Ann Res Antioxid. 2017;2(1):e04 **Mini-Review**

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

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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 microalgae *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.

Core tip

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.

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-sinthetic 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

Type of renal injury	Model of damage (specie, dose, route)	Source of *Spirulina*, doses and route	Scheme of treatments with *Spirulina* (SP) and the renal damage inducing agent	References
Cisplatin (CT) Nephrotoxicity	Rats 5 mg/kg, i.p.	*S. fusiformis* 500,1000,1500 mg/kg, p.o.	SP 6 days and CT on day 3	Kuhad et al, 2006 (35)
	Wistar rats 1 mg/kg, i.p.	*S. platensis* 1000 mg/kg, p.o.	SP 8 days and CT was administered on day 4	Mohan et al, 2006 (36)
Cyclophosphamide (CP) Nephrotoxicity	Rats 150 mg/kg, i.p.	Spirulina 1000 mg/kg, p.o.	SP 7 days and CP was injected on day 7	Sinanoglu et al, 2012 (37)
Nitroquinoline (4NQO) Nephrotoxicity	Rats 20 ppm, p.o. (drinking water)	Spirulina (commercial) 500 mg/kg, p.o.	4NQO was given during 8 weeks, then it was stopped and SP was given for 15 days	Viswanadha et al, 2011 (38)
Gentamicin (GM) Nephrotoxicity	Wistar rats 100 mg/kg, i.p.	*S. fusiformis* 500, 1000, 1500 mg/kg, p.o.	SP 2 days before and 8 days concurrently with GM	Kuhad et al, 2006 (47)
	Wistar rats 80 mg/kg, i.p.	*S. platensis* 1000 mg/Kg, p.o.	SP 2 days before and 7 days concomitantly with GM	Advagic et al, 2008 (48)
	Sprague-Dawley rats, 100 mg/kg, i.p.	*S. platensis* 1000 mg/kg , p.o.	SP 7 days concomitantly with GM	Karadeniz et al, 2008 (49)
Vancomycin (VCM) Nephrotoxicity	Wistar rats 200 mg/kg, i.p.	Spirulina (commercial) 1000 mg/kg, p.o. pycnogenol (Py) 200 mg/kg, p.o.	SP and Py 7 days concomitantly with VCM	Bayomy et al, 2016 (55)
Antituberculosis Nephrotoxicity isoniazid (IZ) and rifampicin (RF)	Wistar rats 50 mg/kg; p.o	*S. fusiformis* 400, 800 mg/kg, p.o.	SP 28 days concomitantly with IZ and RF	Martin et al, 2016 (57)
Cyclosporin A (CsA) Nephrotoxicity	Rats 50 mg/kg	*S. fusiformis* 500 mg/kg, p.o.	SP 3 days before and 14 days concurrently with CsA	Khan et al, 2006 (59)
NAIDS Nephrotoxicity Diclofenac (DFC)	Wistar rats 50 mg/kg i.p	*S. fusiformis* 400 mg/kg, p.o.	SP 5 days and DFC on days 3 y 4	Giridharan et al, 2017 (62)
Mercuric chloride (MC) Nephrotoxicity	Mice 5.0 mg/kg, i.p.	*S. fusiformis* 800 mg/kg, p.o.	SP 10 days before MC and continued up to 30 days after MC	Sharma et al, 2007 (66)
Aluminium (Al and AlF_3) Nephrotoxicity	*Gambusia affinis* fishs Al (3 ppm) in 15 L aluminium fluoride (AlF_3) (35.4 ppm) in 15 L	Spirulina (commercial) 100 mg, p.o. tamarind fruit pulp (TFP), 100 mg, p.o.	SP and TFP pre-treatment 30 days Al and AlF3 for 30-60 days (winter), 90 days (summer)	Sharma et al, 2012 (67)
Lead Nephrotoxicity. Lead acetate (LA)	Wistar rats 25 mg/kg, i.p.	*S. maxima* 5 %, p.o. (with food)	SP 30 days and LA on days 14, 21, and 28	Ponce-Canchihuaman, 2010 (68)
Cadmium ($CdCl_2$) Nephrotoxicity	Wistar rats 6 mg/kg, p.o.	Spirulina (commercial) 500 mg/kg, p.o. Liv 52 500 mg/kg, p.o.	SP and Liv 52 during 30 days concomitantly with $CdCl_2$	Jeyapraskash et al, 2005 (69)
Chromium Nephrotoxicity Sodium dichromate dihydrate (SDD)	Sprague-Dawley rats 520 mg/L, p.o. (drinking water)	*S. platensis* 300 mg/kg, p.o.	SP 3 months concomitantly with SDD	Elshazly et al, 2015 (70)
Fluor Nephrotoxicity (fluoride)	*Gambusia affinis* fishs, 10 ppm in 15 L	Spirulina (commercial) 100 mg in 15 L, p.o. tamarind fruit pulp (TFP) 100 mg in 15 L, p.o.	SP and TFP Pretreatment 30 days, fluoride during 30-60 days (winter), 90 days in summer, p.o.	Sharma et al, 2012 (67)
	Swiss albino mice sub-acute: 190 mg/kg, p.o., sub-chronic: 94 mg/kg, p.o.	Spirulina (commercial) 230 mg/kg, p.o. tamarind fruit pulp (TFP) 230 mg/kg, p.o.	SP and TFP Pretreatment 45 days, fluoride sub-acute 7 days, fluoride sub-chronic: 90 days	Yadav et al, 2016 (87)
Deltamethrin (DLM) Nephrotoxicity	*Nile tilapia* fishs 1.46 µg/L	*S. platensis* 0.5 and 1 %, p.o.	SP 28 days concomitantly with DLM	Abdelkhalec et al, 2014 (74)
	Rats 30 mg /kg, p.o.	*S. platensis* 500, 1000 mg/kg, p.o.	SP 1 h before DLM administration for 5 days.	Abdel-Daim et al, 2013 (73)
Diabetic nephropathy fructose	Wistar rats 30 %, p.o. (drinking water), 4 weeks	*S. versicolor* 50 mg/kg, p.o.	SP 4 weeks in selected diabetic rats	Hozayen et al, 2016 (78)
Ischemia-reperfusion (IR)	Spague-Dawley rats ischemia	*S. platensis* 1000 mg/kg, p.o.	SP 7 days before IR (ischemia for 45 minutes and right nephrectomy)	Abd-Allah et al, 2015 (86)

Table 2. Summary of experiments proving nephroprotective effects of C-phycocyanin against renal injury

Type of renal injury	Model of damage (specie or cell line, dose, route)	Doses and route of c-phycocyanin	Scheme of treatments with C-phycocyanin (C-PC) and the renal damage inducing agent	References
Cisplatin (CT) Nephrotoxicity	Human kidney-2 (HK-2) cells, 1 mg/mL	1 µM	C-PC exposition during 6 hours simultaneously with CT	Lim et al, 2012 (39)
	C57BL/6 mice, 12 mg/kg, i.p.	50 mg/kg, i.p	C-PC 1 h before single injection of CT	
	CD1 mice, 18 mg/kg, i.p	5, 10 and 30 mg/kg, i.p	C-PC 1 h before single CT administration	Fernández-Rojas et al, 2014 (40)
	CD-1 mice, 22 mg/kg, i.p.	30 mg/kg	C-PC 1 h prior to single CT administration	Fernandez-Rojas et al, 2015 (41)
Kanamycin Nephrotoxicity	C57/BL6 mice, 700 mg/kg, i.p.	10 mg/kg, i.p.	C-PC 15 days concomitantly with kanamycin	Núñez et al, 2012 (50)
	Wistar rats, 700 mg/kg, i.p.	60 mg/kg, i.p.	C-PC 9 days concomitantly with kanamycin	
Mercuric chloride Nephrotoxicity	NIH mice, 5 mg/kg, ip	C-phycocyanin 50, 100 mg/kg, p.o. phycobiliproteins 100 mg/kg, p.o.	C-PC 30 min before mercury administration, 5 days	Rodríguez Sanchez et al, 2012 (71)
Diabetic nephropathy	ICR mice	100, 200 mg/kg, p.o.	C-PC 2 weeks before and 4 weeks after alloxane	Ou et al, 2012 (79)
	C57BL/Ks J *db/db* mice	C-phycocyanin (300 mg/kg), p.o. phycocyanobilin (15 mg/kg), p.o.	C-PC during 10 weeks and phycocyanobilin for 2 weeks	Zheng et al, 2013 (80)
Unilateral ureteral obstruction	C57BL6 mice, complete ligation of the left ureter	25 mg/kg, i.p.	C-PC from 1 day before the operation to 6 days post-operatively	Chung et al, 2010 (84)

(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 release (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 biomodels 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.

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