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Review Article
Nutritional and Healthical Aspects of Spirulina (Arthrospira) for Poultry, Animals and Human

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Abstract
Spirulina (Arthrospira) is a microscopic blue-green algae and it is considered as one of the richest sources of organic nutrients that are making it a good nutritional supplement for human and animal feed worldwide. Spirulina contains good quality proteins, vitamins and minerals in addition to a wide variety of natural carotene and xanthophyll phytopigments. Owing to its unique and impressive nutrient composition, Spirulina is used as a dietary inclusion in a large scale of food products not only to enhance their nutritional qualities but also for therapeutic purposes. On this aspect, many researchers studied the beneficial effects of Spirulina and reported its enhancing potential on the productive and reproductive performance, improving general health as well as lowering the problems of different animal diseases like arthritis, diabetes, anaemia, hypertension and cardiovascular disorders. Other studies have demonstrated that Spirulina possess some promising biological activities such as antitumor, antimicrobial, antiviral, anti-inflammatory, hypocholesterolemic, radio protective and metalloprotective effects. These pharmaceutical and medicinal properties of Spirulina could be attributed to some natural constituents such as phycocyanin, carotene, tocopherols, linolenic acid and phenolic compounds that had been shown to have strong antioxidant properties and powerful scavenging activities against Reactive Oxygen Species (ROS) like superoxide and hydrogen peroxide radicals. This review illustrates the beneficial effects of Arthrospira on poultry, animals and human health and throws the light on its ability to protect the body physiological system against oxidative damage and as nutraceutical and source of potential pharmaceuticals based mainly on the highest levels of evidence available in the literature.

Key words: Spirulina, Arthrospira, biological activities, nutritive values, production, reproduction, medicinal properties, health, poultry, animals, human

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Arthrospira is a multicellular filamentous, spiral-shaped blue-green microalgae derived from class Cyanophyta/ Cyanobacteria which is an ancient organisms known by its ability to make photosynthesis it is a member of the Oscillatoriaceae family that grows naturally in warm climates and are found in variety of environments; Sand, soil and marshes and different kinds of aquatic media like fresh water, sea water and brackish water (Sanchez *et al*., 2003; Khan *et al.,* 2005; Charpy *et al.,* 2012). Its long history of safe use makes it unique blue green algae (Seshadri and Umesh, 1992). It has been used as a nutritional supplement for human and animal consumption as it is rich in proteins, lipids, carbohydrates, sterols and some vital elements such as zinc, magnesium and selenium (Estrada *et al.,* 2001; Chamorro *et al*., 2002; Babadzhanov *et al*., 2004). Its high phytonutrients value and pigments are gaining the attention of medical scientists due to their ability to protect the body physiological system against oxidative injury and due to their nutraceutical and potential pharmaceuticals properties. The most intensively investigated species of Spirulina which has been considered as a suitable nutritional supplement for both human and animal with high nutritional and potential therapeutic values are *Spirulina platensis* (*Arthrospira platensis*), *Spirulina maxima* (*Arthrospira maxima*) and *Spirulina fusiformis* (*Arthrospira fusiformis*) (Karkos *et al*., 2011).

Administration of Arthrospira produced a well pronounced hepatoprotective (Jeyaprakash and Chinnaswamy, 2005), nephroprotective (Sharma *et al.,* 2007) as and neuroprotective effects against oxidative damage induced by exposure to hazardous chemicals and environmental pollutants (Banji *et al.,* 2013) and it was also reported to enhance parameters of male fertility (Nah *et al*., 2012). Moreover, supplementation of Spirulina to animal diets could manage many health problems including diabetes and its related complications by lowering blood glucose level, improving insulin resistance and regulating hyper-cholesterolemia (Gupta *et al.,* 2010). In addition, Spirulina has some good medicinal properties against inflammation (Coskun *et al*., 2011), cancer (Ismail *et al.,* 2009) and heart diseases (Khan *et al.,* 2005) beside its immunomodulatory activities (Jamil *et al.,* 2015). Recently, Spirulina has been reported to have multiple beneficial effects in improving productive and reproductive performance of animal and poultry (El-Sabagh *et al.,* 2014; Shanmugapriya *et al*., 2015).

In the current era of changing life style and food habits, increasing antibiotic drug resistance, threats of emerging and re-emerging infectious pathogens/diseases, rising general health problems and higher incidences of non-infectious diseases/disorders, the value of natural food supplements, phytonutrients, plant metabolites and herbs is gaining importance and attention of researchers worldwide (Mahima *et al*., 2012; Rahal *et al*., 2014a, b; Dhama *et al*., 2013, 2014, 2015). The aims of this review are to summarize the multiple beneficial effects of arthrospira on poultry, animal and human health and productivity and throw the light on its nutritive value and therapeutic uses as antioxidant, hepatoprotective, nephroprotective and neuroprotective activities, in addition to its role as antitumor, antigenotoxic and immunomodulatory agent. This review also discusses the hypoglycemic and hypolipidimic potential of Spirulina and give idea about its practical applications in animal and poultry nutrition for increasing productive and reproductive performance based mainly on the highest levels of evidence available in the literature.

Nutritive value: The high poly-nutrients value and phytopigments of Spirulina gave it the highly importance and international demand due to their importance in various applications as production of safe and healthy food products, animal feed and many other diagnostic and therapeutic practices (Vonshak and Tomaselli, 2000). The naturally occurring and high value concentrated nutritional compounds of Spirulina, makes it ideal for consumption as a whole food supplement than the other artificial sources of nutrition, additionally Spirulina has been considered to be safe and so could be used in different food products and various uses such as nutraceuticals and cosmaceuticals and as functional foods (Moraes *et al*., 2010; Borowitzka, 2013).

The nutritional value of Spirulina is well recognized, with its unique high protein content as it is one of the richest sources of proteins (60-70% by dry weight) which is containing all essential amino acids (Ishimi *et al*., 2006). Its protein content resemble that of legumes and could be comparable to that of meat, egg and milk although its reduced content of cysteine, methionine and lysine (Babadzhanov *et al*., 2004). It contains a wide spectrum of nutrients that include essential fatty acids, gamma-linolenic acid, alpha-linolenic acid, linoleic acid, eicosapentaenoic acid, stearidonic acid, arachidonic acid, docosahexaenoic acid and ω-3 and ω-6-poly unsaturated fatty acids (Mendes *et al*., 2003). It also has phycocyanin and other photochemicals like phycocyanobilin chlorophyll and xanthophyll phytopigments (Chamorro *et al*., 2002; Upasani and Balaraman, 2003; Gong *et al*., 2005; Bermejo *et al*., 2008). It contains vitamins B1 (thiamine), B_2 (riboflavin), B_3

(nicotinamide), B_6 (pyridoxine), B_9 (folic acid), C (ascorbic acid; AA) as well as D, A and E vitamins and it is also a source of calcium, potassium, chromium, copper, manganese, iron, phosphorus, magnesium, sodium, zinc and selenium (Belay, 1997; Babadzhanov *et al*., 2004).

Biological activities of Spirulina: Many biological activities, beneficial effects and mechanisms of action could be obtained by using Spirulina (Table 1).

Antioxidant functions: Spirulina has the capability to prevent cell damage through containing both enzymatic and non-enzymatic antioxidant defense system that counteract the effects of Reactive Oxygen Species (ROS) and protect the cells from their deleterious actions under normal and stress conditions (Takeda *et al*., 1995; Alscher *et al*., 1997). Moreover, Spirulina can be used for production of some antioxidant compounds as described by Abd El-Baky (2003) due to its high contents of carotenoids, tocopherols (TOH), ascorbic acid, glutathione (GSH) and chlorophyll derivatives as non-enzymatic defense system while the enzymatic defenses system represented by superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX), peroxiredoxin (PrxR) and ascorbate Peroxidase (AXP) (Mittler *et al.,* 2004; Abd El-Baky *et al*., 2007).

Carotenoids and tocopherols in Spirulina can repair the oxidizing radical directly by its free radical scavenging activity through which they could inhibit the chain propagation steps during lipid peroxidation (Karpinski *et al*., 1999). Spirulina contains 501 mg kg^{-1} of total tocopherols, 70.1 mg g^{-1} of total phycocyanin and 12.35 mg g^{-1} of total carotenoids,

Table 1: Beneficial effects and mechanisms of action of Spirulina

Activities	Mechanisms	References
Antioxidant functions	Spirulina improve the antioxidant enzymes such as SOD, CAT, GSH, GSH-PX and reduce lipid peroxidation (MDA) as well as has scavenging activity of free radical	Abd El-Baky *et al.* (2007), Chen and Wong (2008), Chaiklahan *et al.* (2010), Gad *et al.* (2011), Hwang *et al.* (2011), Kurd and Samavati (2015) and Ibrahim and Abdel-Daim (2015)
Hepatoprotective effect	Spirulina reduce lipid peroxidation, decreased oxidative stress and apoptosis in the liver; prevent the chronic hepatitis from being complicated in to hepatic cirrhosis	Garcia-Martinez *et al.* (2007), Ray *et al.* (2007), Hassan *et al.* (2012), Abdel-Daim *et al.* (2013) and Martin *et al.* (2014)
Nephroprotective effect	Spirulina normalize the renal functions and histological structure	Karadeniz *et al.* (2008), Rodriguez-Sanchez *et al.* (2012) and Zheng *et al.* (2012)
Neuroprotective effect	Spirulina help in reducing cerebral infarction and ischemic brain damage produced by toxic chemicals, lowering ROS, nitric oxide and lipoperoxidation, enhancing the locomotor functions and decreasing the morphological damage to the spinal cord	Wang *et al.* (2005), Banji *et al.* (2013), Tobon-Velasco *et al.* (2013) and Aziz *et al.* (2014)
Hypoglycemic and hypolipidimic effects	Spirulina could lower the total lipid, cholesterol, triglycerides and glucose in blood and improve insulin resistance due to its antioxidant properties	Pandey *et al.* (2011), Joventino *et al.* (2012), Pankaj and Varma (2013), Muga and Chao (2014), Ma *et al.* (2015), Madhavadas and Subramanian (2015) and Vide *et al.* (2015)
Antitumor effect	Spirulina could improve functions of NK-cells, down regulate proliferating cell PCNA and P53 expression and increase production of tumor necrosis factor-(TNF-α) these effects could be attributed to antioxidant and immunomodulatory properties of Spirulina	Romay *et al.* (2003), Khan *et al.* (2005), Li *et al.* (2005), Grawish (2008), Akao *et al.* (2009), Ismail *et al.* (2009), Makhlouf and Makhlouf (2012), Kawanishi *et al.* (2013), Konickova *et al.* (2014)and Ouhtit *et al.* (2014)
Antigenotoxic effect	Spirulina prevent DNA damage, reduce the frequencies of micronucleus in bone marrow and activate cell nucleus enzymes	Pang *et al.* (1988), Qishen *et al.* (1989), Kaji *et al.* (2002), Prahalathan *et al.* (2006) and Hassan *et al.* (2012)
Immunomodulatory effect	Spirulina increased the phagocytic potential of macrophages, enhanced the activities of NK-cell and lysozyme and increased the production of antibodies, interferon gamma (IFN-γ) and cytosines (interleukins; IL-1,4 and 17)	Al-Batshan *et al.* (2001), Nielsen *et al.* (2010), Ragap *et al.* (2012), Soltani *et al.* (2012), Chu *et al.* (2013), Krishnaveni *et al.* (2013), Shokri *et al.* (2014), Jamil *et al.* (2015) and Sahan *et al.* (2015)
Anti-inflammatory effect	In addition to inhibition of colon inflammatory markers; MPO and PGE2 as well as proinflammatory cytosines; TNF-α and IL-1β, IL-6) with restoring the histological structure of colon by decreasing levels of lysosomal enzymes, tissue marker enzymes and glycoproteins	Rasool and Sabina (2008), Coskun *et al.* (2011), Baylan *et al.* (2012) Chu *et al.* (2013), Quader *et al.* (2013), Somchit *et al.* (2014), Abdel-Daim *et al.* (2015), Ali *et al.* (2015), Gutierrez-Rebolledo *et al.* (2015), Pugh *et al.* (2015) and Vide *et al.* (2015)
Growth, productive and reproductive enhancer of animal and poultry	Spirulina could improve the growth, productive and reproductive performance of animal and poultry through improving feed intake, feed conversion, nutrient absorption and utilization body weight gain, carcass yield, egg weight, egg mass, egg component, egg quality as well as the fertility and hatchability rates	Gerencser *et al.* (2012), Nah *et al.* (2012), Dalle Zotte *et al.* (2013), Simkus *et al.* (2013), El-Desoky *et al.* (2013), Yener *et al.* (2013), Arguelles-Velazquez *et al.* (2013), Nedeva *et al.* (2014), Shanmugapriya *et al.* (2015), Pandav and Puranik (2015) and Evans *et al.* (2015)

these chemical constituents of Spirulina indicates its antioxidant and antilipid peroxidation properties (Gad *et al*., 2011). The antioxidant activity of Spirulina could be also attributed to the presence of two main phycobiliproteins ingredients; Phycocyanin and allophycocyanin that are acting mainly against superoxide radicals (Estrada *et al*., 2001; Chaiklahan *et al*., 2010). Similarly, Kurd and Samavati (2015) reported that polysaccharides from *S. platensis* had strong scavenging activities *in vitro* on DPPH and hydroxyl radicals.

Chen and Wong (2008) showed that the *in vitro* antioxidant and anti-proliferative properties of selenium-containing phycocyanin (Se-PC) purified from selenium-enriched *Spirulina platensis*. The antioxidant efficacy of Se-PC was assayed by using four different free radical scavenging assays (2,2'-azinobis-3-ethylbenzothiazolin-6-sulfonic acid (ABTS), 1,1-diphenyl-2-picryhydrazyl (DPPH), superoxide anion scavenging and erythrocyte hemolysis). The results reported that Se-PC exhibited stronger antioxidant impact than phycocyanin by scavenging ABTS, DPPH, superoxide anion and 2,2'-azobis-(2-amidinopropane) dihydrochloride free radicals. The Se-PC also stated dose-dependent protective effects on erythrocytes against H_2O_2-induced oxidative DNA damage as evaluated by the comet assay.

Pretreatment with Spirulina normalized the level of different markers of oxidative damage in rats exposed to cadmium toxicity (Amin *et al*., 2006). The amount of 200 mg kg^{-1} Spirulina significantly increase the level of glutathione peroxidase in the cortex of mice compared to control (Hwang *et al*., 2011). Spirulina decreased the oxidative stress produced by tilmicosin in albino mice besides restoring the levels of some enzymes related to cardiac injury as lactate dehydrogenase, creatine kinase (Ibrahim and Abdel-Daim, 2015).

Hepatoprotective effect: The natural antioxidant components of Spirulina like vitamins (E and C), minerals, phenolic compounds and some fatty acids may act individually or together to give its hepato-protective potential (Garcia-Martinez *et al.,* 2007). Intraperitoneal administration of C-phycocyanin of *Spirulina platensis* succeeded in reduction of lipid peroxidation in the liver microsomes in CCl4-intoxicated rats (Bhat and Madyastha, 2000). Gorban *et al.* (2000) described the role of Spirulina in preventing the chronic hepatitis from being transformed in to hepatic cirrhosis. The hexane extract of Spirulina succeeded to remove arsenic from rat liver tissue by about 89.7% which is a better than other extracts like dichloromethane or alcohol extract (Saha *et al*., 2005). In a more recent study, aqueous extract of *Spirulina platensis* reduced the lipid peroxidation induced by cyclophosphamide in goat liver homogenates through free radical scavenging activity (Ray *et al*., 2007). Also, the treatment with Spirulina significantly reduced the lipid peroxidation and restored reduced glutathione so decreased oxidative stress and apoptosis in liver of animals fed in aflatoxins contaminated diet (Khan *et al*., 2005; Hassan *et al*., 2012).

The hepato-protective effect of *Spirulina platensis* has been also reported in rats intoxicated with deltamethrin where Spirulina could normalize the elevation of ALT, AST, APL, urea, creatinine and uric acid with reduction in both oxidative stress and lipid peroxidation in intoxicated rats (Abdel-Daim *et al.,* 2013). Similarly, *Spirulina fusiformis* provide a more hepato-protective effect in rats treated with Isoniazid (INH) and rifampicin (RIF) compared with hepatoprotective drug Silymarin by restoring liver marker enzymes, the antioxidant status and lipid peroxidation levels to control values (Martin *et al*., 2014).

Nephroprotective effect: Different forms of Spirulina algae found were reported to have a nephro-protective effects against wide varieties of chemicals where Spirulina extract ameliorates the toxic impact of sodium oxalate by counteracting the resulted hyperoxaluria in rats through normalizing the level of antioxidant and glutathione metabolizing enzymes providing a nephro-protective activity (Farooq *et al*., 2004). Spirulina showed a protective effect against nephrotoxicity induced by cyclosporine in rats, where pretreatment or co-treatment with Spirulina attenuated the rise in plasma urea and creatinine as well as kidney MDA and decreased the pathological changes in the kidney (Khan *et al*., 2006). In another study by Kuhad *et al.* (2006) *Spirulina fusiformis* was reported to have a protective role against gentamycin-induced nephrotoxicity in rats due to its free radical scavenging properties. In this context, *Spirulina platensis* showed a therapeutic potential against renal dysfunction induced by gentamycin sulphate in rats by decreasing lipid peroxidation (MDA) and increasing the levels of SOD, GSH, GPX and Nitric Oxide (NO), normalizing the creatinine and urea levels and improving the histological picture of the kidney (Karadeniz *et al*., 2008).

Sharma *et al.* (2007) also reported a protective efficacy of *Spirulina fusiformis* against nephrotoxicity induced by cadmium in Swiss albino mice. On the same context, *Spirulina maxima* could alleviate the oxidative stress in kidneys of mice after exposure to mercuric chloride-(HgCl2-) (Rodriguez-Sanchez *et al*., 2012). Moreover, phycocyanin and phycocyanobilin from Spirulina protect from diabetic nephropathy by their antioxidant activities as described by Zheng *et al.* (2012). Addition of *Spirulina platensis* in drinking water of male Sprague-Dawley rats had a significant protective effect against chromium induced nephrotoxicity by restoring the renal function biomarkers including urea and creatinine levels , the activity of catalase and MDA contents to normal levels with decreasing the chromium induced histological alterations as well (Elshazly *et al.,* 2015).

Neuroprotective effect: Spirulina has also a neuroprotective efficacy where it significantly reduced the volume of infarction of cerebral cortex and increased post stroke locomotor activity in rats. Additionally, administration of Spirulina for long periods could lower the ischemic brain damage (Wang *et al*., 2005) as well as showed a protective role in nervous system against oxidative stress produced by exposure to fluoride in the offspring of pregnant rats exposed to fluoride (Banji *et al.,* 2013). Tobon-Velasco *et al.* (2013) investigated the neuroprotective effect of *Spirulina maxima* against the 6-OHDA-caused toxicity in the rat striatum and they found that *Spirulina maxima* decreased the levels of ROS, nitric oxide and lipoperoxidation in the striatum with restored locomotor activity with preservation dopamine mitochondrial functions. Similarly, treatment of rats with *Spirulina platensis* had some beneficial effects in enhancing the locomotor functions of hind limb and decreases the morphological damage to the spinal cord (Aziz *et al.,* 2014).

Hypoglycemic and hypolipidimic effects: The use of Spirulina as a dietary supplementation has many different useful effects in preventing or managing hyperglycerolemia and hypercholesterolemia as reported by some authors (Iwata *et al*., 1990; Nagaoka *et al*., 2005; Deng and Chow, 2010). *Spirulina maxima* had a positive role in protecting mice from hyperlipidemia produced by Simvastatin by lowering the contents of total lipid and triacylglycerols in the liver total lipids besides reducing the serum triacylglycerols (Ble-Castillo *et al*., 2002). Spirulina also exhibit anti-lipidemic and anti-hyperglycaemic activities through lowering the level of blood glucose, regulating cholesterol and triglycerides and improving insulin resistance as described by Gupta *et al.* (2010) and Deng and Chow (2010). *Spirulina maxima* act as hypoglycemic agent in streptozotocin induced diabetic male wistar rats (Pandey *et al*., 2011). The *Spirulina platensis* protects the hematological parameters against alloxan induced diabetes mellitus in mice (Pankaj and Varma, 2013). The anti-diabetic effect of Spirulina could be returned to its powerful antioxidant properties (Chopra and Bishnoi, 2008).

Spirulina platensis showed both antidiabetic and anti-inflammatory effects on alloxan-induced diabetic rats by decreasing glucose, triglyceride and total cholesterol, TNF-alpha immunostaining, urea and creatinine without changing the liver transaminases (Joventino *et al*., 2012). Dietary supplementation of both Spirulina and fish oil to hamsters showed both hypocholesterolemic and antioxidant properties (Muga and Chao, 2014). The hypocholesterolemic and hypolglycemic effects of Spirulina give it the potential role in treatment of the cognitive dysfunction related to obesity and aging in rats where oral administration of both Spirulina combined with glycyrrhizin to rats reduced the serum glucose, cholesterol and leptin levels as well as the acetylcholinesterase (AChE) activity in the hippocampal tissue homogenates of the obese rats (Madhavadas and Subramanian, 2015). β-carotene extracted from *Spirulina platensis* exhibited hypoglycemic activity where it reduced the blood glucose level and regulated the increased food and water intake of streptozotocin-induced diabetic mice (Ma *et al.,* 2015). Feeding of Silicon-Enriched Spirulina (SES) to hamsters could inhibit the atherogenic effect of High-Fat (HF) diet by reducing the activity of nicotinamide adenine dinucleotide phosphate-oxidase and regulating the activities of superoxide dismutase and glutathione peroxidase in heart and liver so protect them from oxidative damage (Vide *et al.,* 2015).

Antitumor effect: The ability of Spirulina to destruct or inhibit carcinogenesis may be attributed to its antioxidant and immunomodulatory effects as well as presence of like polysaccharides an phycocyanin in high concentrations beside some other important components. In this regard Spirulina was reported to decrease the incidence and size of skin and stomach tumors, buccal squamous cell carcinoma and oral cancer (Dasgupta *et al*., 2001; Romay *et al*., 2003; Khan *et al*., 2005). Radachlorin, derived from *Spirulina platensis* resulted in a tumor regression effects (Privalov *et al*., 2002). Phycocyanin induces apoptosis of HeLa cells by increasing the Fas protein (Li *et al*., 2005). Hot-water extract of Spirulina helped in improving the anticancer effect of Natural Killer (NK) cells in rats (Akao *et al*., 2009). In another study by Ismail *et al.* (2009), Spirulina was found to exhibit a chemopreventive activity against cytotoxicity and carcinogenesis induced by dibutylnitrosamine (DBN) in rat liver by preventing the expression levels of Proliferating Cell Nuclear Antigen (PCNA) and P_{53}.

Polysaccharide has a cytotoxic effect on sarcoma 180 and ascetic hepatoma cells (Lisheng *et al*., 1991). The sulfated polysaccharide calcium Spirulina (ca-sp) inhibit colon carcinoma and fibrosarcoma. Polysaccharide extracted from Spirulina has chemo-protective against the carcinogenesis induced by exposure to irradiation (Zhang *et al*., 2001; Makhlouf and Makhlouf, 2012). Polysaccharides from Spirulina were recorded to increase macrophages' production of Tumor Necrosis Factor-(TNF-) (Parages *et al*., 2012). Polysaccharides from Spirulina also prevented the growth of glioma cells as described by Kawanishi *et al.* (2013). Spirulina inhibited the growth of oral cancer as in case of Syrian hamster cheek pouch mucosa painted with 7, 12-dimethylbenz[a]anthracene (Grawish, 2008).

The anti-cancer effect of *Spirulina platensis* were also tested by Ouhtit *et al.* (2014) where *Spirulina platensis* reduced 7, 12- dimethylbenz[a]anthracene (DMBA)-induced rat breast cancer from 87-13% and its effect was confirmed by morphological and histological examination and Spirulina also decreased the expression of both Ki-67 and estrogen α. Additionally Spirulina induced an apoptotic effect on the cancer cells in vitro by increasing the expression of p53, p21, p21 and Bax and decreasing Bcl-2 expression leading to inhibiting cell proliferation. The anticancer effect of *Spirulina platensis* and *Spirulina platensis*-derived tetrapyrroles [Phycocyanobilin (PCB) and chlorophyllin, a surrogate molecule for chlorophyll A] were also reported by Konickova *et al.* (2014), where they exhibited anti-proliferative effects *in vitro* on human pancreatic cancer cell lines and *in vivo* in xenotransplanted nude mice.

Antigenotoxic effect: Polysaccharide from Spirulina protect DNA exposed to radiation from being damaged specially the process of excision repair and synthesis of unscheduled as reported by Pang *et al.* (1988). Spirulina also has been demonstrated to reduce the frequencies of micronucleus in polychromatic erythrocytes of bone marrow of mice exposed to by gamma-radiation (Qishen *et al*., 1989). Similarly, polysaccharides of Spirulina activate cell nucleus enzymes and enhance the DNA repair process (Kaji *et al*., 2002). On the same context, Prahalathan *et al.* (2006) found that Spirulina protected mice from adverse effects of some toxicants like cyclophosphamide, cisplatin and urethrane by reducing both lipid peroxidation and chromosomal damage. Spirulina also significantly decreased the percentage of DNA fragmentation in liver and lowering the incidence of micronucleus in erythrocytes of animals fed diet contaminated with aflatoxin (Hassan *et al*., 2012).

Immunomodulatory effect: The role of Spirulina as an immunity promoter agent for broiler chickens has been reported by some authors for example, broiler chicks received Spirulina containing diet had a higher total anti-sheep red blood cells (anti-SRBC titers), IgG and PHA-P-mediated lymphoproliferative response, phagocytic potential of macrophages and NK-cell activity over the controls (Qureshi *et al*., 1996a). Dietary supplementation of *Spirulina platensis* upregulated the phagocytic functions of chicken macrophage and the metabolic pathway leading to increase the activity of nitric oxide synthase in a dose dependent manner (Al-Batshan *et al*., 2001). Jamil *et al.* (2015) reported that Spirulina can act as a good growth and immunomodulatory agent for broiler chicks. Spirulina was also reported to enhance functions of cells of the chicken immune system after *in vitro* exposure where chicken macrophages exposed to Spirulina showed phenotypic changes with very low cytotoxic effect. Spirulina treated macrophages found to have higher percentage of phagocytic activities for unopsonized Sheep Red Blood Cells (SRBC) and average number of internalized SRBC compared to controls (Qureshi *et al*., 1996b). Water-soluble extract of *Spirulina platensis* increased the phagocytic activity of macrophages isolated from cats when incubated with Sheep Red Blood Cells (SRBC) and viable *Escherichia coli* (Qureshi and Ali, 1996). A polyherbal preparation (Immon) containing Spirulina showed immunomodulatory and protective effects against infectious anemia virus infection in broilers (Krishan *et al*., 2015).

Spirulina also found to possess an immunomodulatory activity in different fish species where dietary Spirulina enhance the functions of immune system of tilapia (*Oreochromis niloticus*) by enhancing responses of bactericidal against *Aeromonas hydrophila*, phagocytic activity and lysozyme activity (Ragap *et al*., 2012). In a similar study by Sahan *et al.* (2015) addition of Spirulina to diets of Nile Tilapia (*O. niloticus*) at different levels of (0, 5.0, 7.5 and 10.0 g kg^{-1}) for 75 days was found to support the hematological and immune system of fish where 5.0 g kg^{-1} Spirulina in diet resulted in a highly significant increase in parameters of nonspecific immune system (the phagocytic activity of neutrophils and monocytes), while 7.5 g kg^{-1} of Spirulina in diet increased the amounts of RBC and WBC. The immunomodulatory effect of Spirulina has been studied in other types of fish where addition of *Spirulina maximus* in diets of common carp improved hematological parameters including RBC, WBC, Hb, PCV, MCV, MCH and MCHC beside parameters immunological performance including lymphocyte, lysosome activity, monocytes, Alternate Complement Pathway (ACP), IgM, phagocytic Index and Phagocytic Activity (PA) (Krishnaveni *et al*., 2013).

Experimentally, Spirulina could promote the different kinds of immune response of mice as follows; Dietary intake of *Spirulina platensis* enhanced the primary immune response of mice through increasing numbers of splenic antibody-producing cells against SRBC, stimulating the phagocytic activity of macrophages and enhancing the production of interleukin-1 (IL-1). Moreover, Addition of Spirulina Hot Water extract (SHW) to the *in vitro* spleen cell culture increased the proliferation of spleen cells and in enhanced the antibody production (Hayashi *et al*., 1994). Similarly, Spirulina supplementation (50 and 150 mg kg^{-1} body weight) to mice diet could enhance primary immune response in terms of antibody production, but not secondary immune response (splenocyte proliferation and cytokine like IFN-γ and IL-4) to Tetanus Toxoid (TT) vaccine (Chu *et al*., 2013). *Spirulina platensis* extract was found to have immunostimulant effect in Balb/C mice infected with candidiasis (Soltani *et al*., 2012). These findings were confirmed by a more recent study conducted by Shokri *et al.* (2014) water extract of *Spirulina platensis* (800 mg kg^{-1}, 0.2 mL, orally) for 3 days exhibited a remarkable immunomodulatory effect in Balb/C female mice suffered from systemic candidiasis and breast cancer (Spontaneous Mouse Mammary Tumor (SMMT)). The results showed that *Spirulina platensis* decreased the secretion of IL-4 and IL-10 in tumor-bearing mice infected with *Candida albicans*, whereas the levels of IL-17, TNF-α and IFN-γ increased.

Anti-inflammatory effect: Spirulina was found to have a promising anti-inflammatory activity that could be attributed in a large part to its anti-oxidative properties and phycocyanin content (Coskun *et al*., 2011; Baylan *et al*., 2012). Remirez *et al.* (2002) reported that Spirulina showed an anti-inflammatory effect against zymosan-induced arthritis in mice by reducing the levels of β-glucurnidase in the synovial fluid. Similarly, Rasool and Sabina (2008) found that *Spirulina fusiformis* have a protect mice from rheumatoid arthritis due to its anti-peroxidative potential. Ethanolic extract of *Spirulina platensis* possesses significant anti-inflammatory activity in both carrageenan induced rat Paw Edema (acute model) and cotton pellet induced Granuloma (chronic model) tests (Quader *et al*., 2013). Chu e*t al.* (2013) pointed out that Spirulina increase the antibody production after TT vaccination in mouse model indicating its immunomodulatory effect. *Spirulina platensis* showed anti-pyretic activity in rats exposed to 2 g kg^{-1} Brewer's Yeast (BY) and anti-inflammatory and anti-inflammatory activities in rats exposed to prostaglandin E2 by reducing the volume of paw edema (Somchit *et al*., 2014).

Spirulina could modulate the undesirable effects of acetic acid-induced ulcerative colitis in rats demonstrated by increasing the activity of antioxidant enzymes CAT and SOD as well as GSH content with significant reduction in lipid peroxidation markers MDA and protein carbonyl (PCO) in addition to inhibition of colon inflammatory markers; myeloperoxidase (MPO) and prostaglandin (PGE2) as well as proinflammatory cytokines; Tumor necrosis factor (TNF-α) and interleukins (IL-1β, IL-6) with restoring the histological structure of colon (Abdel-Daim *et al*., 2015). Rasool *et al.* (2006) reported the anti-inflammatory effect of *Spirulina fusiformis* on adjuvant-induced arthritis in mice by decreasing levels of lysosomal enzymes, tissue marker enzymes and glycoproteins. Similarly, *Spirulina maxima* exhibit anti-inflammatory effects in Freund's complete adjuvant-induced chronic inflammation in rats by regulating the mobility, body temperature, differential leukocytic count and protect against oxidative stress in the joints of exposed rats (Gutierrez-Rebolledo *et al*., 2015). Additionally, *Spirulina platensis* could inhibit the possible alterations in the histological structure of joints and decrease the serum levels of TNF-α, IL-6 and COX-2 while increase GSH content in serum of rats exposed to Freund's complete adjuvant-induced arthritis (Ali *et al*., 2015). Silicon-Enriched Spirulina (SES) has anti-inflammatory effect on hamsters manifested by decreasing the levels and activities of tumor necrosis factor-α and interleukin-6, nuclear factor-κB and polymorphonuclear cells and normalized the monocyte chemoattractant protein-1 level in plasma which was elevated by the High-Fat (HF) diet (Vide *et al*., 2015). Feeding of mice on Immulina® before and after infection with influenza A (H_1N_1) virus showed a significant decrease in the signs of the disease without any loss in appetite or body weight (Pugh *et al*., 2015).

Effects of Spirulina on productive and reproductive performances of poultry and animals

Poultry: Spirulina could potentially be used in poultry and animal nutrition to improve the productivity and quality of obtained meat as described by Peiretti and Meineri (2008) where dietary inclusion of Spirulina (5, 10 and 15%) to diets of growing rabbit for 24 days did not significantly affect the final weight, weight gain and feed efficiency with no mortalities during the experiment. 10% inclusion level of Spirulina resulted in the highest feed intake while decreasing the digestibility of Organic Matter (OM), Dry Matter (DM), Crude Protein (CP), Gross Energy (GE), Acid Detergent Fiber (ADF) and Neutral Detergent Fiber (NDF) than control diet. dietary inclusions of four different levels of Spirulina (0, 50, 100, or 150 g kg^{-1}) as replacer of soybean and alfalfa did not alter the carcass yield or the proportions of the different carcass parts and organs of growing rabbits (Peiretti and Meineri, 2011). Lipid content was the only affected parameter after chemical analysis of meat and it was higher in Spirulina fed group than control. In addition to a linear increase of the fatty acid γ-linolenic acid (GLA) content in the perirenal fat and meat (longissimus dorsi muscle). The FA pro les and the thrombogenic and atherogenic indexes of the rabbit tissues were higher in the meat of the rabbits fed the control diet than those found in the Spirulina fed groups. Diet supplemented with Spirulina in combination with thyme improved the redness and yellowness of meat of growing rabbits specially longissimus dorsi and provide protection oxidative stress with increasing γ-linolenic acid content of their meats (Dal Bosco *et al*., 2014; Dalle Zotte *et al*., 2014).

In the study of Dalle Zotte *et al.* (2013) the dietary inclusion of 3% Spirulina to growing dwarf rabbits for 14 weeks did not alter the growth performance and energy or nutrients digestibility. However, the GLA level was10-fold higher in the S-enriched diets. Contrarily, Gerencser *et al.* (2012) recorded that Spirulina supplementation to the diet of growing rabbits produced no change in their body weight, weight gain, feed consumption, mortality and morbidity. The only significant difference was found for feed conversion ratio which decreased than control.

Ross and Dominy (1990) found that Spirulina (10 and 20%) did not affect the feed efficiency however depressed the growth of day-old White Leghorn cockerel chicks at 3 week-old. While feeding (1.5, 3.0, 6.0, or 12.0%) of Spirulina to 1- day -old, Hubbard by Hubbard, male broiler chicks for 41 days did not affect the growth rate. The author also recorded that supplementation of Spirulina at different levels (0, 1.5, 3.0, 6.0 and 12.0%) to diet Japanese quail, linearly increases the intensity of yolk color and enhances the fertility.

Venkataraman *et al.* (1994) substitution of fish meal or groundnut cake by Spirulina at iso-nitrogenous concentrations of 140 and 170 g kg^{-1} in poultry diets for 12 weeks did not affected the performance of broilers (feed efficiency, protein efficiency and dressing percentage), weights, compositions or histological structure of different body organs, on the other hand Spirulina containing diet gave more intense color of meat. In another study conducted by Toyomizu *et al.* (2001) dietary Spirulina at 0, 40, or 80 g kg^{-1} for 16 days were found to produce no significant differences in weights of liver, abdominal fat, kidney or pectoralis profundus on of growing broiler chickens as well as live body weight among treatments. On the other hand, Spirulina at 40 g kg^{-1} gave the maximum redness and yellowness of pectoralis superficialis, profundus and sartorius muscles on spectrocolourimetric analyses. Similarly, using of Spirulina as a source of protein for broiler diet improves the redness of as well as yellowness of broiler flesh (Baylan *et al*., 2012).

Kharde *et al.* (2012) feeding of broiler chicks on diet supplemented with Spirulina (300 or 500 mg kg^{-1}) for six weeks significantly increased the mean live body weight, mean weekly weight gain and feed efficiency with decreased feed consumption compared to control. Supplementation of Spirulina (0, 0.10, 0.15 or 0.20%) to diets of Sinai and Gimmizah hens from 28-52 weeks of age, irrespective of hen strain, showed increase in egg production, daily egg mass, egg weight egg yolk percentage, yolk color score, feed conversion ratio, fertility and hatchability, while linearly decrease in yolk and plasma cholesterol (Mariey *et al*., 2012). However, there were no significant differences on percentages of egg shell, egg albumen, Haugh unit, egg weight loss percentages, chick's weight at hatch, odor intensity, flavor or taste of normal egg (fresh or stored).

The dietary inclusion of the 1% of Spirulina to 1- day -old broiler chicks diets significantly improve the body weights, feed conversion ratio, carcass yield percentage and blood parameters than the control group (Shanmugapriya and Babu, 2014). Similarly, Spirulina significantly increase the feed conversion ratio and villi length, villi height, body weight gain while decreasing feed conversion ratio when included in the diet of 1 day -old broiler chicks (Ross 308) by 1% (Shanmugapriya *et al.,* 2015). On the same context, Pandav and Puranik (2015) recorded an increase in body weight and a decrease in feed consumption of broilers fed on diet supplemented with Spirulina enriched with iron and zinc without altering growth performance of broilers.

Evans *et al.* (2015) studied the digestible nutrient values of Spirulina alga at different levels (6, 11, 16 and 21%) on performance and digestibility of amino acid of Hubbard X Cobb 500 broiler. Diets containing up to 16% Spirulina has no statistically significant effects on final body weight, feed intake and weight gain however resulted in the highest level of digestible lysine and cysteine. All studied levels of Spirulina resulted in higher digestible methionine values than control diet.

Animals: Supplementation Holstein calves diets by (0, 2, 6 and 25 g day^{-1} Spirulina) for 57 days did not affect the final weight, daily gain, daily feed intake, feed efficiency, digestion coefficients, BUN, albumin or globulin. While, 25 g of Spirulina decreased digestibility of DM, OM, CP and NDF on the other hand it produced a significant reduction in plasma cholesterol, LDL and HDL concentration (Heidarpour *et al*., 2011).

Addition of the biomass of *Spirulina maxima* enriched with copper (Sm-Cu) to the piglets diet for 87 days resulted in decreasing the percentage of LDL-cholesterol and total cholesterol without affecting the daily weight gain, feed conversion ratio or the amount of N excreted in faeces and urine (Saeid *et al*., 2013). Similarly, Simkus *et al.* (2013) found that feeding Spirulina biomass to pigs resulted in a higher average daily weight gain and greater carcass yield and lowered the intramuscular fat than control. Nedeva *et al.* (2014) also reported that addition of Spirulina to growing Danube White pigs for 47 days significantly increased the growth intensity and reduces the compound feed conversion and nutrients.

Spirulina supplementation (1 g/10 kg b.wt./day) to diets of fattening lambs for 35 days found to improve daily weight gain, final live body weight, feed intake and feed conversion rate compared to the control. In addition to increasing hemoglobin, total leukocytic count, serum globulin, vitamin A and GSH, while decreasing the Aspartate amino transferase (AST), Alanine amino transferase (ALT), cholesterol, glucose and serum malondialdehyde (MDA) concentrations compared with the control (El-Sabagh *et al*., 2014).

Dietary supplementation of Spirulina at low levels to the diet of Australian crossbred sheep increase lamb production, with higher long-chain polyunsaturated fatty acids by up-regulation of the mRNA expression of fatty acid synthase (FASN) and Adrenergic beta-3 receptor (ADRB3) genes. While, high level of Spirulina decrease the intramuscular fat by decreasing the fat deposition in subcutaneous adipose tissue through up-regulating the mRNA expression of B-cell translocation gene 2 (BTG2) (Kashani *et al.,* 2015).

Effect of Spirulina on reproduction of experimental animals: Nah *et al.* (2012) demonstrated the effective role of *Spirulina maxima* Extracts (SME) in improving the fertility of diabetic male rats where *Spirulina maxima* intake for 4 weeks significantly increased the testicular and body weights, normal seminiferous tubules and Leydig cell number and enhanced metabolic parameters, testosterone levels and steroidogenic enzymes mRNA in the streptozotocin (STZ) treated rats. Spirulina also exhibits a protective effect against $HgCl_2$-induced testicular injury and alterations of semen quality and sperm characteristics (El-Desoky *et al*., 2013).

Spirulina has been reported also to protect female rats from toxic impact of many chemicals and toxicants where exposure to Spirulina at 300 mg kg^{-1} normalized the lead-induced increase in mast cells in rat ovaries, during estrous cycle (Karaca and Simsek, 2007). Spirulina keeps the normal histological structure and antioxidant defense system in the rat ovaries from oxidative damage caused by cyclophosphamide (Yener *et al*., 2013).

In addition to the protective role of Spirulina on female reproductive system it was also reported to have a protective effect against teratogenicity caused by cadmium in mice as demonstrated by Paniagua-Castro *et al.* (2011). Similarly, Arguelles-Velazquez *et al.* (2013) described the protective effect of *Spirulina maxima* on the teratogenicity, genotoxicity and DNA oxidation processes induced by cadmium in pregnant female ICR mice. Where, *Spirulina maxima* significantly reduced fetal abnormalities, the quantity of micronucleated normochromatic erythrocytes (MNNE) and micronucleated polychromatic erythrocytes (MNPE) and DNA oxidation level. Spirulina could improve the reproductive performance of alloxan (AXN) induced hyperglycemic mice through increasing the fertility rate, regulating the estrous cycle, keeping the normal length of gestation period, enhancing fetal development, litter counts and litter survival and decreasing the teratogenic effects of diabetic mice (Pankaj, 2015).

Beneficial effects of spirulina in human health: Spirulina showed proinflammatory and immunomodulatory activities on human where Spirulina increased the production of IgA in human saliva that enhances the mucosal immunity (Kyoko *et al*., 1999) whereas feeding of Spirulina to male volunteers increased the production of IFN-γ and damage of NK cells (Hirahashi *et al*., 2002) and reduced Interleukin-4 (IL-4) levels (Mao *et al.,* 2005) which are important in regulating immunoglobulin (Ig) E-mediated allergy. The immunomodulation effects of Spirulina have been also reported by Pertovaara *et al.* (2006) and Selmi *et al.* (2011). The proinflammatory properties of Spirulina could be related to the inhibitory effects of Spirulina on histamine release from mast cells as reported earlier by Yang *et al.* (1997) and Kim *et al.* (1998) and due to presence of C-phycocyanin which could inhibit the cyclooxygenase-2 due to its antioxidant activities (Reddy *et al*., 2003). Immulina has a pro-inflammatory effect in healthy men through the immediate elevation of *Candida albicans* (CA)-induced CD4+ T-Helper (Th) cell with proliferation of B cell and elicited production of tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamm and Interleukin (IL)-2 and 6 (Lobner *et al.,* 2008). Immulina® commercial product of *Spirulina platensis* act also as an immunomodulatory agent by enhancing the activity of NK cells by increasing the mRNA expression of NK cell marker NKG2D and T-cell marker perforin in human consumed 400 mg Immulina® per day for seven days (Nielsen *et al*., 2010).

The immunomodulatory effects of Spirulina could be attributed to its highly nutritive value that could cover the deficiency in the nutrients of high importance in enhancing the immunity by managing the activities of cytosines and NK-cell, secretory IgA, antibody response and T-cells production (Karkos *et al*., 2011). The immunomodulatory properties of Spirulina could also returned to its antiviral activity against a large number of viruses as reported by Hayashi *et al.* (1996) and Ayehunie *et al.* (1998) that Spirulina could inhibit the *in vitro* replication of human cytomegalovirus, human immunodeficiency virus-1 virus (HIV-1), influenza A virus, Herpes simplex type I mumps virus and measles.

The free radical scavenging and immunomodulation properties of Spirulina could also play an important role in giving Spirulina its anticancer potential as oral cancers as reported by Schwartz and Shklar (1987), Schwartz *et al.* (1988), Shklar and Schwartz (1988) and Mathew *et al.* (1995). The antioxidant properties of Spirulina could also make it exhibit many valuable effects on human health as cholesterol lowering effects where Spirulina has been reported to have a hypolipidemic effect in human as described by Nakaya *et al.* (1988) who observed that Spirulina reduced the High-Density Lipoprotein (HDL) cholesterol significantly when given in the diet of male volunteers for 8 weeks. Spirulina also significantly reduced the blood cholesterol, LDL cholesterol and triglycerides with increasing the level of HDL cholesterol in individuals suffering from ischemic heart disease (Ramamoorthy and Premakumari, 1996). Additionally, Spirulina decreased the LDL: HDL ratio in diabetic individuals (Mani *et al.,* 2000).

CONCLUSION

In conclusion, this literature review highlights the ability of Spirulina to protect the body physiological system against oxidative damage and as nutraceutical and source of potential pharmaceuticals. Spirulina has the capability to prevent cell damage through containing both enzymatic (SOD, CAT, GPX, PrxR and AXP) and non-enzymatic antioxidant defense system (carotenoids, TOH, AA, GSH and chlorophyll derivatives) that counteract the effects of ROS and inhibit lipid peroxidation. The antioxidant activity of Spirulina could be also attributed to the presence of two main phycobiliproteins ingredients: phycocyanin and allophycocyanin that are acting mainly against superoxide radicals. Spirulina is reported to have a hepatoprotective, neuroprotective, nephroprotective and anti-diabetic potential through normalizing the level of antioxidant and glutathione metabolizing enzymes, managing hypercholesterolemia and hyperglycerolemia by lowering the contents of total lipid and triacylglycerol, lowering blood glucose level and improving insulin resistance. Presence of phycocyanin and polysaccharides in high concentration gave the ability of Spirulina to inhibit carcinogenesis and protect DNA from damage and to exhibit a promising anti-inflammatory activity. Spirulina also found to possess an immunomodulatory effects by enhancing the functions of cells of the immune system, phagocytic and lysozyme activities and improving the hematological parameters. Spirulina could potentially be used in poultry and animal nutrition to improve the productive and reproductive performance, it is reported to improve productivity and quality of obtained meat, body weight, feed efficiency with decreased feed consumption, increase egg production and quality, feed conversion ratio, fertility, hatchability, carcass yield percentages and blood parameters. Also, further studies should be done to evaluate the safety of Spirulina and its extracts in order to make new approach for considering their use in medicinal purposes and related application.

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