An update on potential applications of *Spirulina* sp. and C-phycocyanin to treat kidney diseases

Sandra Rodríguez-Salgueiro1*, Zulema Ramírez-Carmenate2, Lucía González-Núñez3

1Microscopy Laboratory, Biological Products Group, National Center for Scientific Research, Havana, Cuba
2Vivarium, Molecular Immunology Center, Havana, Cuba
3Department of Biomedical II, Latin American School of Medicine, Havana, Cuba

Abstract

To date, kidney protection is not included in clinical applications of commercial formulations of *Spirulina* sp. In this Mini-review, the potential nephroprotective properties of *Spirulina* sp. and its pigment C-phycocyanin are exposed. Both agents have shown beneficial effects in animal or cellular models of renal injury induced by nephrotoxicity, diabetic nephropathy, ureteral obstruction and ischemia-reperfusion. These renoprotective effects of *Spirulina* sp. and C-phycocyanin are mainly attributed to their well known antioxidant properties.

Introduction

The microalga *Spirulina* sp. has been used extensively in many countries as a dietary supplement due to its nutritional value (1,2). It has been implicated in several pharmacological properties demonstrated in preclinical studies, such as antimicrobial, antiviral, anti-carcinogenic, immunostimulant, antioxidant and also participates in the prevention of heavy metal poisoning (3-6).

Most of the activities and pharmacological properties of *Spirulina* sp. are attributed to the antioxidant capacity of C-phycocyanin, which acts by eliminating reactive oxygen and nitrogen species (7,8). C-phycocyanin, the major component of *Spirulina* sp. (9), is a phycobiliprotein which has proven independent therapeutic effects, such as anticancer, anti-inflammatory, antiseptic and neuroprotective, among others (7,10-12).

Kidneys are organs that perform the important function of purification in the body, since they represent the route of excretion of various toxic substances. This makes the kidneys vulnerable to a variety of pathological processes due to toxicity by external agents or chronic systemic processes (13-16).

Renal damage, with a high incidence globally, can have fatal consequences for affected patients (17-20). For this reason, different laboratories conduct experiments to find nephroprotective agents against renal damage of various etiologies. Since the production of reactive oxygen species is a frequent mechanism of renal damage, antioxidant therapy is one of the most promising as nephroprotective (21-24).

Considering cytoprotective and antioxidant properties of *Spirulina* sp. and its pigment C-phycocyanin, in this review we will discuss the potential nephroprotective properties of both agents.

Materials and Methods

We used a variety of sources for this mini-review, by searching through PubMed, Scopus, Future Medicine, Directory of Open Access Journals. The search was performed using combinations of the following key words and or their equivalents such as C-phycocyanin, *Spirulina* sp., kidney disease, nephroprotection, antioxidant, renal damage.
**Spirulina sp. and C-phycocyanin as nephroprotective agents**

Nephroprotective properties of *Spirulina sp.* and C-phycocyanin have been tested in animal models of renal injury induced by nephrotoxicity, diabetic nephropathy and ureteral obstruction. However, so far, clinical applications of *Spirulina sp.* do not include protection of renal damage (25).

**Models of nephrotoxicity**

Nephrotoxicity can lead to serious renal complications such as acute kidney injury. It has been suggested that the 17% to 26% of patients suffering acute kidney injury is caused by nephrotoxic agents (26).

**Drug-induced nephrotoxicity**

Many types of drugs induce renal damage, which affects the patients morbidity and can even lead to their death. Nephrotoxic drugs are agents with greater contribution to acute kidney injury (27). The drug-specific and patient-specific risk factors that influence the development of drug-related nephropathy have been described elsewhere (26,28,29).

In many conditions, it is imperative to use some drugs despite knowing its potential nephrotoxicity. Thus, it is a need to find protective strategies to overcome it (30).

**Chemotherapeutic drugs**

Cisplatin is a cancer drug that is commonly used in clinical practice, although this drug induces nephrotoxicity in 20% of treated patients. The mechanism of cisplatin nephrotoxicity is complex and involves oxidative stress as well as apoptotic and inflammatory processes (31-33). So far there is no treatment to prevent this side effect of cisplatin. Numerous agents have shown nephroprotective effect in models of renal damage induced by cisplatin. Some of them are antioxidants (34).

Nephroprotective effects of *Spirulina sp.* have been reported using models of cisplatin damage (Table 1) (35,36). *Spirulina sp.* has also exerted protection of renal tissue in animal models of damage induced by other anticancer drugs, as cyclophosphamide and nitroquinoline (Table 1) (37,38).

On the other hand, more recently, C-phycocyanin also showed nephroprotective properties against cisplatin induced renal damage (Table 2) (39-41).

**Antimicrobial drugs**

**Aminoglycosides**

Aminoglycoside antibiotics comprises a group of natural or semi-synthetic products frequently used in the treatment of a variety of infections caused by Gram-negative bacteria and endocarditis (42). Nevertheless, nephrotoxicity induced by aminoglycosides has an incidence of 10%-25% of treated patients. The production of reactive oxygen species in renal tubular cells is the main mechanism involved in aminoglycoside nephrotoxicity (43,44). Many products of natural and synthetic origin have had a beneficial impact in the setting of aminoglycoside nephrotoxicity. From them, antioxidants produce the best results, due to their excellent safety profile and effectiveness by eliminating reactive oxygen species (45,46).

In models of gentamicin-induced acute damage, the protective effects of *Spirulina sp.* have been shown (Table 1) (47-49). The effect of C-phycocyanin against nephrotoxicity induced by aminoglycoside antibiotics has been demonstrated using models of chronic renal damage induced by kanamycin (Table 2) (50).

**Vancomycin**

Vancomycin is a natural antibiotic used to treat serious infections induced by Gram-positive bacteria (51,52). Nephrotoxicity due to vancomycin treatment has an incidence of 5%-7%, but it can be higher when vancomycin is associated with another antibiotic (53). The mechanism of vancomycin nephrotoxicity seems to be mainly related to oxidative stress, since this medication can induce free radicals and therefore, reduction of antioxidant enzymes (27). Several antioxidants have been proved as protective agents against vancomycin nephrotoxicity (54). Specially, *Spirulina sp.* has exerted protective effect (Table 1) (55).

**Antituberculosis drugs**

Nephrotoxicity is a rare complication caused by anti-tuberculosis drugs, like rifampicin, isoniazid, pyrazinamide and ethambutol. Oxidative stress justifies this side effect (56). Recently, protective effect of *Spirulina sp.* in a model of renal damage induced by isoniazid and rifampicin was found (Table 1) (57).

**Immunosuppressive agents**

Cyclosporine A is a drug frequently used to treat autoimmune diseases and also in patients submitted to organ transplantation. However, cyclosporine A induces chronic nephrotoxicity, due to apoptotic pathways acting synergistically producing oxidative stress (58). In an animal model of renal damage induced by cyclosporin A, *Spirulina sp.* was tested with satisfactory results (Table 1) (59).

**Nonsteroidal anti-inflammatory drugs**

Nonsteroidal anti-inflammatory drugs induce renal damage in around 1%-5% of the patients. The proposed mechanisms of this effect are related to inhibition of prostaglandins and oxidative stress among others (60,61). Recently, the renal protective activity of *Spirulina fusiformis* in diclofenac-treated rats was described (Table 1) (62).

**Heavy metals and pesticides induced nephrotoxicity**

Environmental exposure to heavy metals induces renal toxicity, related to oxidative stress (63-65). Treatments with *Spirulina sp.* have been successful against renal toxicity induced by heavy metals, such as mercury (66), aluminium (67), lead (68), cadmium (69), and chromium.
Table 1. Summary of experiments proving nephroprotective effects of *Spirulina* sp. (alone or in combination with another antioxidant) against renal injury

<table>
<thead>
<tr>
<th>Type of renal injury</th>
<th>Model of damage (specie, dose, route)</th>
<th>Source of <em>Spirulina</em>, doses and route</th>
<th>Scheme of treatments with <em>Spirulina</em> (SP) and the renal damage inducing agent</th>
<th>References</th>
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</thead>
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<tr>
<td>Cisplatin (CT) Nephrotoxicity</td>
<td>Rats 5 mg/kg, i.p. Wistar rats 1 mg/kg, i.p.</td>
<td><em>S. fusiformis</em> 500,1000,1500 mg/kg, p.o. <em>S. platensis</em> 1000 mg/kg, p.o.</td>
<td>SP 6 days and CT on day 3 SP 8 days and CT was administered on day 4</td>
<td>Kuhad et al, 2006 (35) Mohan et al, 2006 (36)</td>
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<td>Cyclophosphamide (CP) Nephrotoxicity</td>
<td>Rats 150 mg/kg, i.p.</td>
<td><em>Spirulina</em> 1000 mg/kg, p.o.</td>
<td>SP 7 days and CP was injected on day 7</td>
<td>Sinanoglu et al, 2012 (37)</td>
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<td>Nitroquinoline (4NQO) Nephrotoxicity</td>
<td>Rats 20 ppm, p.o. (drinking water)</td>
<td><em>Spirulina</em> (commercial) 500 mg/kg, p.o.</td>
<td>4NQO was given during 8 weeks, then it was stopped and SP was given for 15 days</td>
<td>Viswanadha et al, 2011 (38)</td>
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<td>Gentamicin (GM) Nephrotoxicity</td>
<td>Wistar rats 100 mg/kg, i.p. Wistar rats 80 mg/kg, i.p. Sprague-Dawley rats, 100 mg/kg, i.p.</td>
<td><em>S. fusiformis</em> 500, 1000, 1500 mg/kg, p.o. <em>S. platensis</em> 1000 mg/kg, p.o.</td>
<td>SP 2 days before and 8 days concurrently with GM SP 2 days before and 7 days concomitantly with GM SP 7 days concomitantly with GM</td>
<td>Kuhad et al, 2006 (47) Advagie et al, 2008 (48) Karadeniz et al, 2008 (49)</td>
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<td>Vancomycin (VCM) Nephrotoxicity</td>
<td>Wistar rats 200 mg/kg, i.p.</td>
<td><em>Spirulina</em> (commercial) 1000 mg/kg, p.o. <em>Pycochelin (Py)</em> 200 mg/kg, p.o.</td>
<td>SP and Py 7 days concomitantly with VCM</td>
<td>Bayomy et al, 2016 (55)</td>
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<td>Antituberculosis Nephrotoxicity</td>
<td>Wistar rats 50 mg/kg; p.o.</td>
<td><em>S. fusiformis</em> 400, 800 mg/kg, p.o.</td>
<td>SP 28 days concomitantly with IZ and RF</td>
<td>Martin et al, 2016 (57)</td>
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<td>Cyclosporin A (CsA) Nephrotoxicity</td>
<td>Rats 50 mg/kg</td>
<td><em>S. fusiformis</em> 500 mg/kg, p.o.</td>
<td>SP 3 days before and 14 days concurrently with CsA</td>
<td>Khan et al, 2006 (59)</td>
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<td>NAIDS Nephrotoxicity Diclofenac (DFC)</td>
<td>Wistar rats 50 mg/kg</td>
<td><em>S. fusiformis</em> 400 mg/kg, p.o.</td>
<td>SP 5 days and DFC on days 3 y 4</td>
<td>Girdharan et al, 2017 (62)</td>
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<td>Mercuric chloride (MC) Nephrotoxicity</td>
<td>Mice 5.0 mg/kg, i.p.</td>
<td><em>S.fusiformis</em> 800 mg/kg, p.o.</td>
<td>SP 10 days before MC and continued up to 30 days after MC</td>
<td>Sharma et al, 2007 (66)</td>
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<td>Aluminium (Al and AlF3) Nephrotoxicity</td>
<td>Gambusia fishs (3 ppm) in 15 L aluminium fluoride (AlF3) (35.4 ppm) in 15 L</td>
<td><em>Spirulina</em> (commercial) 100 mg, p.o. <em>Pycochelin (Py)</em> 100 mg, p.o.</td>
<td>SP and TFP pre-treatment 30 days Al and AlF3 for 30-60 days (winter), 90 days (summer)</td>
<td>Sharma et al, 2012 (67)</td>
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<td>Lead Nephrotoxicity. Lead acetate (LA)</td>
<td>Wistar rats 25 mg/kg, i.p.</td>
<td><em>S. maxima</em> 5 %, p.o. (with food)</td>
<td>SP 30 days and LA on days 14, 21, and 28</td>
<td>Ponce-Canchihuaman, 2010 (68)</td>
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<td>Cadmium (CdCl2) Nephrotoxicity</td>
<td>Wistar rats 6 mg/kg, p.o.</td>
<td><em>Spirulina</em> (commercial) 500 mg/kg, p.o. <em>Liv 52</em> 500 mg/kg, p.o.</td>
<td>SP and Liv 52 during 30 days concomitantly with CdCl2</td>
<td>Jeyaprakash et al, 2005 (69)</td>
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<td>Chromium Nephrotoxicity</td>
<td>Sprague-Dawley rats 350 mg/L, p.o. (drinking water)</td>
<td><em>S. platensis</em> 300 mg/kg, p.o.</td>
<td>SP 3 months concomitantly with SDD</td>
<td>Elshazy et al, 2015 (70)</td>
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<td>Fluor Nephrotoxicity (fluoride)</td>
<td>Gambusia fishs, 10 ppm in 15 L Swiss albino mice sub-acute: 190 mg/kg, p.o., sub-chronic: 94 mg/kg, p.o.</td>
<td><em>Spirulina</em> (commercial) 100 mg in 15 L, p.o. <em>Pycochelin (Py)</em> 100 mg in 15 L, p.o.</td>
<td>SP and TFP Pretreatment 30 days, fluoride during 30-60 days (winter), 90 days in summer, p.o.</td>
<td>Viswanadha et al, 2011 (71)</td>
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<td>Deltamethrin (DLM) Nephrotoxicity</td>
<td>Nile tilapia fishes 1.46 μg/L Rats 30 mg/kg, p.o.</td>
<td><em>S. platensis</em> 0.5 and 1 %, p.o. <em>S. platensis</em> 500, 1000 mg/kg, p.o.</td>
<td>SP 28 days concomitantly with DLM SP 1 h before DLM administration for 5 days.</td>
<td>Abdelkhaleel et al, 2014 (74) Abddel-Daim et al, 2013 (75)</td>
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<td>Diabetic nephropathy fructose</td>
<td>Wistar rats 30 %, p.o. (drinking water), 4 weeks</td>
<td><em>S. versicolor</em> 50 mg/kg, p.o.</td>
<td>SP 4 weeks in selected diabetic rats</td>
<td>Hooyen et al, 2016 (76)</td>
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<td>Ischemia-reperfusion (IR)</td>
<td>Sprague-Dawley rats ischemia</td>
<td><em>S. platensis</em> 1000 mg/kg, p.o.</td>
<td>SP 7 days before IR (ischemia for 45 minutes and right nephrectomy)</td>
<td>Abd-Allah et al, 2015 (77)</td>
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<td>Type of renal injury</td>
<td>Model of damage (specie or cell line, dose, route)</td>
<td>Doses and route of c-phycocyanin</td>
<td>Scheme of treatments with C-phycocyanin (C-PC) and the renal damage inducing agent</td>
<td>References</td>
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<td>Cisplatin (CT) Nephrotoxicity</td>
<td>Human kidney-2 (HK-2) cells, 1 mg/mL</td>
<td>1 μM</td>
<td>C-PC exposition during 6 hours simultaneously with CT</td>
<td>Lim et al, 2012 (39)</td>
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<td>C57BL/6 mice, 12 mg/kg, i.p.</td>
<td>50 mg/kg, i.p.</td>
<td>C-PC 1 h before single injection of CT</td>
<td>Fernández-Rojas et al, 2014 (40)</td>
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<td>CD1 mice, 18 mg/kg, i.p.</td>
<td>5, 10 and 30 mg/kg, i.p.</td>
<td>C-PC 1 h before single CT administration</td>
<td>Fernandez-Rojas et al, 2015 (41)</td>
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<td>CD-1 mice, 22 mg/kg, i.p.</td>
<td>30 mg/kg</td>
<td>C-PC 1 h prior to single CT administration</td>
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<td>Kanamycin Nephrotoxicity</td>
<td>C57BL6 mice, 700 mg/kg, i.p.</td>
<td>10 mg/kg, i.p.</td>
<td>C-PC 15 days concomitantly with kanamycin</td>
<td>Núñez et al, 2012 (50)</td>
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<tr>
<td></td>
<td>Wistar rats, 700 mg/kg, i.p.</td>
<td>60 mg/kg, i.p.</td>
<td>C-PC 9 days concomitantly with kanamycin</td>
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<td>Mercuric chloride Nephrotoxicity</td>
<td>NIH mice, 5 mg/kg, ip</td>
<td>C-phycocyanin 50, 100 mg/kg, p.o. phycobiliproteins 100 mg/kg, p.o.</td>
<td>C-PC 30 min before mercury administration, 5 days</td>
<td>Rodríguez-Sanchez et al, 2012 (71)</td>
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<td>Diabetic nephropathy</td>
<td>ICR mice</td>
<td>100, 200 mg/kg, p.o.</td>
<td>C-PC 2 weeks before and 4 weeks after alloxane</td>
<td>Ou et al, 2012 (79)</td>
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<td>C57BL/Ks J db/db mice</td>
<td>C-phycocyanin (300 mg/kg), p.o. phycocyanobilin (15 mg/kg), p.o.</td>
<td>C-PC during 10 weeks and phycocyanobilin for 2 weeks</td>
<td>Zheng et al, 2013 (80)</td>
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<td>Unilateral ureteral obstruction</td>
<td>C57BL6 mice, complete ligation of the left ureter</td>
<td>25 mg/kg, i.p.</td>
<td>C-PC from 1 day before the operation to 6 days post-operatively</td>
<td>Chung et al, 2010 (84)</td>
</tr>
</tbody>
</table>
C-phycocyanin and kidney diseases

(70), using animal models (Table 1). Phycocyanin has also shown protective effect in a model of damage induced by mercury (71) (Table 2). Pesticides are also a cause of environmental nephrotoxicity (72). Nephroprotective properties of Spirulina sp. against renal damage induced by the pesticide deltamethrin have been found in rat and fish experiments (Table 1) (73,74).

Models of diabetic nephropathy

Diabetic nephropathy leads to end-stage renal disease in 20% to 40% of all diabetics (75). This is due to the interaction of hemodynamic and metabolic changes, which results in the development of inflammatory processes and free radical damage (76,77).

In an experimental study, the alga Spirulina sp. was used as a nephroprotective treatment using a model of diabetic nephropathy induced by fructose (Table 1) (78). C-phycocyanin has also been tried to prevent diabetic nephropathy (Table 2) (79,80).

Model of obstructive renal injury

Unilateral ureteral obstruction is a model used to generate progressive renal fibrosis in rodents, which reproduces acute renal injury and chronic kidney disease in humans. Oxidative stress and inflammation are mainly involved in the development of kidney fibrosis (81,82).

The anti-inflammatory and anti-fibrotic effects of C-phycocyanin were demonstrated in a model of inflammation and fibrosis after ureteral obstruction (Table 2) (83,84).

Model of renal ischemia/reperfusion

The models of renal ischemia/reperfusion are used as biomarkers of acute kidney injury. Renal ischemia-reperfusion leads to inflammatory processes and oxidative stress as a result of the suppression of blood supply followed by reperfusion. There is a high incidence of morbidity and mortality in patients with acute kidney injury (85).

Treatment with Spirulina sp. decreased kidney damage and contributed to tubular regeneration after ischemia-reperfusion in rats (86) (Table 1).

Combined therapies

Combinations of Spirulina sp. and other antioxidant agents have also been used in experiments to prevent kidney damage induced by different agents.

In a model of cadmium-induced renal toxicity, Spirulina sp. was used in combination with the Liv 52 plant mixture, obtaining satisfactory results (Table 1) (69).

Spirulina sp. and tamarind pulp have been used in combination to treat fluorine-induced nephrotoxicity (Table 1) (67,87).

Spirulina sp. combined with pycnogenol prevents vancomycin-induced nephrotoxic damage (Table 1) (55). In general, it has been shown that the combined therapies of Spirulina sp. and some other compound are more effective than the administration of the two compounds separately.

Similarly, combinations of C-phycocyanin with other pigments have been assessed in models of renal damage. In an experiment in mice the effect of C-phycocyanin given with another phycobiliprotein on mercury chloride-induced nephrotoxicity was evaluated (Table 2) (71). In addition, the combination of C-phycocyanin and phycocyanobilin was successful in a model of diabetic nephropathy in mice (Table 2) (80). In both examples, similar protection results than when the pigments were administered separately were obtained.

Conclusion

Spirulina sp. and C-phycocyanin have shown therapeutic potential in several models of renal damage in which oxidative stress is an important factor triggering many diseases. These effects of Spirulina sp. and C-phycocyanin on the kidney are associated with their antioxidant properties. Since kidney diseases have a high incidence globally, it would be advisable to extrapolate these results to the clinic.

Authors’ contribution

SRS and ZRC searched and gathered the related articles. LGN and SRS prepared the draft and edited the final manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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