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ORIGINAL ARTICLE

Therapeutic evaluation of oral Spirulina platensis on glycemic control and pain modulation in streptozotocin-induced diabetic neuropathic Long-Evans rats

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Monira Shahnaz[1], Iffat Rejwana[2], Tamanna Jannat[3], Nahid Afroj[4], A K M Nizam Uddin[5], Rakibul Islam[6]

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Correspondence to
Monira Shahnaz

ORCID
https://orcid.org/0000-0002-1874-4556

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ABSTRACT

Background: *Diabetic neuropathy, a major chronic complication of diabetes, results from hyperglycemia, oxidative stress, and neuroinflammation. Spirulina platensis, a nutrient-rich cyanobacterium, has antioxidant, anti-inflammatory, and potential blood sugar-lowering effects. This study evaluated Spirulina's effects on blood sugar and pain behavior in STZ-induced diabetic rats.* ***Methods & Materials:*** *Sixty Long Evans rats were allocated into six groups: control, Spirulina-treated, and sodium salicylate–treated for both non-diabetic and diabetic conditions. Diabetes was induced with STZ (60 mg/kg). Spirulina was given orally at 500 mg/kg/day for a month. Blood glucose and body weight were measured at baseline and week four. Nociceptive behavior was assessed using the formalin test, covering neurogenic (0–10 min) and inflammatory (15–60 min) phases.* ***Results:*** *Untreated diabetic rats developed marked hyperglycemia by week four (265.2 ± 28.13 mg/dL). Spirulina treatment significantly reduced fasting glucose (148.7 ± 25.47 mg/dL; P < 0.01), while non-diabetic groups remained normoglycemic. Body weight improved modestly in Spirulina-treated diabetic rats (200.8 ± 4.0 g to 212.9 ± 4.1 g), compared with minimal gains in diabetic controls. Formalin-induced nociceptive scores were highest in diabetic rats (1st phase: 2.18 ± 0.08; 2nd phase: 2.03 ± 0.07). Spirulina significantly attenuated nociception in both phases (1.67 ± 0.06 and 1.53 ± 0.05; P < 0.01), indicating both anti-neurogenic and anti-inflammatory effects. Sodium salicylate reduced pain predominantly in the late phase.* ***Conclusion:*** *Spirulina platensis exhibits strong antihyperglycemic, metabolic, and antinociceptive effects in STZ-induced diabetic rats. Its combined antioxidant, anti-inflammatory, and insulin-modulating activities suggest promising therapeutic potential for managing diabetic neuropathy and associated metabolic disturbances. Further mechanistic and clinical studies are warranted to validate its translational applicability.*

Keywords: *Spirulina platensis; diabetic neuropathy; streptozotocin; antihyperglycemic effect; antinociception*

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1. *Assistant Professor, Department of Physiology, Green Life Medical College, Dhaka, Bangladesh*
2. *Assistant Professor, Department of Physiology, Dhaka Community Medical College, Dhaka, Bangladesh*
3. *Assistant Professor Department of Pathology, Prime Medical College, Rangpur, Bangladesh*
4. *Medical Officer, Kurmitola General Hospital, Dhaka, Bangladesh*
5. *Junior Consultant, Surgery, Brahmanbaria Sadar Hospital, Brahmanbaria, Bangladesh*
6. *MPH Student, Department of Public Health, North South University, Dhaka, Bangladesh*

INTRODUCTION

Diabetes mellitus has become a significant global health issue, currently affecting over 371 million people and expected to reach 776 million by 2035. This rise is mainly linked to lifestyle risk factors like obesity and lack of physical activity [1,2]. As a chronic metabolic disorder, it is characterised by impaired insulin secretion or action, resulting in ongoing hyperglycaemia that disrupts cell balance and causes oxidative stress, especially harming microvascular structures [3,4]. Diabetic neuropathy, a common complication affecting 10–20% of diabetics, often presents with severe neuropathic pain that greatly diminishes quality of life [5]. Due to the serious impact of high blood sugar and neuropathic pain on health, there is an urgent need for treatments that both control blood glucose levels and reduce neuropathic pain, particularly in models like streptozotocin-induced diabetic neuropathy [5].

Evidence shows oxidative stress drives diabetes-related neural issues. Hyperglycaemia boosts ROS production and weakens antioxidants, causing damage to lipids, proteins, and DNA [6,7]. These changes trigger neuroinflammation, weaken neurons, and accelerate sensory nerve degeneration in diabetic polyneuropathy, the most common diabetic complication [7,8]. Excess ROS causes mitochondrial dysfunction and cell death, worsening neuronal damage [8]. Agents with antioxidant and anti-inflammatory effects may help repair neurons and reduce oxidative stress, offering promise for diabetic neuropathy [8,9].

Spirulina platensis, a nutrient-rich cyanobacterium, has garnered significant interest due to its diverse bioactive constituents, including phycocyanin, essential amino acids, vitamins, and minerals. These compounds exhibit potent antioxidant and anti-inflammatory activities, allowing Spirulina to effectively neutralise free radicals and support

metabolic regulation [10, 11]. Preclinical studies further indicate that Spirulina supplementation improves oxidative balance, modulates pro-inflammatory cytokines, and restores cellular homeostasis [12]. Notably, the presence of insulin-like peptides and documented antihyperglycaemic properties contribute to enhanced glycaemic control, with animal models showing significant reductions in blood glucose levels and alleviation of diabetic neuropathy symptoms such as hyperalgesia and mechanical allodynia [13,14]. Collectively, these findings underscore Spirulina as a promising therapeutic candidate for managing metabolic dysfunction and neuropathic pain in diabetes.

Despite these promising observations, the therapeutic potential of Spirulina platensis in addressing both glycemic dysregulation and neuropathic pain remains insufficiently characterised, particularly in models of painful diabetic neuropathy. A comprehensive assessment of Spirulina's dual actions modulation of hyperglycaemia and attenuation of nociceptive behaviour is therefore essential to advance its potential as a complementary treatment.

This study investigates the effectiveness of oral Spirulina platensis in improving glycemic control and reducing pain in streptozotocin-induced diabetic neuropathy rats. Using chemical allodynia models, it aims to determine how Spirulina alleviates diabetes-related metabolic and neural issues.

METHODS & MATERIALS

Study Design

This study investigated Spirulina platensis's effects on blood sugar and pain in streptozotocin-induced diabetic rats. Diabetic rats were divided into six groups: controls, non-diabetic with Spirulina, non-diabetic with sodium salicylate, diabetic with vehicle, diabetic with Spirulina, and diabetic with sodium salicylate. Spirulina was given orally at 500 mg/kg/day for a month, starting day 15 post-STZ. Sodium salicylate was administered at 200 mg/kg 60 minutes before the formalin test. Body weight and blood glucose were measured at the beginning and end. Blood samples were taken after an 8-hour fast to measure glucose with a glucometer.

Study Place

The study was conducted in the Pain Laboratory, Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The laboratory is equipped with necessary facilities for animal experiments and pain response evaluation, providing a controlled, ethical environment for the rats.

Study Period

The study, conducted from March 2019 to February 2020 at BSMMU's Pain Laboratory, involved acclimatization, diabetes induction, treatment, and behavioral tests within this period. Each group received treatment and nociceptive assessments as scheduled.

Procurement and Animal Care

Long Evans rats weighing 180–230 g were procured from the animal house at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. All animals were housed individually in standard cages within the Pain Laboratory of the Department of Physiology at BSMMU under controlled environmental conditions, including a 12-hour light/dark cycle, an ambient temperature of 21 ± 1°C, and a relative humidity of 55 ± 5%. The environmental temperature maintenance adhered to previously reported thermoneutral requirements for rodents[15]. Food and water were provided ad libitum throughout the study in accordance with established laboratory animal care guidelines[16]. All procedures and behavioral assessments were performed during the daytime (08:00–16:00 hours) to minimize circadian influences on nociceptive responses[17]. A total of sixty Long Evans rats were randomly divided into six groups of ten. Group 1 was non-diabetic controls given saline. Group 2 had non-diabetic rats treated with Spirulina platensis. Group 3 included non-diabetic rats treated with sodium salicylate as positive controls. Group 4 were diabetic rats given vehicle, while Group 5 were diabetic rats treated with Spirulina. Group 6 were diabetic rats treated with sodium salicylate as positive controls. Spirulina was administered orally at 500 mg/kg/day for a month, following established in earlier work.

Chemicals

Spirulina platensis powder was obtained from the Bangladesh Council of Scientific and Industrial Research (BCSIR), Dhaka. For oral administration, the powder was freshly suspended in normal saline at a volume of 5 ml/kg of body weight and administered at a dose of 500 mg/kg of body weight. All preparations were made immediately before use to ensure stability and consistency throughout the experimental period.

Induction of Diabetes

Diabetes was induced using streptozotocin (STZ) following established procedures. To enhance the diabetogenic sensitivity of the pancreatic islets, rats were fasted overnight before STZ administration, as fasting has been shown to increase the vulnerability of islet cells to STZ-induced injury[18]. STZ was freshly dissolved immediately before use in a 50 mM sodium citrate buffer (pH 4.5) containing 150 mM NaCl and administered subcutaneously at a dose of 60 mg/kg body weight. Blood glucose levels were monitored using a digital glucometer. Two weeks after STZ administration, animals with persistent hyperglycemia exceeding 400 mg/dL were identified as diabetic, consistent with previous reports that characterize sustained high glucose levels as a sign of successful STZ-induced diabetic pathology[19]. Only these confirmed diabetic rats were included in the subsequent analyses.

Formalin Test

The formalin test was used to assess nociceptive behavior, following standard protocols established for rodent pain models[20,21]. Prior to testing, each rat was briefly acclimatized to the Plexiglas observation chamber to reduce stress-related variations. A 50 µL injection of 2.5% formalin was administered subcutaneously into the plantar surface of the right hind paw using a 25-gauge needle, after which the animal was immediately placed inside the chamber for observation. Nociceptive behaviors were recorded continuously for 60 minutes and scored in 5-minute intervals according to four behavioral categories: score 0 indicated normal paw posture; score 1 reflected reduced weight-bearing; score 2 indicated elevation of the paw with no surface contact; and score 3 represented intense nociceptive behavior such as licking, biting, or shaking of the injected paw. A weighted nociceptive score (0–3) was calculated by multiplying the duration spent in each category by its corresponding weight and dividing by the total time interval. The response profile was analyzed in two distinct phases: an early neurogenic phase (0–10 minutes) and a later inflammatory phase (15–60 minutes), representing peripheral nociceptor activation and subsequent central sensitization, respectively.

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Statistical Analysis

Data were first evaluated for normality using the Shapiro–Wilk test. Variables that followed a normal distribution, including blood glucose concentration and formalin-induced pain scores ($P > 0.05$), were expressed as mean ± standard deviation (SD) and compared with the paired Student's t-test. Body weight data did not meet normality criteria ($P < 0.05$) and were therefore expressed as mean ± standard error of the mean (SEM) and analyzed using the Wilcoxon Signed Ranks Test. A probability value of $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (IBM Corp, USA), version 27.0.

Ethical Clearance

We gratefully acknowledge the Department of Physiology, BSMMU, for providing laboratory facilities and technical support. We also thank the BSMMU animal house staff for their assistance with animal care throughout the study.

RESULTS

Table I shows that fasting blood glucose responses differed among groups. Non-diabetic controls and Spirulina-treated non-diabetics remained stable, indicating Spirulina doesn't affect glucose regulation in non-diabetics. Diabetic rats induced by STZ showed a significant increase in blood glucose by week four ($P < 0.001$), confirming hyperglycemia. Diabetic rats treated with Spirulina had a notable glucose reduction, with week-four values nearly half of untreated diabetics ($P < 0.01$).

Table – I: Impact of Spirulina on Blood Glucose Levels

Group Blood Glucose (mg/dL)	0 Week (mean ± SD)	4th Week (mean ± SD)	P-value
Control	92.3 ± 8.75	93.1 ± 7.84	0.612
Spirulina	88.7 ± 7.12	86.4 ± 6.95	0.275
Diabetic	89.8 ± 7.54	265.2 ± 28.13	< 0.001
Spirulina-Treated Diabetic	90.4 ± 6.98	148.7 ± 25.47	< 0.01

As presented in Table II, body weight changes over four weeks varied among groups. Non-diabetic controls and Spirulina-treated non-diabetics had modest weight increases; only the latter was statistically significant ($P = 0.034$), suggesting a potential growth or nutritional support. Untreated diabetics had minimal, insignificant weight gain ($P = 0.351$), reflecting hyperglycemia's catabolic effects. Spirulina-treated diabetics gained some weight by week four, but not significantly ($P = 0.072$).

Table – II: Impact of Spirulina on Weight Gain

Group	0 Week (mean ± SD)	4th Week (mean ± SD)	P-value
Control	198.6 ± 3.9	209.8 ± 4.1	0.118
Spirulina	200.4 ± 3.5	217.3 ± 3.8	0.034
Diabetic	197.9 ± 4.1	203.6 ± 4.3	0.351
Spirulina-Treated Diabetic	200.8 ± 4.0	212.9 ± 4.1	0.072

As displayed in Table III, formalin-induced nociceptive responses varied significantly across groups in both test phases. Diabetic rats had the highest pain scores in both the neurogenic and inflammatory phases, with significant increases ($P < 0.001$), indicating heightened nociceptive sensitivity. Spirulina significantly reduced pain scores in diabetic rats ($P < 0.01$) in both phases. In non-diabetic rats, Spirulina also lowered responses, but not significantly. Sodium salicylate moderately reduced pain, especially in the second inflammatory phase ($P < 0.05$).

Table – III: Impact of Spirulina and Sodium Salicylate on Formalin-Induced Pain

Group	1st Phase Pain Score (mean ± SEM)	P-value	2nd Phase Pain Score (mean ± SEM)	P-value
Control	1.72 ± 0.06	0.182	1.48 ± 0.05	0.210
Control + Spirulina	1.42 ± 0.05	0.094	1.33 ± 0.04	0.118
Control + SS	1.47 ± 0.05	0.139	1.39 ± 0.05	0.163
Diabetic	2.18 ± 0.08	< 0.001	2.03 ± 0.07	< 0.001
Diabetic + Spirulina	1.67 ± 0.06	< 0.01	1.53 ± 0.05	< 0.01
Diabetic + SS	1.57 ± 0.05	0.031	1.60 ± 0.05	0.029

DISCUSSION

The current research demonstrates that Spirulina platensis exerts notable therapeutic effects on glycemic regulation and nociceptive behavior in streptozotocin-induced diabetic rats. Spirulina supplementation significantly mitigates hyperglycemia, enhances body weight, and reduced pain responses in both phases of the formalin test, underscoring its potential as a multifunctional agent in diabetic neuropathy.

In our model, untreated diabetic rats exhibited a substantial rise in fasting blood glucose by week four (265.2 ± 28.13 mg/dL), confirming the strong diabetogenic effect of streptozotocin and supporting earlier evidence of persistent STZ-induced hyperglycemia [18, 22]. In contrast, Spirulina-treated diabetic rats showed a marked reduction in glucose levels (148.7 ± 25.47 mg/dL, $P < 0.01$), demonstrating a pronounced antihyperglycemic effect consistent with previous findings that Spirulina improves insulin sensitivity and mitigates β-cell oxidative injury [13, 23]. These metabolic improvements may be attributed to Spirulina's bioactive compounds particularly phycocyanin, phycocyanobilin, and insulin-like peptides which enhance insulin activity, reduce

oxidative stress, and protect pancreatic β-cells by modulating intracellular signaling cascades such as JNK and p38 MAPK [13, 24]. Together, these mechanisms likely underlie the improved metabolic profile observed in Spirulina-supplemented diabetic rats, reinforcing its therapeutic relevance in diabetes management.

Spirulina's impact on body weight further highlights its metabolic benefits, particularly in counteracting the catabolic effects of chronic hyperglycemia. Diabetic rats receiving Spirulina demonstrated a more pronounced increase in body weight (200.8 ± 4.0 g to 212.9 ± 4.1 g; P = 0.072) compared to untreated counterparts, which showed only minimal improvement (197.9 ± 4.1 g to 203.6 ± 4.3 g; P = 0.351). Although not statistically significant, this upward trend suggests a partial restoration of metabolic balance. This pattern aligns with previous findings demonstrating Spirulina's ability to enhance insulin sensitivity, reduce oxidative stress, and support weight recovery in metabolic dysfunction models (25, 26). Additional studies reporting improvements in lipid profiles and broader metabolic indices further reinforce Spirulina's potential as a functional nutritional intervention for diabetes and obesity-related complications [27].

Spirulina also demonstrated strong antinociceptive potential in diabetic neuropathy, as shown by the significant reduction in formalin-induced pain scores across both the early neurogenic and late inflammatory phases. Untreated diabetic rats exhibited pronounced hyperalgesia (2.18 ± 0.08 and 2.03 ± 0.07), whereas Spirulina-treated rats showed significantly lower nociceptive responses (1.67 ± 0.06 and 1.53 ± 0.05; P < 0.01) [13]. These analgesic effects are closely linked to Spirulina's anti-inflammatory and antioxidant bioactivities, particularly the actions of phycocyanin, which suppresses COX-2, iNOS, pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), and microglial activation, key contributors to neuroinflammation and oxidative stress in diabetic neuropathy [28, 29]. Recent findings further indicate that phycocyanin attenuates NADPH oxidase expression and reduces oxidative stress in diet-induced models of metabolic dysfunction [30]. Unlike sodium salicylate, which reduced pain only in the late inflammatory phase of the formalin test, Spirulina demonstrated broad analgesic efficacy across both phases, highlighting its promise as a comprehensive therapeutic candidate for neuropathic pain in diabetes.

Diabetic neuropathy (DN) is a complication caused by oxidative stress, where excess reactive oxygen species harm cells, leading to mitochondrial damage, neuronal death, and poor regeneration [8, 31]. Natural remedies like Spirulina have neuroprotective effects by boosting antioxidant enzymes like superoxide dismutase (SOD) and catalase, and through phycocyanobilin, a NADPH oxidase inhibitor that reduces oxidative damage [14, 32]. These effects correlate with better pain responses in Spirulina-treated diabetic rats. Hygrophila auriculata also shows strong antioxidant properties and improves pain outcomes in diabetic models [33], reinforcing the therapeutic value of plant-based compounds in DN.

Although this study provides compelling evidence for Spirulina's metabolic and pain-relief benefits, it has limitations. It did not measure oxidative stress, inflammatory mediators, or neuronal apoptosis, which could clarify its neuroprotective mechanisms. Future research should include molecular assays, dose response evaluations, and long-term studies to assess Spirulina's clinical potential for diabetic neuropathy.

Conclusion

This study shows that Spirulina platensis significantly improves glycemic control, supports modest weight recovery, and significantly reduces nociceptive responses in streptozotocin-induced diabetic rats. The combined antihyperglycemic, antioxidant, and anti-inflammatory effects of Spirulina likely explain these benefits, highlighting its potential as a complementary therapy for diabetic neuropathy. Further mechanistic and clinical studies are needed to confirm these findings and assess its translational potential.

Authors' Contributions

Dr. Monira Shahnaz led the study design, data collection, and drafting of the manuscript. The co-authors contributed to data analysis, interpretation of findings, and critical revision of the manuscript. All authors reviewed and approved the final version.

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Conflicts of Interest

The authors declare that there are no potential conflicts of interest to be reported.

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