats treated with Spirulina combined with glycyrrhizin orally showed decreased acetylcholinesterase activity, blood glucose, cholesterol, and leptin levels.[12,31] Spirulina is a meal that is rich in nutrients and is full of antioxidants. It may act as an antioxidant agent and a nutrient-rich diet that can help prevent diabetes problems when combined with kefir.[34]

The microalga *S. platensis* has a high concentration of γ-linolenic acid, proteins, minerals, and vitamins, as well as other biological functions. It is a potential medication for the management of illnesses like diabetes mellitus. Additionally, Spirulina has anti-lipidemic and anti-hyperglycemia activity by lowering blood sugar, controlling triglycerides, and cholesterol, and promoting insulin resistance.[12,31]

Spirulina is thought to have an antihyperglycemic impact because it contains powerful antioxidant bioactive compounds (phycocyanin, beta-carotene, and others) that boost the islet beta-cells ability to secrete insulin or because it facilitates the transit of blood glucose to peripheral organs.[37]

Spirulina reduces blood glucose to the normal range in diabetes streptozotocin-induced diabetic rats. After treatment, in the pancreas, no insulitis was detected. Spirulina's hypoglycemic action is caused by a decrease in the activity of the enzyme hexokinase in the liver and an increase in the enzyme glucose 6-phosphatase in muscles, whereas insulin's hypoglycemic action may be caused by a decrease in intestinal glucose absorption, a rise in peripheral glucose disposal, and a decrease in hepatic glucose production.[38,39]

Because the effect of Spirulina at a dose of 15mg/kg BW gives a higher considerable than 5 and 10mg/kg BW, the former was employed in additional biochemical and clinical research.[40]

Due to its high content of γ -linolenic acid, (ω-6) polyunsaturated fatty acids, *Arthrospira* has been discovered to lower free radical and antioxidant imbalance and lower blood glucose. Spirulina therapy resulted in increases in GSH-Px and SOD levels of 240 and 60% in healthy animals and 19 and 59% in diabetic animals, respectively. *Arthrospira* consumption reduced blood glucose, total cholesterol, triglyceride, and malondialdehyde levels in diabetic rats by 20, 31, 22, and as much as 56%, respectively. Spirulina has been proven *in vitro* and *in vivo* experiments to have effects on diabetic rats that are anti-hyperlipidemic, anti-hyperglycaemic, and antioxidative.[7]

In addition to its antidiabetic efficacy, *S. platensis* extract demonstrated antioxidant activity utilizing the DPPH-reducing power, and measurement of total antioxidant activity. The methanolic extract of *S. platensis* had the highest rich antioxidant activity across all test tests and the greatest inhibitory effects on the diabetes enzymes α-amylase (96.46%) and α-glucosidase (97.42%).[17]

The methanolic extract was analyzed using GC-MS, which identified several bioactive components, including 1-monolinoleoylglycerol trimethylsilyl ether, phytol, cholestan-3-ol, 2-methylene- (3β,5α), and fatty acids. To execute their derived antioxidant and antidiabetic properties, these substances may work in synergy.[17]

Diabetes mellitus also caused a rise in the levels of malondialdehyde, glucose, lipid profile, alanine transaminase (ALT), aspartate aminotransferase (AST), tumor necrosis factor- α (TNF-α), and interleukin-6 (IL-6). Diabetes mellitus also drastically decreased the plasma concentration of antioxidant enzymes and trace minerals in the liver. *S. platensis* (20 & 30 mg/kg BW) was taken orally, and these reduced levels of lipid parameters, malondialdehyde, glucose, AST, ALT, TNF-

α, and IL-6. The plasma concentrations of selenium, zinc, copper, and iron increased at the same levels, as did the activity of antioxidant enzymes. Therefore, *S. platensis* may offer trace minerals to form antioxidant enzymes that ultimately lower glucose levels, anti-inflammatory reactions, and lipid profiles.[41]

The antioxidant activity of *S. fusiformis* is presumably what makes it helpful in streptozotocin-induced diabetic rats. *S. fusiformis* also demonstrates that it is successful in preventing kidney damage induced in diabetic rates by keeping serum markers for renal function including uric acid, creatinine, and urea at close to normal range.[39]

The ability of *S. fusiformis* to lower hyperlipidemia in streptozotocin-induced diabetic rats. Spirulina can help people maintain good glycemic control, as demonstrated by the decline in their increased levels of HbA1C. According to histopathological parameters, *S. fusiformis* shields tissues from oxidative tissue damage, reducing diabetes problems in the liver and pancreas.[39] *S. fusiformis* contains the bioactive substances voronikhin and phycocyanin, which have antihyperglycemic or antidiabetic properties.[42]

A rat's *in vivo* study of *S. platensis* showed that it has antioxidant, hypoglycemic, and hypolipidemic activity.[31] Instead of insulin and other hypoglycemic medications, bioactive substances derived from *S. platensis* like phycocyanin, phycocyanobilin, and phycocyanopeptide work as antioxidants and can be used as an anti-diabetic therapy to lessen their negative effects. Phycocyanin as well as Spirulina phenolic components provide the antioxidant action of *S. platensis*. The selenium-binding phycocyanopeptide and chromophore in phycocyanobilin are credited with phycocyanin's antioxidant properties. The phycocyanin's hypoglycemic impact is ascribed to a chromium-binding peptide that activates insulin receptors.[31]

Spirulina was able to lessen the generation of free radicals and reactive oxygen species, as well as the oxidative stress brought on by hyperglycemia. Additionally, it was able to stop DPP-IV, alpha-amylase, and alpha-glucosidase from working. In doing so, it dramatically lessened the impact that streptozocin had on the liver and kidneys at the organ level and on antioxidant enzymes with regard to the cellular level. Spirulina is a viable supplement for diabetes patients since it can lower the lipid, liver, and kidney disease indicators in rats that have been given streptozocin to develop these diseases. The antioxidant properties of the biomass as a whole may be the basis for Spirulina's antidiabetic effects, or some bioactive components may also play a role.[33]

Spirulina's mode of action might involve an increase in the levels of the insulinotropic polypeptide that is glucose-dependent and the glucagon-like peptide-1 incretin hormone, which are active. Additionally, it has very potent *in vivo* and *in vitro* antioxidant properties that are actively used in type 2 diabetes treatment. The substantial levels of phytoconstituents like Vitamin E, iron, chromium, phycocyanins, chlorophyll, carotenes, saponins, flavonoids, and other phenolic compounds that have previously demonstrated antioxidant activity may be the cause of the Spirulina's antioxidant effects. Spirulina has a very high potential as a natural treatment and management option for the difficulties of the liver and kidney caused by diabetes.[33]

A functional food that manages blood glucose levels, *S. maxima* is a good candidate for diabetes therapy. In Streptozotocin-induced diabetic rats, *S. maxima* was an effective neutraceutical for lowering blood sugar levels. It also helped the animals gain weight.[43]

By lowering the increased blood sugar level, the take of *S. platensis* methanolic extract at doses of 15 and 10 mg/Kg BW produced antihyperglycemic activity. There was a notable decline in the various liver, renal, and hyperlipidemia linked to diabetic functions. Additionally, compared to the alloxan-induced diabetic animals, the alcoholic extract therapy enhanced the total protein, body weight, hemoglobin, and albumin levels. Additionally, administering the extract to diabetic rats improved the histological conditions of the pancreas and liver. These findings supported the use of *S. platensis* methanolic extract when creating pharmaceutical formulations for the treatment of diabetes and its symptoms.[17]

Kefir and Spirulina have a high nutritional and antioxidant capacity, and studies in diabetic rats show that this combination can improve antioxidant status and manage glycemic status. Kefir and Spirulina demonstrated great nutritional value, potent antioxidant properties, a low alcohol content, and the potential to regulate the glycemic state and superoxide dismutase activity of streptozotocin-nicotinamide-induced diabetic rats. The dietary approach to the control of diabetes may include kefir-spirulina based on its characteristics.[34]

Cellular experiments were performed to investigate the potential contribution of ion channels and cAMP to the insulinotropic effects of *S. platensis* extracts in both *in vitro* and *in vivo* settings. In a concentration-dependent way, the *S. platensis* extract induced the release of insulin from mice islets and pancreatic beta-cells. Glucose, tolbutamide, isobutylmethylxanthine, and a depolarizing concentration of KCl all contributed to the insulin-releasing activity. By removing extracellular Ca^{2+} and using diazoxide and verapamil, the insulin secretory action was reduced. Dipeptidyl peptidase IV enzyme activity was shown to be considerably inhibited by *S. platensis* butanol fraction. *S. platensis* enhanced the amount of unabsorbed sucrose in the stomach and significantly reduced postprandial hyperglycemia after oral sucrose load. The butanol fraction increased gut

motility and inhibited glucose absorption during *in situ* intestinal perfusion with glucose.[44] Taking *S. platensis* butanol fraction orally for 28 days reduced blood sugar levels, raised plasma insulin levels, increased pancreatic insulin storage, increased liver glycogen levels, and enhanced lipid profiles. The butanol fraction of *S. platensis* contained p-coumaric acid, catechin, β-carotene, and other antioxidant polyphenolics, according to the characterization of the active components. Therefore *S. platensis* might be used in conjunction with other treatments to combat type 2 diabetes.[44,45]

Mechanism of antidiabetic compounds

The mechanism of action underlying the antidiabetic effects of Spirulina-derived compounds is not completely understood, but several studies have identified potential mechanisms: i) insulin sensitization: Spirulina extracts have been shown to enhance insulin sensitivity in both animal models and human studies (Figure 1). This effect may be attributed to the presence of polysaccharides and phycocyanin, which improve glucose uptake and utilization by cells;[46] ii) inhibition of gluconeogenesis: Spirulina extracts have demonstrated the ability to inhibit hepatic gluconeogenesis, the process by which the liver produces glucose from non-carbohydrate sources. This inhibition could be due to the presence of gamma-linolenic acid and other fatty acids that regulate glucose metabolism;[47,48] iii) Antioxidant activity: Spirulina extracts are rich in antioxidants like phycocyanin, carotenoids, and vitamin E. These compounds scavenge free radicals and reduce oxidative stress, a major contributor to diabetes complications; iv) protein content and bioactive peptides: Spirulina has a high protein concentration (60-70% dry weight) and contains bioactive peptides derived from its protein content. These components may contribute to the antidiabetic effects of Spirulina;[31] v) anti-inflammatory activity: chronic inflammation plays a key role in insulin resistance and type 2 diabetes. Spirulina extracts possess anti-inflammatory properties that can reduce inflammation in adipose tissue and improve insulin sensitivity;[41,45] vi) insulin receptor activation: Spirulina phycocyanin's hypoglycemic impact has been linked to a chromium-binding peptide that activates insulin receptors, enhancing insulin signaling and glucose uptake;[31] vii) gut microbiota modulation: emerging evidence suggests that gut microbiota plays a critical role in glucose metabolism and insulin resistance. Spirulina extracts have been found to modulate the composition of gut microbiota, potentially improving glucose homeostasis in animal models.[49]

While these mechanisms offer insights into the potential therapeutic effects of Spirulina in managing diabetes, further research is needed to fully understand the underlying molecular pathways and validate these findings through rigorous clinical investigations. Spirulina is generally considered safe in commonly used doses and only rare potential unwanted mild effects may include mild digestive problems and allergies in some individuals also it may interact with certain medications in some people. Therefore, to be aware of the appropriate dosage which can vary depending on age, health condition, and individual needs.

Conclusions

Spirulina, a natural substance renowned for its abundance of essential nutrients and potential pharmacological properties, has emerged as a promising avenue for various health conditions. The derivation of antidiabetic compounds from Spirulina unveils a spectrum of mechanisms through which they may exert their effects, encompassing insulin sensitization, inhibition of gluconeogenesis, antioxidant activity, anti-inflammatory activity, and modulation of gut microbiota. However, a more profound understanding of these mechanisms and their therapeutic applications in diabetes management necessitates further exploration.

Although Spirulina has been embraced as a nutritional supplement, with promising outcomes in reducing blood glucose levels and complementing existing treatments for type 2 diabetes, a comprehensive comprehension of its impact on human health remains imperative. Elucidating optimal dosages for therapeutic utilization and undertaking extensive research endeavors are pivotal in unlocking the full potential of Spirulina in the realm of medicine and healthcare. By delving into these aspects, the profound benefits of Spirulina could be harnessed to their maximum extent, thereby revolutionizing the landscape of medical interventions and advancing the boundaries of healthcare practices.

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