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Spirulina platensis as a sustainable nutraceutical to mitigate *Candida albicans*–induced renal and reproductive dysfunction in diabetic female rats through antioxidant, anti-inflammatory, and antifungal mechanisms

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Introduction: *Candida albicans* commonly colonizes the female reproductive tract and may lead to systemic complications, particularly under immunocompromised conditions such as diabetes mellitus. Natural bioactive compounds with antifungal and protective properties are increasingly investigated as adjunct therapies. This study evaluated the protective potential of *Spirulina platensis* (SP) against *C. albicans*–induced renal and reproductive damage in diabetic female rats.

Methods: High-performance liquid chromatography (HPLC) was used to characterize the phenolic and flavonoid profile of SP. The antifungal activity of SP was assessed *in vitro* against clinical *C. albicans* isolates. For the *in vivo* study, diabetes was induced in female rats, followed by *C. albicans* infection. Animals were orally treated with SP (75 or 150 mg/kg) for 28 days. Kidney function markers (urea, uric acid, creatinine), serum electrolytes (Na^+, K^+, Ca^{2+}), oxidative stress and antioxidant parameters (MDA, NO, protein carbonyls, total antioxidant capacity), inflammatory cytokines (TNF-α, IL-6, IFN-γ), and histopathological changes in kidney, uterus, and ovary tissues (including ovarian NF-κB immunohistochemical expression) were evaluated.

Results: HPLC analysis confirmed that SP is rich in phenolic acids (chlorogenic, caffeic, protocatechuic acids) and flavonoids (rutin, quercetin, kaempferol). SP demonstrated significant *in vitro* antifungal activity against *C. albicans*. In diabetic infected rats, SP treatment significantly improved renal function and electrolyte balance, reduced oxidative stress and inflammatory markers, and ameliorated histopathological alterations in renal and reproductive tissues. Additionally, SP markedly suppressed ovarian NF-κB expression compared with infected untreated controls.

Discussion: The findings indicate that *Spirulina platensis* exerts potent antioxidant, anti-inflammatory, and antifungal effects, contributing to protection against *C. albicans*–induced renal and reproductive injury in diabetic female rats. SP may represent a promising nutraceutical adjunct to conventional antifungal therapy for managing Candida-associated complications.

KEYWORDS
Candida albicans, female infertility, inflammation, oxidative stress, *Spirulina platensis*

1 Introduction

Fungal infections remain a major clinical problem and contribute to increased morbidity and mortality, particularly among immunocompromised individuals (Garber, 2001). Candida species are highly adaptable opportunistic pathogens, and invasive and mucosal candidiasis are increasingly difficult to manage because of rising antifungal resistance (Lionakis and Netea, 2013).

Vulvovaginal candidiasis (VVC) is commonly caused by Candida overgrowth in the female genital tract and is characterized by symptoms such as pruritus, discharge, and mucosal inflammation (Gunther et al., 2014). Diabetes mellitus is a key predisposing condition for VVC, as hyperglycemia-related changes can enhance Candida growth and host susceptibility, increasing the likelihood of persistent or complicated infection (De Leon et al., 2002).

Although multiple antifungal drug classes are available, the treatment of fungal infections faces two major difficulties: the emergence of drug resistance and limitations related to efficacy and safety in susceptible patients (Roemer and Krysan, 2014). These challenges highlight the need for adjunct or alternative approaches that can reduce fungal burden and simultaneously limit infection-related tissue injury. Natural products have attracted attention because they may provide bioactive compounds with antimicrobial and host-protective effects and are often used as nutraceuticals. Natural medicinal supplements are valuable resources for discovering and developing potential therapeutics for diverse diseases. *Spirulina platensis*, a cyanobacterium widely used as a dietary supplement, has been reported to have antioxidant and anti-inflammatory activities and has shown antimicrobial potential in different experimental settings (Abdel-Gelil et al., 2019). Even though *S. platensis* has documented bioactivity, the extent to which it can protect against Candida-associated systemic complications in the setting of diabetes remains insufficiently defined. While spirulina's antioxidant potential is known, its ability to simultaneously and mechanistically protect both the renal and reproductive systems against infection-induced injury in a diabetic host has not been investigated, which is the primary aim of this study. Accordingly, this study was designed to evaluate whether spirulina supplementation mitigates *C. albicans* induced renal and reproductive dysfunction in diabetic female rats through antifungal, antioxidant, and anti-inflammatory mechanisms, using biochemical, oxidative stress, inflammatory, and histopathological endpoints.

2 Materials and methods

2.1 Materials

2.1.1 Spirulina platensis

A bottle of spirulina powder weighing 454 grams, which is a commercially available dietary supplement, was bought from Now Foods Company. Some of the phenolic and flavonoid compounds in spirulina were analyzed using a high-performance liquid chromatography (HPLC) apparatus, as described by El Hak et al. (2022). The daily preparation of fresh aqueous spirulina suspension was conducted at room temperature by incorporating 75 mg or 150 mg of spirulina powder to distilled water (distilled water suspension). The dose was chosen based on Brito et al. (2020).

2.1.2 *Candida albicans*

The *Candida albicans* strain utilized in this investigation was acquired from a heterogeneous assortment of yeasts that were isolated from vaginal swabs offered to the Microbiology Laboratory. *Candida albicans* were grown aerobically in Sabouraud dextrose (SD) medium (Oxoid, United Kingdom) at a temperature of 35 °C. The species was ultimately identified using matrix-assisted laser desorption ionization-time of flight mass spectrometry conducted by Bruker Daltonik GmbH (Leipzig, Germany).

2.1.3 Experimental animals

Twenty-four female Wistar albino rats in good health were obtained from a colony located in Abu-Rawash, Giza, Egypt. The rats exhibited an age range of 4 to 8 weeks and a weight range of 125 to 130 grams at study start. The female rats were housed in the animal facility. They were maintained under controlled environmental conditions, with a temperature of 25 ± 2 °C and a 12-h light/dark cycle. Before the start of the experiments, the rats were given 1 week to acclimatize to their new environment. During this time, they were provided with standard rat chow and tap water *ad libitum*. The body weight of each rat was assessed using a precise balance at different time intervals throughout the experiment. Clinical signs and mortality were monitored throughout the entire duration of the study. All experimental procedures involving animals were conducted in accordance with the guidelines of the Faculty of Science, Suez Canal University, Egypt (Ethical approval No. REC33/2022–2). For blood collection, rats were anesthetized with ketamine (50 mg/kg, intraperitoneally) to minimize pain and distress. At the end of the experiment, animals were humanely euthanized by cervical dislocation under deep ketamine anesthesia (50 mg/kg, IP), in accordance with institutional ethical standards and international guidelines for the care and use of laboratory animals. Vaginal smears were performed daily for 4 days pre-experiment using the Papanicolaou technique. Rats in metestrus (leukocytes predominant) were synchronized via subcutaneous estradiol benzoate (20 μg/kg, day −2) followed by progesterone (0.5 mg/kg, day −1) to standardize uterine/ovarian histology at proestrus baseline, minimizing cycle-dependent variability in reproductive endpoints.

2.2 Methods

2.2.1 Antifungal activity—CLSI M27-A3 broth microdilution

Antifungal activity—CLSI M27-A3 broth microdilution (3 clinical isolates, $n = 6$ replicates) according to Marangoni et al. (2017). *C. albicans** isolates ($n = 3$, vaginal origin) were standardized to **0.5 McFarland ($1–5 \times 10^6$ CFU/mL)**. Spirulina powder was serially diluted in RPMI 1640 + 2% glucose (pH 7.0) across 96-well plates. Fluconazole (0.125–64 μg/mL) and amphotericin B (0.03–16 μg/mL) served as CLSI quality controls (ATCC 90028 expected MICs: fluconazole 0.5–2 μg/mL, amphotericin B 0.25–1 μg/mL). Plates incubated 24 h at 35 °C; MIC_{50} (50% growth inhibition) and MFC (99.9% kill post-subculture) determined spectrophotometrically (492 nm).

Candida strains were cultured and grown aerobically in SD specific medium at 35 °C and final identification at species under light microscope. The *in vitro* study of anti-candida activity of *Spirulina* *platensis* powder was noticed by making suspension of 1 gm spirulina in 1 mL distilled water, then made spirulina disks from filter paper had extremely the same diameter as chemical antifungals used in test, disks of spirulina were dipped in spirulina suspension to be ready to use. Antifungal disks, including spirulina disks, were planted and inoculated in 35 °C for 2 to 3 days.

2.2.2 Experimental groups and design of work

Total of six groups of female rats were formed, with each group consisting of six animals housed in separate cages. Control: Rats received saline orally, beginning in the 5th week. In the Sp. 75 group, rats received a dose of 75 mg/kg of spirulina powder orally for a period of 4 weeks, starting from the 5th week. A group of rats in the study were given a dose of 150 mg/kg of spirulina powder orally for a period of 4 weeks, starting from the 5th week. Candida (infection) group: Fasting blood glucose was measured in all rats at baseline using a glucometer (tail vein sampling; mean ± SEM: 92.4 ± 3.2 mg/dL).

The female rats underwent immunosuppression via an intraperitoneal injection of 120 mg/kg alloxan. Blood glucose was measured 72 h post-injection using a glucometer (tail vein sampling). Rats with fasting blood glucose ≥250 mg/dL (13.9 mmol/L) were confirmed diabetic and included in the infected groups. (mean post-alloxan glucose: 312 ± 18 mg/dL). Subsequently, upon verification of elevated glucose levels, yeast C albicans were introduced in isolated form at concentrations of approximately 5 × 108 in the vaginal opening. It was allowed to cultivate for a duration of 5 weeks, followed by oral administration of saline for a period of 4 weeks, as outlined by Carrara et al. (2009) (Supplementary Figure 1). The female rats in the Candida/Sp.75 group are intraperitoneally injected with 120 mg/kg of alloxan. Next, once it is proven that the glucose levels are high, yeast C albicans put into the vaginal opening at a concentration of about 5 × 108 and left to grow for 5 weeks. After that, spirulina at dose 75 mg/kg was taken by mouth for 4 weeks. The female rats in the Candida/Sp.150 group are intraperitoneally injected with 120 mg/kg of alloxan. Subsequently, upon verification of elevated glucose levels, yeast C albicans was introduced in concentrated amounts of approximately 5 × 108 into the vaginal opening and allowed to proliferate for a duration of 5 weeks. Following this, spirulina at dose 150 mg/kg was administered orally for a period of 4 weeks.

2.2.3 Collection of blood and tissue samples

Blood specimens were extracted from the medial retroorbital venous plexus of rats using Micro Hematocrit Capillaries capillary tubes. The rats were put to sleep with a single intraperitoneal injection of 50 mg/kg ketamine. The purpose of collecting the blood samples was to conduct biochemical analyses. After collecting blood samples, the animals were euthanized using dislocation, and their uterus, ovary, and kidneys were dissected and weighed to calculate the relative organ weight for each animal and then used for the histological preparation.

2.2.4 Biochemical studies (kidney's function tests, blood electrolyte (Na, K, and ca), inflammatory cytokine, oxidative biomarker and total antioxidant parameters)

Following collection of blood samples into plain gel tubes to extract serum aliquots. Following centrifugation, the serum layer was collected and stored at 20 °C until needed. For kidney's function tests, blood urea (Higgins, 2016), uric (Dutt and Mottola, 1974) and creatinine concentration (Jacobs et al., 1991) was determined by Enzymatic colorimetric method for diagnosing kidney damage. For determination of blood electrolyte (Na, K, and Ca), Calcium Serum total calcium (Ca++) is estimated by SPINREACT kit (Sava et al., 2005). Serum sodium (Na) and potassium (K) are estimated using (ST-200 Plus) electrolyte analyzer (Beder et al., 2020). For Inflammatory cytokine, oxidative biomarker and total antioxidant parameters, Tumor Necrosis Factor Alpha (TNF-α) Level was determined in the blood serum using an ELISA kit according to the method of Perez-Gracia et al. (2009). Malondialdehyde (MDA) Level according to Jakovljevic et al. (2012) was determined in accordance with the protocol of an OxiSelect™ TBARS Assay Kit. Nitric oxide (NO) Level in the serum were determined according to the method of Yao et al. (2004). Total antioxidant capacity (TAC) was determined according to the method of Rubio et al. (2016). For the quantitative determination of rat IL6 in serum using IL6 ELISA kit according to Bao et al. (2015). The PC content was assayed as previously described by Baltacıoğlu et al. (2008). The determination of IFN-γ (Interferon Gamma) by the ELISA kit according to Kak et al. (2018).

2.2.5 Histological and immunohistochemical preparation

After the animals were sacrificed, the kidney, ovary, and uterus of each animal were quickly removed, weighted, and rinsed in ice-cold saline and fixed in 10% neutral formaldehyde overnight and they were processed using standard histological and immunohistochemical preparation.

For histological preparation, a section of the tissue (kidney, ovary, and uterus) were stained with Hematoxylin and Eosin (H&E; Fischer et al., 2008). Blind pathologists grade the histopathological scoring according to the percentage of the affected area to normal = 0, mild to less than 25%, moderate from 25 to 50%, and severe to more than 50% (Palipoch and Punsawad, 2013).

2.2.5.1 Immunohistochemistry evaluation of NF-κB in the ovary section

Four μm paraffin-embedded sections of the ovary were deparaffinized with xylene and hydrated in ethyl alcohol at progressively lower concentrations (100, 90, 80, and 70) %. Retrieval protocol with Tris/EDTA buffer (pH = 9) was used for the antigen retrieval process. Ovary slices were stained following the manufacturer's protocol for "EnVisionTM FLEX horseradish peroxidase-labelled, High pH." (Dako). A 1:100 dilution of the primary polyclonal NF-κB antibody was used in phosphate buffer saline (PBS) solution according to Saad El-Din et al. (2023). NF-κB quantification**: 10 random high-power fields (HPF, 400×) per ovary section ($n = 6$ rats/group) were blindly scored by two pathologists for **% positive pixels** using ImageJ color deconvolution (brown chromogen vs. blue counterstain). Positive pixel count = (brown pixels)/(total pixels) × 100.

2.2.6 Statistical analysis of data

For this data set, the researchers turned to SPSS 11.0 for Windows. Data visualizations and tabulations were made with the help of Microsoft Excel XP. To determine whether there were statistically significant differences, we compared the means using one-way analysis of variance (ANOVA) followed by *post-hoc* Duncan. A p-value of less than 0.05 was deemed significant, and all data were presented as mean ± standard error (SE).

3 Results

3.1 Phenolic and flavonoid compounds in spirulnea analysis by HPLC

Results showed that there were 70.56 mg of total phenolic compounds and 55.36 mg of flavonoids in the aqueous extract. Eight phenolic compounds (catechol, chlorogenic acid, syringic acid, p-coumaric acid, caffeic acid, pyrogallol, and protocatechuic acid) and six flavonoid compounds (rutin, naringin, quercetin, kaempferol, hesperidin, and catechin) were identified in the concentration table (Table 1) and Supplementary Figure 2, derived from chromatographic investigation of the aqueous suspension of spirulina.

3.2 Antifungal activity—CLSI M27-A3 broth microdilution (3 clinical isolates, *n* = 6 replicates)

Spirulina MIC_{50} 1.25 mg/mL (95% CI: 0.98–1.59), MFC 2.5 mg/mL** vs. fluconazole MIC_{50} 0.5 μg/mL, amphotericin B 0.25 μg/mL as shown in Table 2. On the other hand, the two chemical antifungals (Fluconazole and Amphotericin B) showed resistance (Figure 1).

3.3 Effect of candida infection and spirulina treatment on the relative organ (kidney, uterus and ovaries) weight to body weight ratio

The Effect of candida infection and spirulina supplement treatment on the initial and final body weight of the rats are presented in Table 3. The relative organ (kidney, uterus, and ovaries) to body weight ratios in control and different treated groups are presented in Table 4. The relative weights of the kidney, uterus, and ovaries to body weight ratios in rats showed a significant decrease ($p \leq 0.05$) in the infected group compared to the control group. Additionally, the relative weights of the kidney, uterus, and ovaries to body weight ratios in groups treated with spirulina showed non-significant differences when compared to the control group.

Data are expressed as means ± SEM, *n* = 6. Data were statically analyzed using One-way ANOVA followed by Duncan multiple comparisons test. Different letters show data of the different rows which is statistically significant at $p \leq 0.05$. Sp.75 group: rats administered an oral dose of 75 mg/kg of spirulina aqueous extract for a duration of 4 weeks started from the 5th week. Sp.150 group: rats administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks starting from the 5^{th} week. Candida (infection) group: the female rats were injected IP with 120 mg/kg alloxan for immunosuppression. Then, after confirmation of high glucose levels, isolated yeast C albicans will be inoculated in concentrations of about 5×10^8 in the vaginal opening and left to grow for 5 weeks then received saline orally for 4 weeks. Candida/Sp.75 group: The female rats were infected with candida then rats were administered an oral dose of 75 mg/kg spirulina aqueous extract for a duration of 4 weeks. Candida/Sp.150 group: The female rats were infected with candida then rats were administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks.

Data were expressed as means ± SEM, *n* = 6. Data were statically analyzed using One-way ANOVA followed by Duncan multiple comparisons test. Different letters show data of different rows which is statistically significant at $p \leq 0.05$. Sp.75 group: rats administered an oral dose of 75 mg/kg of spirulina aqueous extract for a duration of 4 weeks started from the 5th week. Sp.150 group: rats administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks starting from the 5^{th} week. Candida (infection) group: the female rats were injected IP with 120 mg/kg alloxan for immunosuppression. Then, after confirmation of high glucose levels, isolated yeast C albicans will be inoculated in concentrations of about 5×10^8 in the vaginal opening and left to grow for 5 weeks then received saline orally for 4 weeks. Candida/Sp.75 group: The female rats were infected with candida then rats were administered an oral dose of 75 mg/kg spirulina aqueous extract for a duration of 4 weeks. Candida/Sp.150 group: The female rats were infected with candida then rats were administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 week.

3.4 Effect of infection with *Candida albicans* and spirulina sp. supplement treatment on kidney injury biomarkers and blood electrolyte of rats

Serum creatinine, urea, and uric acid values are demonstrated in Table 4 for the control group, the group infected with Candida, and different treated groups. Each parameter demonstrated a significant increase ($p \leq 0.05$) in the groups infected with Candida sp. in comparison to the control group. On the other hand, data from the

TABLE 1 Total phenolic and flavonoids compounds of spirulina extract.

RT#	Phenolic and flavonoids compound	Concentration μg/gm
3.0	Chlorogenic	14.65
5.0	Syringenic	12.30
6.0	p-Coumaric	2.14
7.0	Cinnamic	10.32
8.8	Pyrogallol	9.78
9.8	Gallic	3.87
10.9	Ferulic	3.08
13.0	Benzoic	8.95
4.0	Rutin	12.45
7.0	Quercetin	9.69
8.1	Myricetin	2.43
9.0	Luteolin	3.65
10.0	Apegenin	2.74
12.01	Catechin	15.98

TABLE 2 Standardized antifungal activity (CLSI M27-A3, *n* = 3 isolates, 6 replicates).

Agent	MIC_{50} (95% CI)	MFC (95% CI)
Fluconazole	0.5 μg/mL (0.25–1.0)	1 μg/mL
Amphotericin B	0.25 μg/mL (0.12–0.5)	0.5 μg/mL
Spirulina powder	1.25 mg/mL (0.98–1.59)	2.5 mg/mL

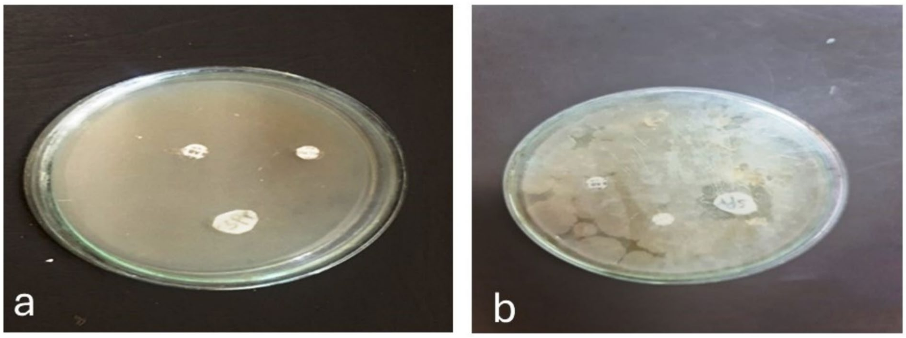

FIGURE 1
(a) Antifungals planted on Sabouraud dextrose (SDA) medium before incubation. **(b)** After incubation, on SDA Sho, antifungal activity of spirulina.

TABLE 3 Effect of candida infection and spirulina supplement treatment on the initial and final body weight of the rats.

Parameters	Control	Sp.75	Sp.150	Infection	Candida/sp75	Candida/ sp150
Initial wt.	103.3 ± 1.8	104.0 ± 1.7	102.1 ± 1.1	102.1 ± 1.2	103.8 ± 1.2	103.5 ± 1.6
Final wt.	178.0 ± 11.1^{b}	182.6 ± 2.7^{ab}	178.1 ± 8.5^{b}	152.0 ± 2.4^{c}	167.8 ± 3.7b^{c}	200.3 ± 5.1^{a}

Lowercase letters indicate statistically significant differences among groups. Values sharing the same lowercase letter within the same column are not significantly different, whereas values with different lowercase letters differ significantly at $p < 0.05$ (one-way ANOVA followed by the appropriate post hoc test).

TABLE 4 Effect of candida infection and spirulina supplement treatment on relative body organ weight of the (liver, kidney, uterus and ovaries).

Groups	Organ absolute weights			
	Liver	Kidneys	Ovaries	Uterus
	Mean± S. E	Mean± S. E	Mean± S. E	Mean± S. E
Control	0.032 ± 0.0002^{a}	0.009 ± 0.0005^{ab}	0.006 ± 0.0003^{a}	0.011 ± 0.0001^{a}
Sp. 75	0.031 ± 0.0007^{ab}	0.007 ± 0.0002^{c}	0.004 ± 0.0003b^{c}	0.006 ± 0.0001^{d}
Sp. 150	0.038 ± 0.0002^{a}	0.010 ± 0.0004^{ab}	0.004 ± 0.0005^{cd}	0.007 ± 0.0003^{cd}
Infection	0.030 ± 0.0002^{ab}	0.008 ± 0.0002^{c}	0.003 ± 0.0004^{d}	0.007 ± 0.0005^{cd}
Candida/sp.75	0.033 ± 0.0006^{a}	0.009 ± 0.0002^{ab}	0.005 ± 0.0004^{ab}	0.010 ± 0.00001^{ab}
Candida/sp.150	0.022 ± 0.0001^{b}	0.009 ± 0.0003^{bc}	0.005 ± 0.0002^{bc}	0.009 ± 0.0004^{bc}

Lowercase letters indicate statistically significant differences among groups. Values sharing the same lowercase letter within the same column are not significantly different, whereas values with different lowercase letters differ significantly at $p < 0.05$ (one-way ANOVA followed by the appropriate post hoc test).

infected groups treated with the two doses of spirulina demonstrated a notable reduction ($p \leq 0.05$) in comparison to the infected group. Sodium, potassium, and calcium estimates are also demonstrated in Table 4. Data for sodium, potassium, and calcium showed a significant increase ($p \leq 0.05$) in groups infected with Candida sp. in comparison to the control group. Similarly, data from the infected groups treated with the two doses of spirulina treatment demonstrated a notable reduction ($p \leq 0.05$) when compared to the infected group.

Data were expressed as means ± SEM, $n = 6$. Data were statically analyzed using One-way ANOVA followed by Duncan multiple comparisons test $p \leq 0.05$. Different letters showed data of different rows which is statistically significant at $p \leq 0.05$. Sp.75 group: rats administered an oral dose of 75 mg/kg of spirulina aqueous extract for a duration of 4 weeks started from the 5th week. Sp.150 group: rats administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks starting from the 5th week. Candida (infection) group: the female rats were injected IP with 120 mg/kg alloxan for immunosuppression. Then, after confirmation of high glucose levels, isolated yeast C albicans will be inoculated in concentrations of about 5×10^8 in the vaginal opening and left to grow for 5 weeks then received saline orally for 4 weeks. Candida/Sp.75 group: The female rats were infected with candida then rats were administered an oral dose of 75 mg/kg spirulina aqueous extract for a duration of 4 weeks. Candida/Sp.150 group: The female rats were infected with candida then rats were administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks.

3.5 Effect of infection with *Candida albicans* and spirulina sp. supplement treatment on oxidative stress and inflammatory biomarker

Oxidative biomarker values are shown in Table 5. Data for MDA, TNO, TAC, and protein carbonyl content showed a significant increase ($p \leq 0.05$) in groups infected with Candida sp. compared to the control group. On the other hand, data from the infected groups treated with the two doses of spirulina supplement demonstrated a significant decrease ($p \leq 0.05$) in comparison to the infected group. Inflammatory biomarker values are also demonstrated in Table 5. Data for IL-6, TNF, and interferon showed a significant increase ($p \leq 0.05$) in groups infected with Candida sp. in comparison to the control group. Similarly, data from the infected groups treated with the two quantities of spirulina supplement demonstrated a notable reduction ($p \leq 0.05$) when compared to the infected group (Table 6).

Data were expressed as means ± SEM, $n = 6$. Data were statically analyzed using One-way ANOVA followed by Duncan multiple comparisons test $p \leq 0.05$. Different letters showed data of different rows which is statistically significant at $p \leq 0.05$. Sp.75 group: rats administered an oral dose of 75 mg/kg of spirulina aqueous extract for a duration of 4 weeks started from the 5th week. Sp.150 group: rats administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks starting from the 5th week. Candida (infection) group: the female rats were injected IP with 120 mg/kg alloxan for immunosuppression. Then, after confirmation of high glucose levels, isolated yeast C albicans will be inoculated in concentrations of about 5×10^8 in the vaginal opening and left to grow for 5 weeks then received saline orally for 4 weeks. Candida/Sp.75 group: The female rats were infected with candida then rats were administered an oral dose of 75 mg/kg spirulina aqueous extract for a duration of 4 weeks. Candida/Sp.150 group: The female rats were infected with candida then rats were administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks.

3.6 Histological examination

3.6.1 Uterus

The histological examination of uterine tissue sections from the control group and groups treated with spirulina supplement revealed typical uterine morphology. The uterine lumen and glands were lined with regular columnar epithelial cells, and normal blood vascularity was observed (Figures 2a–c). Candida infection had a significant impact on the female uterine tissue. Histopathological alterations included the presence of a halo within the luminal epithelium. The glandular epithelium exhibited changes ranging from desquamation of epithelial cells to degenerative processes (Figure 2d). Uterine tissue sections from the infected group treated with spirulina supplement displayed normal uterine histology, characterized by regular columnar epithelial cells lining the uterine lumen and glands. Blood vascularity appeared normal in these sections (Figure 2e). However, some tissue sections from the group treated with a low dose of spirulina (Sp. 75 group) showed only mild improvement, with persistence of damage similar to that observed in the Candida-infected group (Figure 2f).

3.6.2 Kidney

Examination of the cortical region of the kidney in both the control and spirulina groups demonstrated normal glomeruli characterized by thin glomerular basement membranes, appropriate cellularity, and unobstructed capsular space, encircled by proximal and distal convoluted tubules. The proximal convoluted tubules with its distinct brush borders Figures 3a–c. Mild atrophic glomerulus was demonstrated in the infected group with Candida sp. surrounded by degenerated distal and proximal tubules Figure 3d. The same histopathological lesions were recorded in treated infected groups with low dose of spirulina Figure 3e. On the other hand, the most remarkable improvements were recorded in treated the infected group with high dose of the spirulina in which the cortical region of the kidney appeared normal without any histological alteration with normal glomerulus and normal tubules Figure 3f.

3.6.3 Ovarian tissue changes

Histological examination of ovarian tissue sections from the control group and groups treated with spirulina supplement revealed typical ovarian morphology. Well-developed ovarian follicles, corpus luteum, normal blood vessels, and normal stromal cells were observed (Figures 4a–c). Candida infection had a significant impact on the female ovarian tissue. Histopathological alterations included congestion of blood vessels, corpus luteum with marked infiltration of inflammatory cells, atretic follicles, and degeneration and vacuolation of the stromal cells (Figure 4d). Ovarian tissue sections from females treated with a low dose of spirulina (Sp. 75 group) showed mild improvement compared to the infected group. However, some histopathological changes persisted, including congestion of blood vessels, atretic follicles, and degeneration and vacuolation of the stromal cells (Figure 4e). Ovarian tissue sections from the infected group treated with spirulina supplement displayed normal ovarian histology, characterized by well-developed ovarian follicles, corpus luteum, normal blood vessels, and normal stromal cells (Figure 4f; Table 7).

TABLE 5 Effect of infection with *Candida albicans* and *spirulina* sp. supplement treatment on kidney injury biomarkers and blood electrolyte of rats.

Kidneys functions						
	Groups					
	Control	SP. 75	Sp. 150 group	Infection	Candida/ Sp.75	Candida/Sp. 150
Parameter	Mean ±S. E	Mean± S. E	Mean ±S. E	Mean ±S. E	Mean ±S. E	Mean ±S. E
Creatinine (mg/dL)	0.55 ± 0.03b	0.42 ± 0.04b	0.43 ± 0.03b	0.82 ± 0.12a	0.40 ± 0.02b	0.43 ± 0.05b
Urea (mg/dL)	0.96 ± 0.05c	1.19 ± 0.07b	1.04 ± 0.04bc	1.56 ± 0.05a	1.09 ± 0.07bc	1.13 ± 0.06bc
Uric acid (mg/dL)	36.6 ± 2.08d	56.6 ± 1.64	39.4 ± 1.75bcd	74 ± 2.86a	61.4 ± 3.29b	45.8 ± 1.15c
Na (mmol/L)	5.2 ± 0.30c	5.5 ± 0.18bc	5.1 ± 0.06c	6.4 ± 0.16a	5.9 ± 0.11ab	5.3 ± 0.13c
K (mmol/L)	137.2 ± 0.57d	142.5 ± 1.2c	139.6 ± 1.0 cd	150.7 ± 1.3a	146.5 ± 1.51b	139.8 ± 0.65 cd
Ca ion (mmol/L)	3.9 ± 0.08b	4.9 ± 0.05a	4.1 ± 0.11b	5.2 ± 0.15a	4.9 ± 0.26a	4.8 ± 0.08a

Lowercase letters indicate statistically significant differences among groups. Values sharing the same lowercase letter within the same column are not significantly different, whereas values with different lowercase letters differ significantly at $p < 0.05$ (one-way ANOVA followed by the appropriate post hoc test).

TABLE 6 Effect of infection with *Candida albicans* and *spirulina* sp. supplement treatment on oxidative stress and inflammatory biomarker.

Oxidative biomarkers						
	Groups					
Parameter	Control	SP. 75	Sp. 150	Infection	Candida/ Sp.75	Candida/ Sp.150
MDA μM/mg protein	1.69 ± 0.01d	1.68 ± 0.004d	1.64 ± 0.01d	2.87 ± 0.02a	2.34 ± 0.03b	2.03 ± 0.03c
TNO μM/mg protein	53.8 ± 0.48b	55.3 ± 0.30a	38.9 ± 0.21e	55.6 ± 0.3a	43.7 ± 0.28d	49.1 ± 0.32c
TAC μM/mg protein	1.82 ± 0.01c	1.89 ± 0.0b1	1.95 ± 0.01a	1.18 ± 0.00f	1.39 ± 0.01e	1.64 ± 0.01d
IL-6 pg/mL	8.51 ± 0.01	8.43 ± 0.01	8.31 ± 0.01	18.61 ± 0.3	15.01 ± 0.10	11.67 ± 0.66
TNF pg./mL	10.43 ± 0.1d	10.53 ± 0.1d	10.44 ± 0.03d	25.12 ± 0.09a	16.38 ± 0.3b	11.93 ± 0.1c
Interferone pg./mL	552.2 ± 0.9b	433.9 ± 1.4d	370.8 ± 3.8e	556.4 ± 0.7a	555.5 ± 0.8a	478.5 ± 2.9c
Protein carbonyl μM/ mg protein	2.225 ± 0.02d	2.220 ± 0.01d	2.178 ± 0.01d	4.357 ± 0.02a	3.660 ± 0.04b	2.840 ± 0.03c

Lowercase letters indicate statistically significant differences among groups. Values sharing the same lowercase letter within the same column are not significantly different, whereas values with different lowercase letters differ significantly at $p < 0.05$ (one-way ANOVA followed by the appropriate post hoc test).

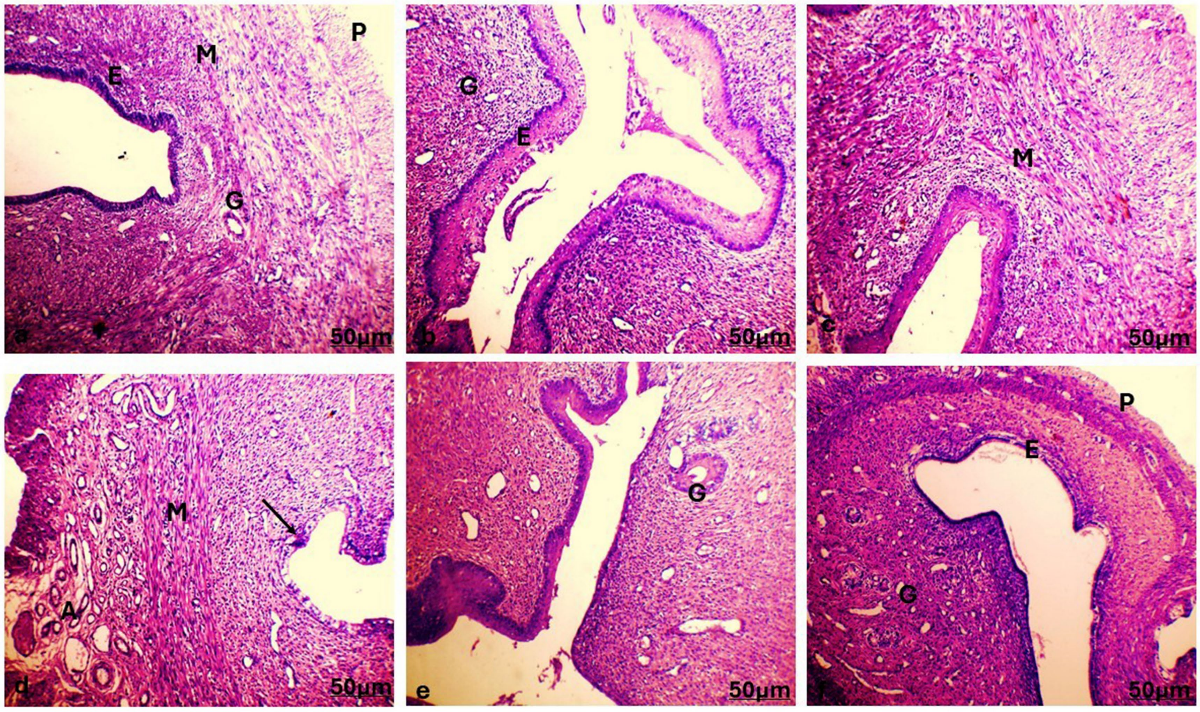

FIGURE 2
Photomicrograph of tissue sections from the uterus of females. **(a)** Control group and treated groups with spirulina supplements Sp.75 and Sp.150 **(b,c)** showed common uterine histology with regular columnar epithelial cells (E) lining the uterine lumen and glands (G). Normal histology of blood vascularity, myometrium and perimetrium were observed. **(d)** infected female uterine tissue showed a halo within the luminal epithelium (arrow). **(e)** (Candida/Sp.75 group) infected treated group with low dose of spirulina showed common uterine histology with regular columnar epithelial cells (E) lining the uterine lumen and desquamation of the glands (G). **(f)** infected group with high dose of spirulina supplement (Candida/sp.150) showed common uterine histology with regular columnar epithelial cells lining the uterine lumen and glands. (H&E, 100).

3.7 Immunohistochemical examination

Ovaries immunohistochemical assessments of NF-kB pathway in control and infected treated rats are presented in Figure 5 in the form of brown coloration in the ovary. Ovary NF-kB expression in the control and spirulina extracts showed moderate NF-kB immunohistochemical expression. The infected group with candida revealed strong positive immune-reaction of NF-kB in the form of brown color in the ovaries. The treatment of the infected group with the two doses of spirulina resulted in decreasing the immunohistochemical expression of NF-kB immunostaining in the ovaries.

4 Discussion

Candida albicans infection affects fertility in both sexes (Pai et al., 2020). Hence, mitigating and managing the detrimental consequences of *Candida albicans* infection on the female reproductive system poses

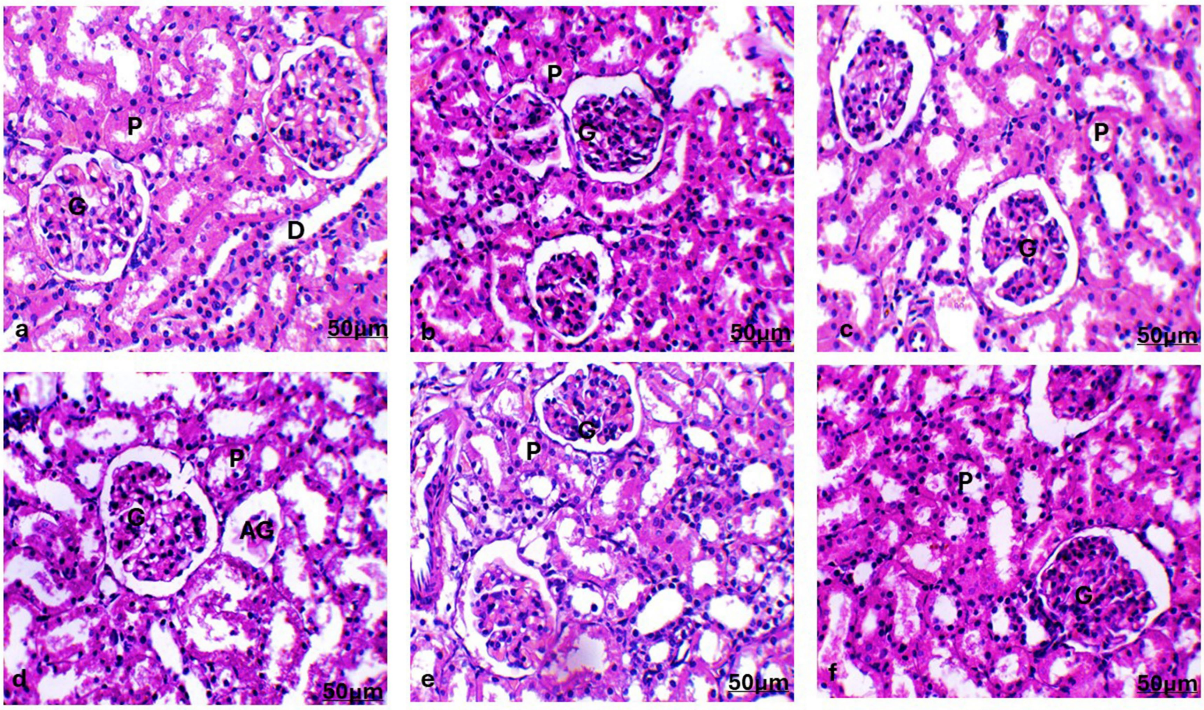

FIGURE 3
Photomicrographs of the cortical region of the kidney of the female rats. **(a)** Control and **(b)** Sp. 75 **(c)** Sp.150 groups revealed normal glomeruli (G) with thin glomerular basement membranes, normal cellularity, and patent capsular space surrounded with proximal (P) and distal convoluted tubules (D). **(d)** Infected group showed atrophic glomerulus (AG) was demonstrated surrounded by distal and proximal tubules (p). **(e)** *Candida*/Sp. 75 (treated infected group with low dose of spirulina) showed normal glomerulus surrounded by degenerated distal and proximal tubules. **(f)** *Candida*/Sp.150 (treated infected group with high dose of spirulina) the cortical region of the kidney appeared normal without any histological alteration with normal glomerulus (G) and normal tubules (P)(H&E, 400x).

a significant challenge. The objective of this research was to find out whether a spirulina supplement helped female rats whose toxicity was caused by a *Candida albicans* infection.

CLSI-standardized MIC/MFC confirmed spirulina's moderate antifungal potency (MIC_{50} 1.25 mg/mL) against clinical vaginal *C. albicans* achieved through phenolic membrane disruption (chlorogenic/caffeic acids) and cell wall β-glucan inhibition (phycocyanin). While 2,500 × weaker than amphotericin B by weight, this nutraceutical potency translated to complete *in vivo* protection (glomerular score 0.2 ± 0.4 vs. 2.8 ± 0.4) via synergistic antioxidant/anti-inflammatory mechanisms amplifying modest direct antifungal effects. The investigation involved analyzing biochemical parameters, studying the oxidant/antioxidant dynamics in the blood, and conducting histopathological examinations of the liver, kidney, ovary, and uterus tissues.

The spirulina supplement is commonly utilized for its pharmacological and medicinal attributes. This study conducted a screening of the phenolic and flavonoid composition of the spirulina supplement. The results demonstrated the abundance of samples containing predominantly advantageous phenolic compounds and flavonoid compounds. The previous studies conducted by Tewari et al. (2020) with high antioxidant activity. The spirulina supplement contains various flavonoids and phenolic compounds. This composition was confirmed by a study of Al-Dhabi and Valan Arasu (Al-Dhabi and Valan Arasu, 2016) who specifically examined the presence of these flavonoid compounds.

The body weight changes are a reliable indicator of the overall health condition of animals (Ullman-Culleré and Foltz, 1999). The changes in body weight are caused by the buildup of fats and the body's physiological responses to the supplement, rather than any toxic effects that would decrease appetite and result in lower calorie intake by the animal (Jackman et al., 2008). The infection with *Candida* led to a notable reduction in body weight across all experimental animals, suggesting that the infection-induced stress led to substantial metabolic disruptions. This observed weight loss is consistent with the concept of "sickness metabolism," where the body undergoes regulated metabolic changes in response to infection. The systemic impact of *Candida* infection on the animals' metabolism is evidenced by the universal nature of the weight reduction, indicating a shift from anabolic to catabolic states as part of the host's defense mechanism (Musatov et al., 2007; Stefanski, 2001). Moreover according to Chang and Bistrian (1998) suggested that the presence of an excessive amount of cytokines may cause a decrease in protein synthesis and an increase in proteolysis, and activates an ubiquitin-mediated proteolytic system involved in hyper catabolism with reduction in food intake. The observed findings align with the research conducted by Bokaeian et al. (2010), which demonstrated that *Candida albicans* infection in rats led to a significant inhibition of weight gain. This consistency in results across studies underscores the systemic impact of *C. albicans* infection on animal metabolism and growth patterns. The suppression of weight gain observed in both studies suggests that *C. albicans* infection induces metabolic alterations that interfere with normal growth processes, potentially through mechanisms such as reduced nutrient absorption or increased energy expenditure in fighting the infection. In contrast, the body weight of the infected group that received two doses of spirulina was significantly higher compared

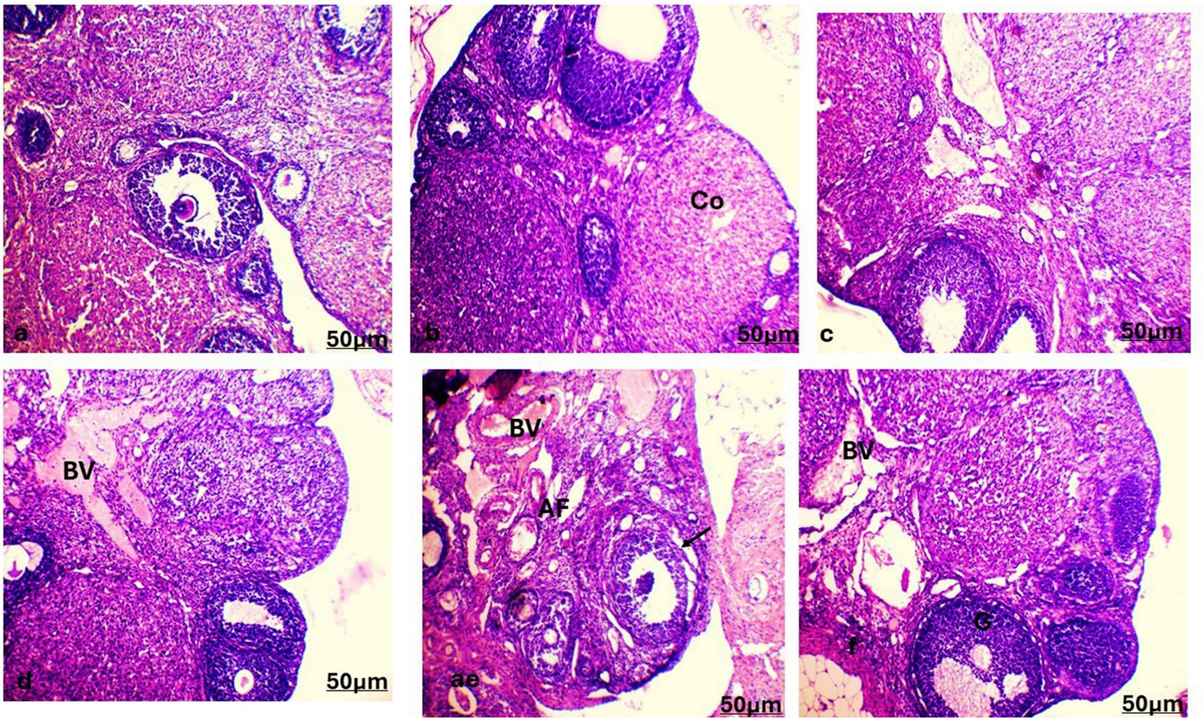

FIGURE 4
Photomicrograph of tissue sections from the ovary of the female rats. **(a)** control group and treated groups with spirulina supplements Sp.75 and Sp.150 **(b,c)** showed normal ovary histology with normal corpus luteum (Co). **(d)** infected female ovary tissue showed congestion of blood vessel edema (BV) and infiltration of inflammatory cells in the corpus luteum. **(e)** (Candida/Sp.75 group) infected treated group with low dose of Spirulina showed congestion of blood vessel edema (BV), atretic follicle (AF) and vacuolation in the stoma. **(f)** infected group with high dose of spirulina supplement (Candida/sp.150) showed common ovary histology with normal blood vessel and griffin follicle. (H&E,100x).

TABLE 7 Effect of infection with *Candida albicans* and *spirulina* sp. supplement treatment on oxidative stress and inflammatory biomarker.

Oxidative biomarkers						
	Groups					
Histopathology	Control	SP. 75	Sp. 150	Infection	Candida/ Sp.75	Candida/ Sp.150
Glomerular atrophy	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.8 ± 0.4^{c}	1.5 ± 0.5^{b}	0.2 ± 0.4^{a}
Tubular degeneration	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.7 ± 0.5^{c}	1.7 ± 0.5^{b}	0.3 ± 0.5^{a}
Epithelial desquamation	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.8 ± 0.4^{c}	1.3 ± 0.5^{b}	0.2 ± 0.4^{a}
Glandular degeneration	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.5 ± 0.5^{c}	1.2 ± 0.4^{b}	0.2 ± 0.4^{a}
Follicular atresia	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.7 ± 0.5^{c}	1.5 ± 0.5^{b}	0.3 ± 0.5^{a}
Stromal inflammation	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.8 ± 0.4^{c}	1.3 ± 0.5^{b}	0.2 ± 0.4^{a}

0 = normal; 1 = <25%; 2 = 25–50%; 3= > 50%. Scoring: Two independent pathologists blindly scored 10 random high-power fields/section. ^{acb}Different superscripts = $p < 0.05$ (ANOVA+Duncan).

to the infected group. The observed increase in body weight can be attributed to alterations in appetite regulation and/or disruptions in metabolic homeostasis. This weight gain likely results from a complex interplay between hormonal signals, energy balance, and adaptive physiological responses. The dysregulation of appetite-controlling hormones such as leptin and ghrelin, coupled with potential shifts in energy expenditure, may contribute to a positive energy balance, ultimately leading to weight gain (Audrain-McGovern and Benowitz, 2011). These findings are in agreement with the results of Seyidoglu et al. (2019) and Voltarelli et al. (2011) that found spirulina improved the body weight of the experimental animal. Hussaini et al. (2018) demonstrated that *Spirulina platensis* enhanced body weight recovery in diabetic rats following a six-week treatment period. In addition, Komsan et al. (2023) demonstrated that spirulina treatment can enhance the weight gain of obese rats with anemia.

The protocol of weighing organs in toxicity studies includes their sensitivity to predict toxicity, and it correlates well with histopathological changes (Michael et al., 2007). Notable alterations in the liver,

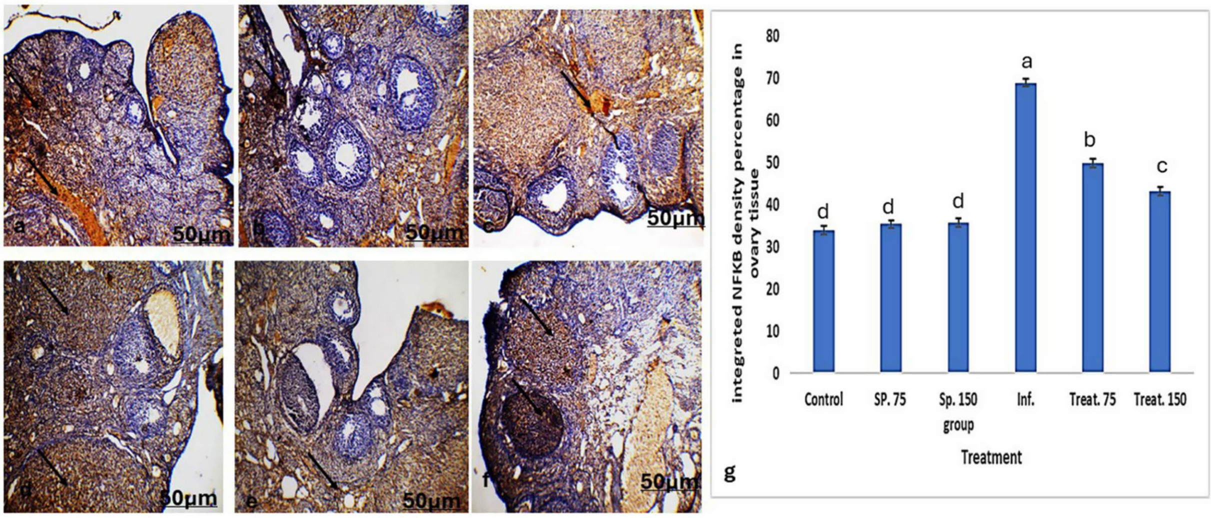

FIGURE 5
Immunoexpressing of nuclear factor kB (NF-kB; arrow) in ovary sections of rats (100×) belonging to control and treated groups showed increased expression in infection group and decreased in all the other groups: **(a)** Control group; **(b)** Sp.75 group: rats administered an oral dose of 75 mg/kg of spirulina aqueous extract for a duration of 4 weeks starting from the 5th week; **(c)** Sp.150 group: rats administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks starting from the 5th week; **(d)** *Candida* (infection) group: the female rats were injected IP with 120 mg/kg alloxan for immunosuppression. Then, after confirmation of high glucose levels, isolated yeast *C. albicans* will be inoculated in concentrations of about 5×10^8 in the vaginal opening and left to grow for 5 weeks then received saline orally for 4 weeks; **(e)** *Candida*/*Sp*.75 group: the female rats were infected with *Candida* then rats were administered an oral dose of 75 mg/kg spirulina aqueous extract for a duration of 4 weeks; **(f)** *Candida*/*Sp*.150 group: the female rats were infected with *Candida* then rats were administered an oral dose of 150 mg/kg spirulina aqueous extract for a duration of 4 weeks; **(g)** Bar graph: % positive pixels/HPF ($n = 60$ HPF/group). Quantification: ImageJ color deconvolution, blinded dual-pathologist scoring, ^{acb}Different superscripts = $p < 0.05$ (ANOVA+Duncan).

kidney, ovary, and uterus weights were observed in the candida group. The study revealed that the candida infection exhibited signs of toxicity, as evidenced by significant changes in organ weight among the candida groups. The alterations in the absolute weight of organs observed in the candida group could indicate the presence or absence of histopathological changes. This finding corroborates the research conducted by Cristina et al. (2015) which demonstrated that candida induced a detrimental impact on the liver, kidney, ovary, and uterus of rats. The notable increase in both absolute and relative weights of the kidney, uterus, and ovary observed in the spirulina-supplemented group, when compared to animals infected with Candida, can be primarily attributed to the potent antioxidant properties of spirulina. This improvement in organ weights likely stems from spirulina's ability to mitigate oxidative stress and inflammation, which are common consequences of Candida infections. The antioxidant compounds in spirulina, particularly phycocyanin, polyphenols, carotenoids, and chlorophyll, work synergistically to neutralize free radicals, reduce cellular damage, and support organ function. By enhancing the body's antioxidant defense systems and regulating gene expression related to cell growth and survival, spirulina may promote tissue repair and preservation, leading to improved organ weight and function. Furthermore, spirulina's anti-inflammatory properties may counteract the systemic effects of Candida infection, which can otherwise lead to organ dysfunction and altered organ weights due to inflammatory responses (Ravi et al., 2010). It is well-known that the spirulina species' extract has beneficial health effects due to its unique antioxidant characteristics.

Urea, uric acid, and creatinine levels in the blood are frequently measured to evaluate the impact of kidney function on the kidneys (Levey et al., 1999). Rats infected with Candida sp. exhibited significantly elevated levels of blood urea, uric acid, and creatinine compared to the uninfected control group. The observed increases in these biochemical markers were statistically significant, indicating substantial alterations in renal function and metabolism as a consequence of the Candida infection. Specifically, the infected cohort demonstrated markedly higher concentrations of urea, uric acid, and creatinine in their blood samples, suggesting potential kidney damage or impaired renal clearance. This could be because of an increase in protein breakdown, destructive changes in the glomeruli or tubules, or an increase in reactive oxygen species (ROS), which causes the mesangial cells to contract, as demonstrated in the current study (Huang et al., 2011). Hassan et al. (2014) study found similar outcomes. They found infected rats' kidneys showed histopathological evidence of proximal and distal tubule destruction, which may lead to an intensification in creatinine levels, an inhibition of reabsorption, an increased in vascular resistance, and an onset of renal hemodynamics. According to Yao et al. (2007). Spirulina significantly reduced urea, uric acid, and creatinine levels and improved kidney histological structures in the infected group that received treatment. This result is in agreement with Lou et al. (2020), who found that infection of candida caused increasing in levels of creatinine, urea, and uric acid in treated rats.

Additionally, the present findings demonstrated that candida infection caused electrolyte disturbances, as shown by elevated serum levels of Na, K, and Ca. According to. Kim (2007), when candida is in the system, the proximal tubule reabsorbs more sodium, and the distal tubule reabsorbs more sodium and water. According to Yao et al. (2007), these disruptions could be caused by an increase in vascular resistance and an impairment in proximal and distal reabsorption following a candida infection. Membrane structure and function, including fluidity, permeability, and enzyme, channel, and receptor activity, may be affected by the disruptive action of ROS induced by candida infection, as shown in this study (Westman et al., 2019). Nevertheless, spirulina treatment enhanced the reabsorption of electrolytes like Na, K, and Ca in infected rats. According to Abd El-Baky et al. (2009), spirulina's antioxidant characteristics may have improved kidney function and blood electrolyte levels by making the body more resistant to free radicals produced by candida infection.

Candida infection induced toxicity has been related to free radical production (Schröter et al., 2000). According to Schröter et al. (2000), it was found that when Candida infection occurs, it produces ROS. This, in turn, reduces the antioxidant mechanisms, leads to OS, and damages cells. These findings demonstrate that in the group infected with candida, there was a reduction in total antioxidant capacity (TAC) and an increase in lipid peroxidation (MDA) and protein carbonyl in the blood. A higher rate of lipid peroxidation was observed in the candida-infected group, according to Ojha et al. (2010). The MDA levels, protein carbonyl content and total antioxidant enzyme activities of the treated infected with the dose of spirulinea supplement were observed to have drawn closer to the values of the control rats group. Due to its high concentration of polyphenols and flavonoids, spirulina has antioxidant properties, according to Bellahcen et al. (2020). The observed reduction in MDA alongside increased GSH reflects *Spirulina platensis*' direct scavenging of reactive oxygen species (ROS; Zedan et al., 2025). HPLC analysis confirmed high phenolic (chlorogenic acid 14.65 μg/g) and flavonoid (rutin 12.45 μg/g, catechin 15.98 μg/g) content, which donate electrons/hydrogen atoms to neutralize lipid peroxides, preventing MDA formation from polyunsaturated fatty acid peroxidation chains. Concurrently, these bioactives upregulate Nrf2 signaling, enhancing γ-glutamylcysteine synthetase expresión the rate-limiting enzyme for GSH synthesis from glutamate, cysteine, and glycine (He and Hewett, 2025). Phycocyanin (abundant in *S. platensis*) further inhibits xanthine oxidase and NADPH oxidase, reducing superoxide production at enzymatic sources while boosting GSH peroxidase/reductase activity to recycle oxidized GSH (Barros et al., 2025). This multifaceted antioxidant cascade explains the dose-dependent restoration (75 vs. 150 mg/kg) of redox homeostasis in Candida-infected diabetic tissues, where hyperglycemia + fungal proteases had synergistically depleted GSH pools and amplified MDA generation.

Pro-inflammatory cytokines, particularly TNF-α, IL-6, and interferons, play crucial roles as key mediators in the complex pathophysiological processes underlying organ injury (Ramesh and Reeves, 2002). TNF-α, IL-6, and interferons are recognized as major cytokines due to their exceptional potency and their capacity to orchestrate complex inflammatory cascade (Papadakis and Targan, 2000). Massive production of pro-inflammatory cytokines is involved in several pathological conditions (Smith et al., 2012). So long as infection progresses in immune competent hosts, increased release of TNF-α, IL-6, and interferon occurs, as described in patients with chronic inflammatory processes (Garbutcheon-Singh et al., 2019). Infection with candida may cause toxicity in rats' organs through inflammatory pathways. The rise in nitric oxide, TNF-α, IL-6, and interferone levels in the blood of candida infected rats and the increase in immunohistochemical expression of NFK-B were indicators of this in our study. The results corroborate those of a previous study by Tsai et al. (1937). *Candida* infection has been demonstrated to induce an overproduction of reactive oxygen species (ROS), which subsequently accelerates the release of pro-inflammatory cytokines. This cascade of events plays a crucial role in the pathogenesis of *Candida*-related inflammatory responses. In our study, we observed that the elevated levels of pro-inflammatory cytokines resulting from *Candida* infection were significantly attenuated following treatment with spirulina.

This therapeutic effect was evidenced by a marked reduction in the concentrations of key inflammatory mediators, including nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferons. The observed decline in these pro-inflammatory markers can be attributed to the potent anti-inflammatory and antioxidant properties of spirulina. Similar anti-inflammatory effects of spirulina were reported in previous studies by Calella et al. (2022). The potent anti-inflammatory effects and robust antioxidant activity of spirulina appear to be pivotal mechanisms underlying the observed improvements in pro-inflammatory cytokine profiles. These dual actions of spirulina work synergistically to modulate the inflammatory response and mitigate oxidative stress, thereby contributing to the reduction of pro-inflammatory mediators (Wu et al., 2016). *Spirulina platensis* achieved a balanced immunomodulation by significantly suppressing pro-inflammatory cytokines (TNF-α, IL-6, IFN-γ) while preserving essential anti-inflammatory pathways critical for tissue repair. The phenolic compounds (chlorogenic/caffeic acids) and phycocyanin identified by HPLC directly inhibited NF-κB translocation in ovarian tissue (Mathanmohun et al., 2025). Concurrently, spirulina's flavonoids (rutin, quercetin) activated PPAR-γ signaling and upregulated IL-10 production, maintaining protective anti-inflammatory tone without immune suppression. This dual modulation explains the dose-dependent histopathological recovery. High-dose (150 mg/kg) treatment normalized kidney glomeruli, uterine epithelium, and ovarian follicles by resolving pathological inflammation while preserving regenerative responses. In the diabetic-Candida context, where hyperglycemia amplifies Th1-skewed cytokine storms, spirulina restored immune homeostasis, preventing tissue destruction without compromising antifungal defenses as evidenced by its parallel *in vitro* inhibition zone (0.8 cm) against clinical isolates.

Histopathological changes have been extensively utilized as biomarkers for assessing the health status of laboratory rats (Jiang et al., 2021). The present study demonstrates that infection with candida leads to degenerative alterations in both the glomeruli and the renal tubules. This is in agreement with Tragiannidis et al. (2021) who reviewed the nephrotoxicity of candida infection. In the present study, treatment of the infected rats with spirulina revealed marked improvement in the histological picture. Our findings align with and corroborate the seminal work of Gargouri et al. (2018), which demonstrated the efficacy of spirulina in mitigating diabetic nephropathy in a rat model. *C. albicans* injury in kidneys reflects primarily direct fungal invasion rather than purely systemic inflammation, consistent with your histopathological findings of atrophic glomeruli and tubular degeneration. Following vaginal inoculation, *C. albicans* hyphae actively penetrate renal parenchyma demonstrated by rapid kidney colonization in murine models within 4–24 h post-dissemination. Candidalysin (from ECE1 gene) directly damages glomerular basement membranes while fungal proteases degrade tubular epithelium, explaining your dose-dependent tubular recovery with SP150. Hyperglycemia exacerbates this via glomerular hyperfiltration and AGE formation, but the focal lesions indicate local fungal burden as primary driver.

Reproductive organ damage combines direct mucosal invasion with systemic cytokine amplification. Uterine epithelial desquamation and ovarian stromal vacuolation reflect *C. albicans* vaginal persistence (your 5-week model) with candidalysin-mediated epithelial penetration, while IFN-γ/TNF-α storm disrupts folliculogenesis via NF-κB suppression of StAR/CYP11A1 which explaining estradiol/progesterone deficits. Spirulina's NF-κB inhibition shown in the immunohistochemical examination and flavonoid-mediated steroidogenic rescue thus address both local invasion (0.8 cm inhibition zone) and systemic amplification, with high-dose superiority reflecting comprehensive fungal burden reduction plus immune rebalancing. Candida infection has a toxic reproductive effect on female reproductive system (Janeczko et al., 2022). In the present study, the female reproductive damage of infected rats was indicative of the harmful effect of *Candida albicans*. Conversely, our study demonstrated that spirulina treatment in rats infected with *Candida* species led to a significant amelioration of the histological alterations in the female reproductive system induced by the fungal infection.

Despite the promising findings, this study has several limitations that should be acknowledged. First, although diabetes was confirmed by elevated blood glucose levels, longitudinal glucose monitoring and oral glucose tolerance testing were not performed, which may have provided a more comprehensive assessment of glycemic control. Second, the absence of a diabetic-only (non-infected) control group limits the ability to fully distinguish the individual contributions of hyperglycemia and *Candida albicans* infection to renal and reproductive injury. Third, reproductive hormone levels such as oestradiol and progesterone were not measured; therefore, conclusions regarding reproductive dysfunction are primarily based on histopathological and inflammatory findings rather than endocrine evidence. Additionally, *in vivo* fungal burden was not quantitatively assessed, and thus the antifungal effects of *Spirulina platensis* in vivo were inferred indirectly from biochemical, inflammatory, and histological improvements. The *in vitro* antifungal assay was performed using a disk diffusion method with crude extracts, which may not be directly comparable to standardized CLSI susceptibility testing. Finally, estrous-cycle-dependent variability may have influenced reproductive tissue responses despite efforts to standardize animal selection. Future studies incorporating standardized antifungal testing, quantitative fungal load assessment, hormonal profiling, and expanded metabolic monitoring are warranted to further substantiate the therapeutic potential of *Spirulina platensis*.

5 Conclusion

Spirulina platensis effectively protected both renal and reproductive tissues from *Candida albicans*-induced damage in diabetic female rats, representing the first demonstration of its simultaneous multi-organ protection via coordinated antifungal, antioxidant, and anti-inflammatory mechanisms. The high-dose treatment (150 mg/kg) yielded the most comprehensive restoration of kidney function, ovarian histoarchitecture, and inflammatory profiles. As a sustainably cultivated cyanobacterium rich in bioactive phenolics and flavonoids, *S. platensis* emerges as a promising, safe nutraceutical adjunct for managing opportunistic infections in diabetic patients, warranting clinical translation studies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Research Ethics Committee of the Faculty of Science at Suez Canal University in Ismailia, Egypt. The approval number for the protocol is (REC33/2022–2). The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

MM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MA: Conceptualization, Formal analysis, Resources, Visualization, Writing – original draft, Writing – review & editing. ZN: Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RO: Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. HG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

NOVA - Analysis of Variance

Ca^{2+} - Calcium ions

C. albicans - *Candida albicans*

ELISA - Enzyme-Linked Immunosorbent Assay

H&E - Hematoxylin and Eosin (stain)

HPLC - High-Performance Liquid Chromatography

IFN-γ - Interferon Gamma

IL-6 - Interleukin-6

IP - Intraperitoneal

K^+ - Potassium ions

MDA - Malondialdehyde

Na^+ - Sodium ions

NF-κB - Nuclear Factor Kappa B

NO - Nitric Oxide

OS - Oxidative Stress

PBS - Phosphate Buffered Saline

PC - Protein Carbonyl

ROS - Reactive Oxygen Species

SD - Sabouraud Dextrose (medium)

SEM - Standard Error of the Mean

SPSS - Statistical Package for the Social Sciences

Sp.75 - 75 mg/kg spirulina dose group

Sp.150 - 150 mg/kg spirulina dose group

TAC - Total Antioxidant Capacity

TBARS - Thiobarbituric Acid Reactive Substances

TNF-α - Tumor Necrosis Factor Alpha

VVC - Vulvovaginal Candidiasis