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Impact of dietary *Arthrospira* (Spirulina) biomass consumption on human health: main health targets and systematic review

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Abstract

Arthrospira (known commercially as Spirulina) is an edible cyanobacterium traditionally used for centuries as human food by various cultures. Its biochemical profile includes many bioactive molecules with enormous potential in human health. The aim of this paper is to systematically review the scientific evidence about the effects of dietary *Arthrospira* biomass consumption on a range of health outcomes. A search was made in PubMed and the Cochrane Library for randomised controlled clinical trials in which *Arthrospira* was used as a dietary supplement. An additional search was conducted for studies on rodents. Studies were organised by health outcomes. A total of 25 randomised clinical trials were included in the study. Four analysed the role of *Arthrospira* in dyslipidaemia, four in diabetes, one in hypertension, two in exercise, two in immune response, four in inflammation and precancerous lesions, and two in allergic rhinitis. Three studies analysed the antiviral effect of *Arthrospira* and a further three assessed its effect on nutritional status. For most of the targeted health outcomes in the selected clinical trials, daily consumption of *Arthrospira* biomass provided considerable benefits. However, more extensive studies that meet higher quality criteria are needed to confirm the reported results before any validated and absolute health claims can be made for this microorganism.

Keywords *Arthrospira* · Spirulina · Clinical trial · Systematic review · Supplementation · Human health

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Introduction

Arthrospira is an edible cyanobacterium traditionally consumed by some human civilisations (Ciferri 1983; Abdulqader et al. 2000). Spirulina is the commercial name of *Arthrospira platensis* and *Arthrospira maxima* (Tomaselli 1997), which were previously known as *Spirulina platensis* and *Spirulina maxima*, and which are commonly used as food, dietary supplements and feed supplements (Belay 2008). The rediscovery of *Arthrospira* and its biochemical properties in the 1960s led to mass production of microalgae for commercial purposes in the late 1970s and the development of an algae-based industry (Durand-Chastel 1980; Shimamatsu 2004; de la Jara et al. 2016).

Arthrospira is a source of amino acids, fatty acids, minerals and pigments. Its protein content is known to reach 60–70% of dry weight, with a profile that includes the full range of essential amino acids (Dillon et al. 1995). In addition, given the absence of a cellulosic cell wall, its protein digestibility can be as much as 83–90% compared to 95.1% for the standard casein (Falquet 1997).

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Arthrospira has other important biochemical characteristics: for instance, its lipid profile contains palmitic, linoleic and γ-linolenic acid (GLA), which together account for 88–92% of the total fatty acid content (Mühling et al. 2005). The presence of GLA is important from the nutritional point of view because of its rarity in our daily food and possible prophylactic role in treating various chronic disease states (Fan and Chapkin 1998) such as atopic eczema, cyclic mastalgia, premenstrual syndrome, diabetes, cardiovascular disease, inflammation and cancer (Horrobin 1992). The pigments contained in *Arthrospira* are chlorophyll *a*, β-carotene, zeaxanthin, cryptoxanthin, C-phycocyanin and allophycocyanin (Yan et al. 2011; Kumar et al. 2015) (Table 3), all of which are used by the organism to collect light for photosynthesis and protect it from photo-oxidative damage. Chlorophyll and its derivatives are well known; their bioactivity includes cancer prevention due to antioxidant and antimutagenic activity, mutagen trapping, modulation of xenobiotic metabolism and induction of apoptosis (Ferruzzi and Blakeslee 2007). Phycocyanin, its main pigment, is known to have potent antioxidant, anti-inflammatory, hepatoprotective and anticarcinogenic properties (Sekar and Chandramohan 2008; Soni et al. 2015). Other molecules such as sulphated polysaccharides are present in *Arthrospira* biomass. A compound known as calcium spirulan (Hayashi et al. 1996) has also been studied for its antiviral properties (Hayashi et al. 1993; Ayehunie et al. 1998).

The bioactivity of all these compounds has been shown independently in many in vitro and in vivo studies. As this information reaches the market, *Arthrospira* and other microalgal supplements are chosen by consumers for nutritional, immune-boosting and detoxifying purposes (Rzymski and Jaśkiewicz 2017; Wells et al. 2017). However, the question of the therapeutic or preventive roles of *Arthrospira* in most diseases remains controversial. Clinical trials are isolated and sometimes lack scientific rigour, e.g., in the use of inappropriate model systems or non-rigorous experimental design (Wells et al. 2017). Quality scales give readers a quantitative index of the likelihood that the reported methodology and results are free of bias (Moher et al. 1995) and therefore the lack of such quality restricts the use of claims regarding health, nutrient content and structure or function that are needed to fully develop an algae-based food industry (Grobbelaar 2003).

The main aim of this paper is to systematically review the current scientific evidence guaranteed by quality criteria about the effect of dietary *Arthrospira* whole biomass on a range of health outcomes in human trials. In order to identify targets for future validation in clinical trials, we also assessed studies on rodents. The final result will provide an overview of the current and potential roles of dietary *Arthrospira* consumption in human health.

Material and methods

Search strategy

One of the objectives of this study is to identify fields of human health in which the effect of dietary *Arthrospira* consumption has been addressed. A literature search was conducted to retrieve suitable clinical trials. It was considered important to include preclinical research on rodents, given that these results form the basic science knowledge that will be transferred to clinical applications.

The literature search for human studies was conducted in PubMed and Cochrane, and for studies on rodents (rats and mice) PubMed was used. Both searches were performed in June 2017. The medical subject headings (MeSH) of the National Library of Medicine were used to devise the key word search terms. The words, terms and combinations used were "Spirulina" plus "clinical trial", "Spirulina" plus "rats" and "Spirulina" plus "mice". In PubMed the term Spirulina includes the entry terms *Arthrospira*, *Arthrospira maxima* and *Spirulina maxima*.

Data collection

For human studies, we collected items with no time restriction that met all the inclusion criteria: (a) human studies, (b) studies written in English and (c) studies using *Arthrospira* as a dietary supplement. We excluded reviews, congress abstracts, and clinical trials that had fewer than 10 participants, used pharmaceutical or botanical preparations with *Arthrospira* as an ingredient, or were based on *Arthrospira* extracts.

For rodent studies, selected items had to meet the following inclusion criteria: (a) mice or rat studies, (b) studies written in English, (c) studies using *Arthrospira* as a dietary supplement and (d) studies published in the last 10 years.

Quality assessment

Three independent reviewers assessed the methodological quality of the studies identified. The full texts of articles for studies that met or appeared to meet the inclusion criteria were retrieved. The reference section in these papers was reviewed to identify relevant publications not captured electronically.

The Jadad scale was used to evaluate the quality of the studies, allocating a score from zero (very poor) to five (rigorous), based on randomisation, blinding and description of withdrawals (Halpern and Douglas 2005). Only studies meeting randomisation, blinding and control inclusion should be included in a systematic review. However, considering the lack of scientific rigour found in most of the studies, blinding was considered optional for inclusion. Results are summarised in Table 1.

Table 1 Clinical trials used in the present study. Quality criteria were *R* randomisation, *B* blinding, *C* control; presence or absence were labelled + and −

Activity / Field			Author, year, country	No	Quality criteria		
					R	B	C
Oxidative stress -related diseases	Metabolic dysfunctions	Dyslipidaemia	Zeinalian et al, 2017, Iran	1	+	+	+
			Chitsaz et al, 2016, Iran	2	+	-	+
			Mazopakis et al, 2014, Greece	3	-	-	-
			Ngo-Matip et al. 2014, Cameroon	4	+	-	+
			Torres-Durán et al, 2012, Mexico	5	-	-	-
			Torres-Durán, 2007, Mexico	6	-	-	-
			Samuels et al, 2002, India	7	+	-	+
			Ramamoorthy & Premakumari, 1996, India	8	-	-	+
		Diabetes	Serban et al, 2015, Romania	9	+	+	+
			Marcel et al, 2011, Cameroon/Switzerland	10	+	+	+
			Anitha & Chandralekha, 2010, India	11	-	-	+
			Kaur et al, 2008, India	12	-	-	+
			Lee et al, 2008, South Korea	13	+	-	+
			Parikh et al, 2001, India	14	+	-	+
			Mani et al, 2000, India	15	-	-	+
		Hypertension	Miczke et al, 2016, Poland	16	+	+	+
			Juárez-Oropeza et al, 2009, Mexico	17	-	-	-
	Exercise		Johnson et al, 2016, USA	18	+	+	+
			Lu et al, 2006, Taiwan	19	+	+	+
	Immune response		Park and Lee, 2016, Korea	20	+	+	+
			Selmi et al 2011, USA	21	-	-	-
			Park et al, 2008, Korea	22	+	+	+
	Inflammation and precancerous lesions		Patil et al, 2015, Saudi Arabia	23	+	-	+
			Zwiri et al, 2015, Saudi Arabia	24	+	-	+
			Shetty et al, 2013, India	25	-	-	+
			Mulk et al, 2013, India	26	+	-	+
			Labhe et al, 2001, India	27	-	-	+
			Mathew et al, 1995, India	28	+	-	+
	Allergy		Cingi et al, 2008, Turkey	29	+	+	+
			Mao et al, 2005, USA	30	+	+	+
Antiviral			Ngo-Matip et al, 2015, Cameroon	31	+	-	+
			Winter et al, 2014, Germany	32	+	+	+
			Teas & Irhimeh, 2012, USA	33	+	-	-
			Băicuş C & Tănăsescu C, 2002, Romania	34	+	+	+
Nutrition			Matondo et al, 2016, Congo	35	-	-	+
			Masuda et al, 2014, Zambia	36	-	-	+
			Ouedraogo et al, 2013, Burkina Faso	37	-	-	+
			Ramesh et al, 2013, India	38	-	-	-
			Yu et al, 2012, China	39	-	-	-
			Li et al, 2012, China	40	+	-	+
			Simpore et al, 2006, Burkina Faso	41	+	-	+
			Simpore et al, 2005, Burkina Faso	42	+	-	+

Results and discussion

Many in vitro and in vivo studies have evaluated the efficacy of various *Arthrospira* compounds in health (Deng and Chow 2010; Karkos et al. 2011). However, as far as we know, except for the meta-analysis by Serban et al. (2016) targeting the impact of *Arthrospira* supplementation on plasma lipid concentrations, there has been no systematic evaluation of the effect of *Arthrospira* biomass on health using clinical trials guaranteed by quality criteria such as double-blind, placebo controlled, randomised trials. To our knowledge, this study is the first systematic review to examine clinical trials on the effect of dietary supplementation with *Arthrospira* on human health that meet a quality scale criteria, specifically the Jadad scale criteria (Halpern and Douglas 2005).

Health outcomes targeted in animal and human studies

A total of 154 studies were retrieved from the databases: 129 rodent studies (79 on rats and 50 on mice) and 42 human clinical trials. Flowcharts of the selection process for animal and human studies are shown in Figs. 1 and 2, respectively. Retrieved studies were classified by main outcome to target the major fields of action of *Arthrospira* in health (Figs. 3 and 4). We found that even though each study keeps to one main health target, outcomes could be found linked together. Lipid profile, for instance, was frequently included in trials targeting diabetes or immune response. Lipid parameters such as total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol HDL-C were the most prevalent outcomes (Table 2). Xenobiotic metabolism and oxidative stress was the most recurring field in animal studies, followed by inflammation, metabolic diseases, cancer, neuroprotection and immune response. Human studies focused on dyslipidaemia, hypertension and diabetes, which were grouped for this study as metabolic dysfunctions, exercise performance, immune response and ageing, inflammation and cancer, and allergy. The two groups (humans and animals) had common health targets, such as immune response, metabolism, virus control, allergy immune response, ageing, inflammation, cancer and nutrition.

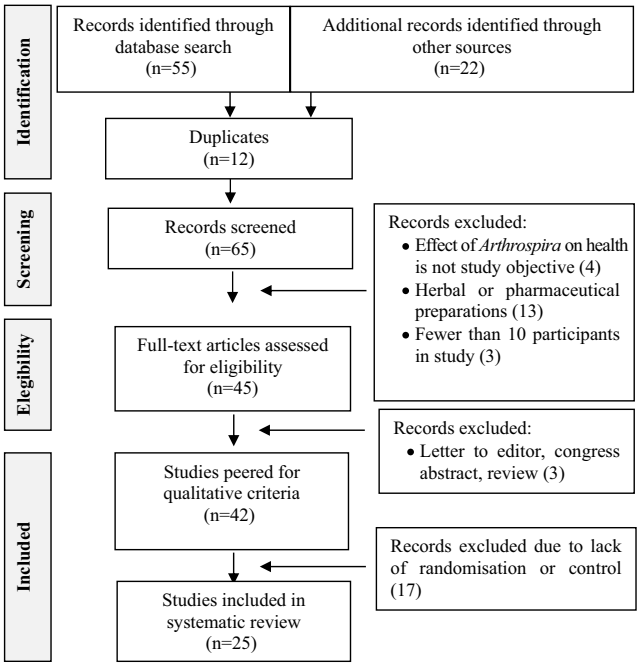

Fig. 2 Review process in human literature flowchart

Unexpectedly, the use of *Arthrospira* for nutritional purposes was poorly represented in both groups, even though this microorganism is considered an important protein source (Falquet 1997). The results show that most studies about the benefits of consuming *Arthrospira* have targeted its antioxidant bioactivity rather than its nutritional potential.

Effect of *Arthrospira* in animal models

Animal studies outnumbered human studies (129 on animals, 42 on humans). The earliest study on rodents in the MedLine database is from 1988. Oxidative stress and xenobiotic metabolism was the field that returned the highest number of studies (56). These studies addressed the protective effect of *Arthrospira* biomass on organs, mainly the liver and kidney, based on its antioxidant protection against various substances including heavy metals (lead and cadmium) and tumorigenic compounds (nitroquinoline, organochlorides), and medication such as antibiotics (gentamicin), immunosuppressants (cyclosporine) and chemotherapy medication (cisplatin). Inflammation and metabolism,

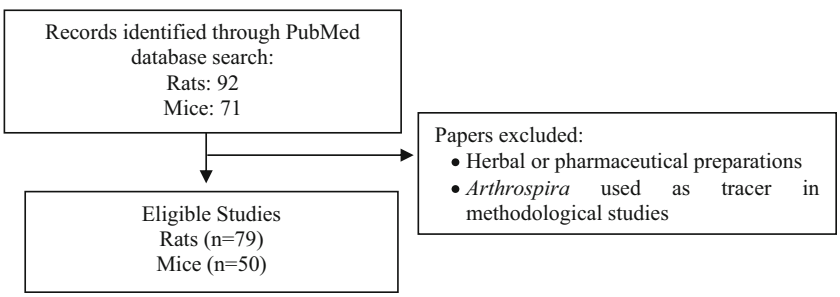

Fig. 1 Review process in rodent literature flowchart

including diabetes and hyperlipidaemia, with 21 and 19 studies respectively, are next in the ranking of studies on consumption of *Arthrospira* for disease prevention, followed by studies based on the protective action of *Arthrospira* against mutagenicity and teratogenicity (16), neuroprotection (7) and immune response (3). A common factor in these studies is the use of *Arthrospira* as a vector of antioxidant compounds. A small group was identified with the targeted fields of nutrition (3 studies), antimicrobial activity (1) and allergy (1) (Fig. 3). These findings support the hypothesis that the main benefit of consuming *Arthrospira* could be associated with the high antioxidant capacity of this organism rather than its use as a source of protein.

Animal models offer a wider range of possibilities for examining toxicity of interventions or studying disease pathology and mechanisms, whereas most clinical trials focus only on clinical efficacy (Hooijmans and Ritskes-Hoitinga 2013). This was confirmed in the present work, given that a high number of animal studies not only addressed the effect of *Arthrospira* on the organism, but also attempted to find the mechanism underlying the improvement in the disease. Because of the high number of works found on rodents only, it was decided simply to group them to assess the most common fields of study. However, it would be worthwhile carrying out an in-depth review of this information and making a critical appraisal of animal studies. A study of this kind could include a calculation of the human dose equivalent (HDE) to estimate the starting doses to prevent or treat serious pathologies in humans such as cancer, which, due to their vulnerable nature, are frequently addressed in animal studies but rarely in clinical studies.

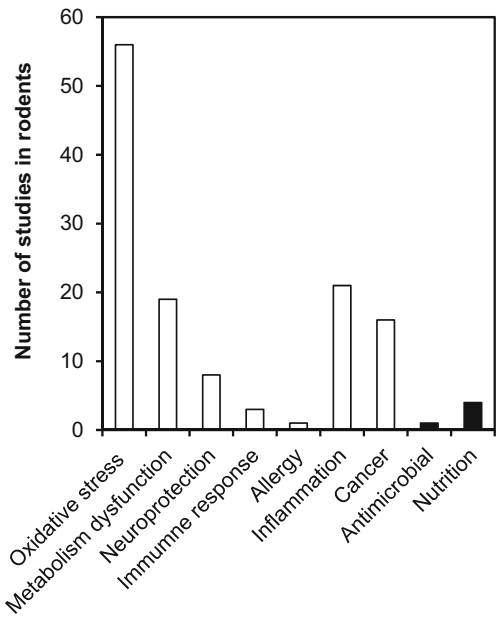

Fig. 3 Number of studies on the effect of *Arthrospira* consumption in rodents (rats and mice). White bars correspond to health outcomes related to the antioxidant capacity of *Arthrospira*. Black bars correspond to studies related to other properties of *Arthrospira*

Human studies

The literature search identified 42 potentially relevant reports, from which 25 studies with a total of 2329 participants were selected for the systematic review. The earliest clinical trial in the database was from 1995. Studies were classified and grouped by health outcomes (Table 1). Eight studies were found on dyslipidaemia, seven on diabetes, two on hypertension, two on exercise, three on immune response and ageing, six on inflammation and precancerous lesions, and two on allergy. In other fields, four studies were retrieved for antiviral activity and eight for nutrition. However, only 25 of the 42 studies identified met quality standards and were systematically reviewed. Figure 4 shows the inclusion percentage of studies in the systematic review in their category after peering for quality criteria. Studies related to exercise and allergy were the most rigorous, followed by antiviral studies, whereas those on nutrition had the lowest quality criteria.

The information extracted from targeted studies on humans comprised author, publication year and country; study design; study size and participant characteristics (age, gender and inclusion/exclusion criteria); description of the intervention; follow-up period; outcomes and results (Table 2). Twenty works on the antioxidant effect of *Arthrospira* that met quality criteria were found. Four of these analysed its role in dyslipidaemia, four were on diabetes, two on hypertension, two on exercise, two on immune response, four on inflammation and precancerous lesions, and two on allergic rhinitis. A further three studies analysed the antiviral effect of *Arthrospira* and three others studied the effect of *Arthrospira* on nutritional status. Most works reported a positive response between *Arthrospira* consumption and improvement in the targeted health outcome (Table 2).

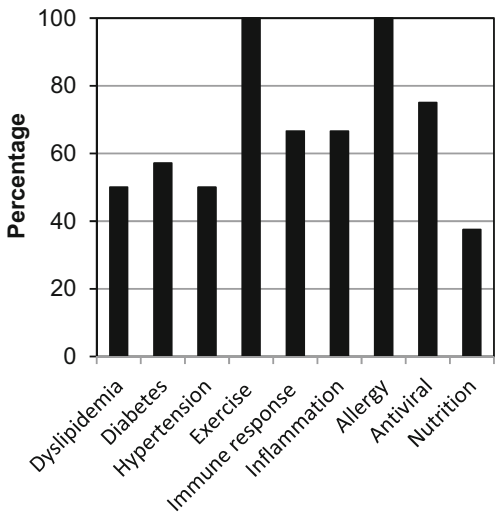

Fig. 4 Percentage of studies included in the systematic review in their category

Arthrospira consumption and oxidative stress-related diseases

Because oxidative stress is an inevitable result of life in an oxygen-rich environment (Davies 1995), aerobic organisms are fully equipped with mechanisms to prevent this type of stress. Certain compounds maintain equilibrium with pro-oxidants, giving rise to total antioxidant capacity (Ferrari 2012). When this equilibrium is lost because of increased exposure to high concentrations of reactive oxygen species (ROS) caused by alcohol, smoking, heavy metals, pesticides, electromagnetism, nuclear radiations or UV exposure, the cell is no longer capable of neutralising them and damage is caused. From the medical point of view, oxidative stress is linked to the prevalence of many human diseases such as neurodegenerative disease (e.g., Alzheimer's, Parkinson's and amyotrophic lateral sclerosis), inflammatory disease (e.g., rheumatoid arthritis), cardiovascular disease (e.g., muscular dystrophy), allergies, immune system dysfunction, diabetes, age-related diseases and cancer, all of which are increasing in prevalence. The influence of ROS may be detrimental to virtually all biomolecules (lipids, proteins and nucleic acids), resulting in structural and functional changes and eventually in necrotic or apoptotic cell death (Rizzo et al. 2009).

Using an exogenous source of antioxidant compounds to help the animal cell to neutralise the ROS level is feasible (Lobo et al. 2010). *Arthrospira* is known to have antioxidant properties, which are attributed to its biochemical profile containing phytopigments (Table 3), tocopherol, γ-linolenic acid and phenolic compounds (Chu et al. 2010; Lobo et al. 2010). *Arthrospira* consumption may play a role in preventing oxidative stress, but in our selection, only three studies explored the relation between *Arthrospira* consumption and oxidative stress using specific antioxidant biomarkers to establish this relationship (Table 2). Lu et al. (2006) found a higher significant increase in superoxide dismutase (SOD) after *Arthrospira* treatment (1324.09 to 1852.45 μHb) ($p < 0.01$) than with soy protein treatment (control group) (1251.1 to 1510.1 μHb) ($p < 0.05$). A study on obese and non-obese people (Park and Lee 2016) found a significant decrease in thiobarbituric acid-reactive substances (TBARS) (7.12 nmol mL^{-1}, $p < 0.01$) in the non-obese group after *Arthrospira* consumption and a significant increase in total antioxidant status (TAS) (1.6 to 2.09 nmol L^{-1}, $p \leq 0.01$) in the same group. Park et al. (2008) reported that after 16 weeks of *Arthrospira* consumption (8 g day^{-1}), TBARS decreased significantly in both males ($p < 0.01$) and females ($p < 0.05$) compared to the control group. A significant increase occurred in TAS in males (1.6 to 2.2 nmol L^{-1}, $p < 0.01$) and in SOD (1.6 to 2.7 U mg^{-1}, $p < 0.01$) in females. The study by Winter et al. (2014) included in the antiviral group also assessed antioxidant potential through the measurement of the total antioxidant capacity of the serum (TAOS). This value is reported to provide an integrated index of antioxidant potential. In the placebo group, the authors found a decreasing value of TAOS ($r = 0.48$, $p = 0.008$) reflecting the progression of infection while the intervention group had a significantly increased effect on the TAOS ($r = 0.51$, $p = 0.007$) reflecting a possible rehabilitation of patients with initially low TAOS.

Dyslipidaemia Dyslipidaemia is an increase in plasma TG or LDL-C levels that contributes to the development of atherosclerosis, increasing the risk of cardiovascular events (e.g., myocardial infarction, ischemic stroke and death). Causes of dyslipidaemia may be primary (genetic) or secondary (e.g., lifestyle, sedentary routine, diabetes mellitus, excess alcohol, hypothyroidism, liver disease and drugs). It is estimated that prevalent cases of dyslipidaemia in the nine major countries (the USA, France, Germany, Italy, Spain, the UK, Japan, India and China) will increase at the rate of 1.76% a year to surpass 500 million in 2022 (Shi et al. 2014). Tóth et al. (2012) reported that the prevalence of standard lipid abnormalities among US adults is 53%, of which 27% have high LDL-C, 23% have low HDL-C and 30% have high TG. In addition, 21% of US adults have mixed dyslipidaemia, defined as the presence of high LDL-C combined with at least one other lipid abnormality. Nearly 6% of US adults have all three lipid abnormalities. Approximately 6.6% of adults have low HDL-C combined with hypertriglyceridemia. In China, the prevalence of dyslipidaemia in adults was estimated in a meta-analysis conducted by Huang et al. (2014) as 41.9% of adults with lipid abnormalities. Dyslipidaemia is closely associated with increased endothelial production of ROS. Clinical studies have documented strong positive associations between plasma levels of oxidative stress parameters and atherogenic lipoproteins in patients with cardiovascular disease (Rizzo 2009). Dyslipidaemia treatment involves dietary changes, exercise and pharmacologic therapy.

A meta-analysis of the impact of *Arthrospira* supplementation on plasma lipid concentrations (Serban et al. 2016) showed a significant effect in reducing TC, LDL-C and TG and raising HDL-C. This is consistent with our findings which retrieved eight interventions investigating the association between *Arthrospira* consumption and dyslipidaemia. All included lipid markers total cholesterol (TC), total triglycerides (TG), low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C). In every case, the authors reported improvements in some of these parameters after *Arthrospira* treatment, mainly in TC and TG. However, only four of eight studies in this field met the quality criteria for systematic review.

Table 1 shows that the study by Zeinalian et al. (2017) was the most rigorous. The authors reported that obese individuals who were administrated a dose of 1 g day^{-1} of *Arthrospira* for 12 weeks had a significant reduction in body weight (BW), body mass index (BMI) and appetite compared to individuals who were supplemented with 1 g day^{-1} of starch as control.

Table 2 Summary of the clinical trials included in the systematic review of the effect of dietary *Arthrospira* in humans (*IC* inclusion criteria, *EC* exclusion criteria, *DC* discontinuation criteria, *F/M* female/male)

No	Study design	Sample population	Intervention	Control	Duration	Jadad score	Results
1	Randomised double-blind placebo-controlled trial	(n=56) IC: age= 20-50 years BMI ≥30 kg m^{-2} EC: kidney disease, atherosclerosis, cancer, acute infections, recent surgery, medication or supplements, pregnancy, lactation, menopause	(n=29) F/M: 24/5 *A. platensis* (1 g day^{-1})	(n=27) F/M: 23/4 *Starch* (1 g day^{-1})	3 months	**3**	VEGF: no changes observed after treatment in intervention or control Weight, WC, TG, LDL-C: decrease (non-significant) observed after treatment in intervention and control BMI: decrease (significant, $p<0.01$) in both groups: 1.9% after intervention, 0.73% in control group Appetite: decrease (significant, $p<0.01$) after intervention (4.16%) TC: decrease (significant, $p<0.01$) after intervention (4.67%) HDL-C: increase (significant, $p<0.05$) in both groups: 1.73% after intervention, 4.36% in control group
2	Randomised controlled trial	(n=61) IC: age= 20-50 years BMI ≥25 kg m^{-2} EC: Kidney disease, autoimmune liver disease, hemochromatosis, lung disease, virus infections, alcoholic fatty liver, diabetes, hepatitis B and C, dyslipidemia	(n=21) F/M: 11/10 *Chlorella vulgaris* (1 g day^{-1}) (n=20) F/M: 10/10 *A. platensis* (1 g day^{-1})	(n=20) F/M: 10/10 Control (nothing extra)	8 weeks	**2**	Better achievements in intervention groups compared to control. HDL-C: increase (non-significant, $p>0.05$) after interventions (*Chlorella* and *Arthrospira*) compared to control Weight: decrease (significant, $p<0.05$) after interventions (*Chlorella* and *Arthrospira*) compared to control TG: decrease (significant, $p<0.05$) after *Chlorella* intervention ALT, AST: decrease (significant, $p<0.05$) in control group compared with intervention groups
4	Longitudinal trial in a randomised cohort	(n=169) IC: HIV-infected antiretroviral adults naive to treatment. Mean age: 35.6±9 years EC: CD4 ≤ 400 cell μL_1 Lipid modifying therapies	(n=82) *A. platensis* (10 g day^{-1}) + fresh local balanced diet	(n=87) Fresh local balanced diet	6 months + 6-month follow up	**1**	BMI: decrease (non-significant) in intervention and control groups FBS: decrease (significant $p<0.01$), in intervention and control groups. After 12 months, significant decrease after intervention (from 105.89 to 95.35 mg L^{-1}) TG: decrease (significant, $p<0.01$) after intervention (from 206.9 to 123.5 mg dL^{-1}); increase (non-significant) for control TC: increase decrease (significant, $p<0.01$) after intervention (from 228.7 to 141.4 mg dL^{-1}); (non-significant) for control LDL-C: decrease (significant, $p<0.01$) after intervention (from 127.0 to 29.3 mg dL^{-1}); increase (non-significant) for control HDL-C: increase (significant, $p<0.001$) after intervention (from 48 to 100.98 mg dL^{-1}); increase (non-significant) for control AI: decrease (significant, $p<0.0001$) after intervention (TC/HDL-C: from 10.83 to 2.22 and LDL-C/HDL-C: from 8.24 to 0.96; increase (non-significant) for control

7	Randomised control trial	(n=23) Mean age= 7-7.5 years IC: Nephrotic syndrome Willingness to participate	(n=15) F/M: 3/12 *Arthrospira* (1 g day^{-1}) + medication	(n=8) F/M: 3/5 Medication	2 months	**2**	Weight and height: slight increase after intervention BMI and WHR: no changes observed FBS: decrease (non-significant) in both groups, higher after intervention (from 93.46 to 81.13 mg dL^{-1}) TC: decrease (significant, $p<0.05$) in both groups, higher after intervention (from 328.46 to 212.13 mg dL^{-1}) TG: decrease in both groups, significant ($p<0.05$) higher after intervention (from 227.98 to 160.26 mg dL^{-1}) LDL-C: decrease (significant, ($p<0.05$) in both groups, higher after intervention (from 225.20 to 131.6 mg dL^{-1}) HDL-C: decrease (non-significant) in control and intervention groups VLDL-C: decrease (non-significant) in control; decrease significant ($p<0.05$) after intervention (from 45.59 to 32.05 mg dL^{-1})
9	Single-blind Randomised trial	(n=30) IC: Age= 30-70 years Type II Diabetes mellitus for 2 years. Metformin treatment EC: BMI>40 kg m^{-2}, inflammatory disease, cancer, renal disease. Antihyperlipidemic treatment	(n=15) *Arthrospira* (0.8 g day^{-1}) + Metformin	(n=15) Placebo + Metformin	2 months	**4**	Weight: decrease (significant, $p<0.05$) in both groups, higher in control (from 100.7 to 96.5 kg) Glycaemia: decrease (significant, $p<0.05$) in both groups, higer after intervention (from 149.5 to 121.1 mg dL^{-1}) TG: decrease (significant, $p<0.05$) in control from 198.7 to 139.3 mg dL^{-1} and non-significant after intervention TC: decrease (significant, $p<0.05$) in both groups, higher in control (from 211.25 to 144.8 mg dL^{-1}) LDL-C: decrease (non-significant) in both groups HDL-C: increase (significant, $p<0.05$) in control from 45.8 to 48.5 mg dL^{-1} and non-significant after intervention Uric acid: decrease (significant, $p<0.05$) in control from 6.8 to 5.58 mg dL^{-1} and non-significant after intervention Hb A1c: decrease (significant, p<0.05) in both groups, higher in control (from 7.2 to 6.3 %)
10	Single-blind Randomised trial	(n=33) IC: Insulin-resistant HIV-infected adults EC: Acute intercurrent infection, antihyperlipidemic treatment, diabetes, renal failure, pregnancy, smoking	(n=17) F/M: 13/4 *Arthrospira* (19 g day^{-1})	(n=16) F/M: 13/3 Soya beans (19 g day^{-1})	2 months	**3**	Waist circumference decrease (non-significant) after intervention FFM: increase (non-significant) after intervention group and decrease in control group TBF: increase (non-significant) after intervention group and control group TC, TG: no significant difference in any group. Lower trend detected for TC after intervention IS: increase (significant, $p<0.001$) in both groups, higher after intervention (224.7%) FBG: increase (non-significant) after intervention and control group CD4: increase (non-significant) in either group
13	Randomised controlled trial	(n=37) Male= 20 Female= 17 IC: Diabetic adults EC: medication for diabetes, dyslipidemia, inflammatory diseases and vitamin supplements	(n=19) *A. platensis* (8 g day^{-1})	(n=18) Control (nothing extra)	12 weeks	**3**	FBG, HbA, Insulin, TC, AI, SBP, DBP: no significant differences between groups TG: decrease (significant, $p<0.05$) after intervention (from 125.8 to 98.5 mg dL^{-1}); increase (non significant) in control group LDL-C: increase (non-significant) in both groups HDL-C: increase (non-significant) in both groups Adiponectin: increase (non-significant) in both groups, higher after intervention IL-6: non-significant decrease after intervention, increase (non-significant) in control group TNF-α: higher decrease (non-significant) after intervention MDA: decrease (significant, $p<0.01$) after intervention (from 2.57 to 1.85 μM L^{-1}); non-significant decrease in control group

14	Randomised controlled trial	(n=25) IC: Type 2 Diabetes adults EC: medication for dyslipidemia.	(n=15) F/M: 6/9 *Arthrospira* (2 g day^{-1})	(n=10) F/M: 4/6 Control (nothing extra)	2 months	**2**	TC, HDLC: no differences FBS: Decrease (significant, p<0.05) after intervention (from 161.7 to 27.4 mg/dL^{-1}) HbA1C: decrease (significant, p<0.05) after intervention (from 9 to 8 mg dL^{-1}) BG: decrease (significant, p<0.05)) after intervention)from 261.0 to 181.1 mg dL^{-1}) TG: decrease (significant, p<0.05) after intervention (from 163.9 to 146.2 mg dl^{L-1}) LDLC: increase (significant, (p<0.05) in control (from 127.8 to 137.2 mg dL^{-1}) APO A1: increase (significant p<0.05) after intervention (from 123.4 to 134.8 mg) APO B: increase (significant, p<0.05) in control (from 111.3 to 130.1 mg); decrease (significant, p<0.001) after intervention (from 122.1 to 106.0 mg) A1/B ratio: decrease (significant, p<0.05) in control group from 1.2 to 1.0, decrease (significant, p<0.01)) after intervention (from 1.2 to 1.3)
16	Randomised double-blind placebo-controlled trial	(n=40) IC: BMI≤29.99 kg m^{-2} 40-60 years Stable body weight Controlled hypertension (160-100 mmHg with stable treatment) EC: Obesity, secondary hypertension, diabetes, coronary disease, dietary supplementation, liver or kidney malfunctioning, infection, smoking or alcohol consumption	(n=40) F/M: 19/21 *A. maxima* (2 g day^{-1})	(n=40) F/M: 20/20 Cellulose (2 g day^{-1})	3 months	**5**	Weight: decrease (significant, p<0.05) after intervention (from 75.5 to 70.5 kg) BMI: decrease (significant, p<0.05) after intervention (from 26.9 to 25 kg m^{-2}) SBP: decrease (significant, p<0.05) after intervention (from 149 to 143 mmHg) DBP: decrease (significant, p<0.05) after intervention (from 84 to 79 mmHg) ASI: decrease (significant, p<0.05) after intervention (from 7.2 to 6.9 m s^{-1})
18	Randomised double blind placebo-controlled trial	(n=17) IC: Healthy male 20-43 years Physically active EC: Sedentary lifestyle, chronic disease, smoking	(n=9) Male= 12 *A. platensis* (3 g day^{-1})	(n=8) Male= 13 Gelatine (2 g day^{-1})	2 months	**4**	Physical fatigue: increase (significant, p<0.01) in exercise output (30 min aerobic exercise) after 1 week of *Arthrospira* intervention; increase not significant after 8 weeks PFST: significant improvement after 1 and 8 weeks intervention (p<0.05) UKT: significant improvement after 1 and 8 weeks intervention (p<0.05)

19	Randomised double blind placebo controlled trial	(n=16) IC: College student Age: 19.5-22 years	(n=8) F/M: 5/3 *A. platensis* (7.5 g day^{-1})	(n=8) F/M: 5/3 Soy protein (7.5 g day^{-1})	3 weeks	**4**	CK, Urine pH, RQ: differences (non-significant) between intervention and control MDA: decrease (significant, $p<0.01$) after intervention (from 56.21 to 50.37 nmol mL^{-1}) SOD: increase (significant, $p<0.01$ for intervention and $p<0.05$ for control) higher after intervention (from 1324.09 to 1852.45 u gHb^{-1}) GPx: increase (non-significant) after intervention LDH: increase (non-significant) after intervention LA: increase (significant, $p<0.01$) after intervention (from 20.40 to 45.57 mg dL^{-1}) TE: increase (significant, $p<0.05$) after intervention (from 713 to 765 s)
20	Randomised double-blind, placebo controlled trial	(n=78) F/M: 35/43 IC: age >60 years EC: consumption of vitamin supplements, drugs for inflammatory disease (e.g., Crohn's disease, rheumatoid arthritis), dyslipidemia, hypertension	(n=25) Non-obese (<25 kg m^{-2}) (n=16) Obese (≥25 kg m^{-2}) *A. platensis* (8 g day^{-1})	(n=20) Non-obese (<25 kg m^{-2}) (n=17) Obese (≥25 kg m^{-2}) Starch 100% (8 g day^{-1})	16 consecutive weeks	**5**	TC: decrease (significant, $p<0.05$) for non-obese (191.1 to 179.2 mg dL^{-1}) and non-significant for obese after intervention LDL-C: decrease (significant $p<0.05$) for non-obese (120.5 to 109.9 mg dL^{-1}) and non-significant for obese after intervention HDL-C: higher decrease (non-significant) in obese than in non-obese groups after intervention, increase (non significant) in control TG: decrease (non-significant) in all groups except obese with placebo, where values increased non-significantly AI: non-significant effects IL-2: increase (significant; $p<0.01$) after intervention in both obese and non-obese groups, increase (non-significant) in control IL-6: decrease (significant, $p<0.05$) in non-obese control group (from 1.19 to 2.5 pg mL^{-1}) TNF-α: no changes in either group TBARS: time-by-treatment decrease (significant, $p<0.01$) in non-obese group after intervention (from 7.12 to 5.37 nmol mL^{-1}) TAS: increase (significant, $p<0.01$) in non-obese after intervention (from 1.6 to 2.09 nmol L^{-1}) and increase (significant, $p<0.05$) in control obese (from 1.56 to 2.09 nmol L^{-1})
22	Randomised double-blind, placebo controlled trial	(n=78) IC: age >60 years EC: consumption of vitamin supplements, drugs for inflammatory disease (e.g., Crohn's disease, rheumatoid arthritis), dyslipidemia, hypertension	(n=41) F/M: 17/23 *A. platensis* (8 g day^{-1})	(n=37) F/M: 18/19 Starch 100% (8 g day^{-1})	16 consecutive weeks	**5**	HDL-C, TG, AI, TNF-α, MCP-1, C3: no changes in either group TC: decrease (non-significant) for males and significant ($p<0.05$) for females (from 200.5 to 184.8 mg dL^{-1}) after intervention LDL-C: no effect for males and significant decrease ($p<0.05$) for females (from 126.7 to 112.1 mg dL^{-1}) after intervention IL-2: increase (significant, $p<0.05$) after intervention in males (from 9.43 to 13.6 pg mL^{-1}) and females (from 9.39 to 13.8 pg mL^{-1}). Increase (significant, $p<0.05$) in female control (from 10.9 to 13.3 pg mL^{-1}) IL-6: decrease (significant, $p<0.05$) in female intervention group (from 1.02 to 1.8 pg mL^{-1}) TBARS: decrease (significant, $p<0.01$) in male intervention group (from 7.8 to 5.6 nmol mL^{-1}) and in female intervention group (from 6.5 to 5.9 nmol mL^{-1}) TAS: increase (significant, $p<0.01$) in male intervention group (from 1.6 to 2.2 nmol L^{-1}) SOD: increase (significant, $p<0.01$) in female treatment group (from 1.6 to 2.7 U mg^{-1}) GPx: increase (non-significant) in male intervention and control groups and decrease (non-significant) in female intervention group

23	Randomised control trial	(n=42) F/M: 18/24 IC: Mean age: 31.2±12.4 years Diagnosed OSMF EC: severe psychiatric, cardiac, gastrointestinal or metabolic disorders, pregnancy or lactation	(n=21) *A. platensis* (0.5 g day^{-1}) (n=21) Aloe vera gel	(n=42) Baseline	3 months	**1**	Mouth opening: improvements (significant, $p<0.05$) in *Arthrospira* group Ulcers/vesicles/erosions: improvements(significant, $p<0.05$) in *Arthrospira* group Pain, burning sensation: improvements (non-significant) in both groups
24	Randomised controlled trial	(n=112) F/M: 52/60 IC: Mean age: 32.8 years Diagnosed OSMF EC: severe psychiatric, cardiac, gastrointestinal or metabolic disorders, pregnancy or lactation	(n=56) *Arthrospira* (1 g day^{-1})	(n= 56) Pentoxifylline (0.8 g day^{-1})	3 months	**1**	Mouth opening: improvement (significant, $p<0.001$) in control group Ulcers/vesicles/erosions: improvements (significant, $p<0.001$) after intervention Pain: improvement in both groups, statistically significant ($p<0.001$) in control group Burning sensation: improvement in both groups, statistically significant ($p<0.001$) in control group
26	Randomised trial with drug as control	(n=40) IC: Mean age: 31 years Diagnosed OSMF EC: hypertension, diabetes mellitus, anaemic stomatitis, radiation fibrosis, scleroderma, immunosuppressive diseases, peptic ulcer, bleeding disorders	(n=20) Male=20 *Arthrospira* (1 g day^{-1})	(n= 20) F/M: 1/19 Pentoxifylline (0.8 g day^{-1})	4 months	**1**	Mouth opening and tongue protrusion: improvement in control and intervention Burning sensation: improvement (significant, $p<0.05$) after intervention
28	Randomised placebo controlled trial	(n=87) IC: Mean age: 35.6 ±9 years Oral leukoplakias	(n=44) F/M: 6/38 *S. fusiformis* (1 g day^{-1})	(n=43) F/M: 15/28 Placebo	1 year	**1**	CR: 11% in control group and 57% after intervention ($p<0.001$) for homogeneous lesions 46% for lesions ≤ 2 cm and 46% in lesions >2 cm after intervention PR: 0% in control group and 14% after intervention ($p<0.001$) MT: 17% in control group and 6% after intervention ($p<0.051$) Serum levels of vitamins (retinol, tocopherol) and pigments (carotenoids) not effect after intervention
29	Randomised double-blind placebo controlled trial	(n=129) IC: clinical history of allergic rhinitis EC: medication for allergy or rhinitis	(n=85) F/M: 50/35 *Arthrospira* (2 g day^{-1})	(n=44) F/M: 25/19 Dyed rice flour (2 g day^{-1})	6 months	**4**	Intervention significantly ($p<0.001$) improved symptoms (stuffy, runny, itchy nose and sneezing) and physical findings compared with placebo including nasal discharge, sneezing, nasal congestion and itching

30	Randomised double-blind crossover vs placebo trail	(n=36) IC: age 18-55 years Clinical history of allergic rhinitis EC: Other health problems	(n=12) *Arthrospira* (2 g day^{-1}) (n=12) *Arthrospira* (1 g day^{-1})	(n=10) Placebo	3 months	**4**	INF-γ, IL-2: No effect after intervention IL-4: decrease (significant, $p<0.01$) after higher dosage intervention (from 21.9 to 14.9%)
31	Longitudinal trial in randomised cohort	(n=141) IC: Mean age: 35.6 ±9 years HIV- infected naive to antiretro-viral treatment EC: CD4 count≥400 cells/μL	(n=78) F/M: 62/20 *A. platensis* (10 g day^{-1}) + usual diet	(n=63) F/M: 57/30 Fresh local balanced diet	12 months	**1**	BMI: no significant changes between groups over time FBS: decrease (significant, $p<0.00$) after 12 months intervention from 105.89 to 95.39 mg L^{-1}. No change in control group. HB: increase (significant, $p<0.00$) after intervention Viral load HIV-1: decrease (significant, $p<0.00$) after 6 and 12 months intervention (from 74770.33 to 30872.33 copies mL^{-1}) increase in control group CD4 count: increase (significant, $p<0.00$) after 6 and 12 months intervention (from 596.32 to 614.92 cell μL^{-1}), decrease in control group .
32	Randomised double-blind placebo-controlled trial	(n=58) IC: HIV-infected adult female	(n=30) *A. platensis* (5 g day^{-1})	(n=28) Pea protein mixed with Dextrans (5 g day^{-1})	3 months	**4**	BW: 0.65 kg increase in both groups: intervention ($p = 0.517$) and control ($p = 0.005$). Weight difference between groups not significant ($p= 0.105$) CD4 count: decrease (significant, $p< 0.001$) for control (-52 cells mm^{-3}) and intervention (-66 cells mm^{-3}) Viral load HIV-1: no changes between groups TAOS: trends in both groups significantly opposite ($p< 0.001$). TAOS increased after intervention (56 μM) ($p= 0.007$) and decreased in control group by −22 μM ($p =0.008$) Albumin: non-significant difference between groups Urea concentration: no change between groups Creatinine: increase (significant, $p<0.01$) after intervention (from 0.7 to 0.75 mg dL^{-1}) eGFR: increase (non-significant) after intervention
34	Randomised double-blind trial	(n=24) IC: age 18-60 years ALAT ≥150% of maximum normal value Chronicity of disease Viral aetiology (B or C hepatitis) EC: Another aetiology Acute hepatitis associated diseases. Hepatic cirrhosis diagnosis	(n=not indicated) F/M: 9/21 *A. platensis* (3.2 g day^{-1})	(n= not indicated) F/M: 11/18 Placebo (3.2 g day^{-1})	1 month	**4**	ALAT: increase (significant, $p<0.05$) in control group. Mean of 10 U L^{-1} after intervention, mean of 45 U L^{-1} in control group ASAT: increase (significant; $p<0.05$) in control group. Mean of 2.5 U L^{-1} in *Arthrospira* group after intervention and 50 U L^{-1} in control group
40	Randomised controlled trial	(n=228) IC: age 41-57 years EC: Fever >38° C reactive protein >10 mg L^{-1}	(n=52) Meal + *Arthrospira* (4 g day^{-1}) (n=53) Meal + *Arthrospira* (2 g day^{-1})	(n=59) Meal	10 weeks (5 days/week)	**3**	Total body stores of vitamin A: increase (significant, $p<0.01$) after 2 g intervention group from 0.345 to 0.632 mmol and from 0.340 to 0.807 mmol after 4 g intervention group

41	Randomised controlled trial	(n=550)
		
		IC: age<5 years, undernourishment
		
		EC: Severe dehydration
		
		DC: Abandonment, death, interruption of treatment
			(n=510)
			
			(n=170) Group A Misola (200 g day^{-1})
			
			(n=170) Group B *Arthrospira* (10 g day^{-1}) + traditional meals
			
			(n=170) Group C *Arthrospira* (10 g day^{-1}) + Misola (200 g day^{-1})
				(n=40)
				
				Group D traditional meals
					2 months	**2**	• A:
							  • Weight for height: 34.14% increase
							  • Weight for age: 26% increase (p<0.001)
							• B:
							  • Weight for height: 37.50% increase (p<0.001)
							  • Weight for age: 20% increase (p<0.001)
							• C:
							  • Weight for height: 62.90% increase (p<0.001)
							  • Weight for age: 38% increase (p<0.001)
							• D:
							  • Weight for height: 17.35% increase
							  • Weight for age: 14% increase

42	Randomised controlled trial	(n=170)
		
		84 HIV-infected
		86 HIV-negative
		
		IC: age<5 years, undernourishment
		
		EC: refusal to participate
		
		DC: Abandonment, death, interruption of treatment
			(n=90)
			
			(n=46) Group A HIV negative treated with *A. platensis* (20 g day^{-1}) + traditional meals
			
			(n=44) Group B HIV-positive treated with *A. platensis* (20 g day^{-1}) + traditional meals
				(n=80)
				
				(n=40) Group C HIV-negative traditional meals
				
				(n=40) Group D HIV-positive traditional meals
					2 months	**2**	A:
							  • Weight for height: 42.1% increase (p<0.0003)
							  • Weight for age: 22.19% increase
							B:
							  • Weight for height: 22.2% increase
							  • Weight for age: 14.63% increase
							C:
							  • Weight for height: 17.3% increase (p=0.004)
							  • Weight for age: 13.53% increase
							D:
							  • Weight for height: 10.41% increase
							  • Weight for age: 7.47% increase
							
							HB: increase (significant, p<0.000) in both groups, from 8.53 to 9.73 g dL^{-1} in HIV-negative children and 8.01 to 9.42 g dL^{-1} in HIV-positive children
							Leukocytes: increase (non-significant) in HIV-negative children and HIV-positive children
							Lymphocyte: increase (non-significant) in HIV-negative children and HIV-positive children
							Neutrophils: decrease (non-significant) in HIV-negative children and HIV-positive children

A1/B ratio, ratio APO A1/APO B; *AI*, atherogenicity index, expressed as TC/HDL-C or LDL-C/HDL-C; *ALAT*, alanine aminotransferase; *ALP*, alkaline phosphatase; *ALT*, alanine aminotransferase; *APO A1*, apolipoprotein A1; *APO B*, apolipoprotein B; *ASAT*, aspartate aminotransferase; *ASI*, arterial stiffness; *AST*, aspartate aminotransferase; *ATL*, alanine transaminase levels; *BG*, blood glucose; *BMI*, body mass index; *BP*, blood pressure;*c-EVR*, loss of detectable hepatitis C virus RNA; *CDV*, cardiovascular disease; *CK*, total creatine kinase; *CLDQ*, Chronic Liver Disease Questionnaire; *CD8/CD38*, immune activity; *CR*, complete response; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *FBG*, fasting blood glycaemia; *FBS*, fasting blood sugars; *FFM*, fat-free mass; *FEV1*, forced expiratory volume; *FG*, fasting glycaemia; *FVC*, forced vital capacity; *G*, glucose; *GPx*, glutathione peroxidase; *HAZ*, height-for-age z-score; *HBP type I*, high blood pressure type I; *HBP type II*, high blood pressure type II; *HB*, haemoglobin; *Hb A1C*, glycated haemoglobin; *HC*, haematocrit; *IDO*, indoleamine 2,3-dioxygenase; *IS*, insulin sensitivity; *LA*, lactate; *LDH*, lactate dehydrogenase; *MT*, malignant transformation; *M*, malondialdehyde; *MET*, metabolic equivalent; *MCP-1*, monocyte chemoattractant protein; *MUAC*, mid-upper arm circumference; *MUACZ*, mid-upper arm circumference *z*-score; *OSMF*, oral submucous fibrosis; *PFST*, piper fatigue scale test; *PR*, partial response; *p-ETR*, reduction of virus load; *PEFR*, peak expiratory flow rate; *RBC*, red blood cell; *RQ*, respiratory quotient; *SBP*, systolic blood pressure; *SGOT*, serum glutamic oxaloacetic transaminase; *SGPT*, serum glutamic pyruvic transaminase; *SITT*, short insulin tolerance test; *SOD*, superoxide dismutase; *TBF*, total-body fat; *TAOS*, antioxidant status in blood serum; *TE*, time to exhaustion; *TP*, total protein; *TBARS*, thiobarbituric acid-reactive substance; *TAS*, total antioxidant status; *UKT*, Uchida-Kraepelin test, mental fatigue; *VLDL-C*, very low-density cholesterol; *VEGF*, vascular endothelial growth factor; *WC*, waist circumference; *WAZ*, weight-for-age *z*-score; *WHR*, waist measurement/hip measurement; *WHZ*, weight-for-height *z*-score;

This dosage of *Arthrospira* partially modified serum lipids, significantly decreasing TC in comparison with the placebo. The authors also found an increase in HDL-C, but it was significant in both groups. The results were independent of age, gender or physical activity. Chitsaz et al. (2016) compared *Chlorella* and *Arthrospira* consumption to treat non-alcoholic fatty liver disease. They found that after supplementation of 1 g day^{-1} for 8 weeks, anthropometric indices decreased significantly. Alanine transaminase values (ALT) were significantly different between intervention and non-intervention groups. The study by Ngo-Matip et al. (2014) also met randomisation and control inclusion and showed that supplementation with *Arthrospira* combined with a balanced diet can retard lipid abnormalities in immunosuppressed patients. In a study of HIV-infected people antiretroviral-naive to treatment, they found a significant increase in HDL-C and a significant decrease in LDL-C and triglycerides in the group supplemented with 10 g day^{-1} of *Arthrospira* for 6 months combined with a fresh local balanced diet, compared to the group that had only a balanced local diet. The atherogenic index (TC/HDL-C) also decreased significantly in the group supplemented with *Arthrospira*. Samuels et al. (2002) treated patients with hyperlipidemic nephrotic syndrome with either medication plus 1 g day^{-1} of *Arthrospira* or medication only for 2 months. They found that TC and LDL-C decreased in both groups, with a higher significant decrease in the *Arthrospira* group. Triglycerides decreased in both groups but the decrease was significant only in the *Arthrospira* group.

Studies in other fields of this review which met quality criteria included lipid parameters in their outcomes, showing that *Arthrospira* consumption improves health status in terms of dyslipidaemia for seropositive diabetics (Marcel et al. 2011) and the elderly (Park et al. 2008). Marcel et al. (2011) observed a lower total-body fat and a downward trend for TC in the *Arthrospira*-treated group, although this group showed no significant differences in TC and TG levels.

Diabetes Oxidative stress also plays a key role in diabetes (Maritim et al. 2003) and its microvascular and cardiovascular complications (Giacco and Brownlee 2010). Pancreatic beta cells in type 2 diabetes are lost due to oxidation (Li et al. 2015). Free radicals are formed disproportionately in diabetes by glucose oxidation, non-enzymatic glycation of proteins, and subsequent oxidative degradation of glycated proteins (Maritim et al. 2003). HIV and HCV infections are both characterised by increased oxidative stress (Shin et al. 2012), which increases complications.

Seven studies analysing the effect of dietary *Arthrospira* in diabetes were retrieved, but only four met quality criteria. Serban et al. (2015) studied patients treated with metformin and placebo or metformin and *Arthrospira*. They found that after supplementation of 0.8 g day^{-1} for 2 months, glycaemia decreased significantly in both groups, although the decrease was higher in the *Arthrospira* group. The authors analysed the lipid profile and found that supplementation with *Arthrospira* did not improve the results compared with the medication group. Marcel et al. (2011) studied the effect of supplementation for 2 weeks with 5 g day^{-1} of *Arthrospira* on insulin resistance in HIV-infected adult patients compared with soybean supplementation. They reported a significant increase in insulin sensitivity in the *Arthrospira* group despite a lower follow-up rate and fewer intake days (45 vs 59) in the *Arthrospira* group due to complaints about poor palatability. They also reported that *Arthrospira* seemed to be better than soybean at correcting HIV/HAART (human immunodeficiency virus/highly active antiretroviral therapy)-associated insulin resistance and concluded that *Arthrospira* supplementation may play a key role in HIV/HAART-associated insulin resistance. Lee et al. (2008) found that *Arthrospira* supplementation of 8 g/day for 12 weeks in patients with type 2 diabetes mellitus significantly lowered plasma triglycerides and plasma malondialdehyde level and increased plasma adiponectin. They also found that patients with higher initial total cholesterol and LDL-cholesterol showed higher reduction in plasma concentration of total cholesterol, LDL-C, interleukin-6 (IL-6) and blood pressure. Parikh et al. (2001) determined the efficacy of *Arthrospira* supplementation of 2 g day^{-1} for 2 months. They reported an appreciable reduction in fasting blood glucose and postprandial blood glucose. A significant reduction in glycosylated haemoglobin (GH) was also found, indicating a long-term improvement in glucose regulation. In the lipids, triglycerides were significantly lowered, as were atherogenic indices (TC:HDL-C and LDL-C:HDL-C). An increase in the ratio of apolipoprotein A1 to apolipoprotein B was also observed.

Hypertension Earlier studies have shown that phycocyanin can ameliorate systemic blood pressure by enhancing endothelial nitric oxide synthase (eNOS) expression in the aorta (Ichimura et al. 2013). Two studies analysing the role of dietary *Arthrospira* in hypertension were retrieved, but only one met quality criteria.

Miczke et al. (2016) studied the effect of daily supplementation for 3 months with 2 g day^{-1} of *Arthrospira* in patients with hypertension and obesity. They reported a significantly positive effect on systolic blood pressure and a tendency to decrease in diastolic blood pressure, suggesting a hypotensive and body mass reduction effect due to *Arthrospira*. The work by Lee et al. (2008), included in this review in the field of diabetes, also found a reduction in blood pressure after 3 months of *Arthrospira* supplementation.

Exercise Regular physical exercise has many health benefits, including a reduced risk of cardiovascular disease, cancer and diabetes. Paradoxically, it also promotes the production of

reactive oxygen and nitrogen species (RONS) (Powers and Jackson 2008), which contribute to muscle fatigue. In addition to the cellular strategies to regulate reactive species, such as superoxide dismutase, glutathione peroxidase and catalase, dietary antioxidants contribute to cellular protection against radicals and other ROS. Important dietary antioxidants include vitamin E, vitamin C and carotenoids, all of which are found in *Arthrospira* composition. Two studies in this field met the quality criteria. Lu et al. (2006) studied the preventive effects of *A. platensis* on skeletal muscle damage under exercise-induced oxidative stress induced by exhaustive exercise. They reported a significant decrease in malondialdehyde (MAD) levels and a significant increase in lactate (LA), SOD and time to exhaustion (TE) levels. A positive interaction between the parameters lactate dehydrogenase (LDH) and glutathione peroxidise (GPx) with time was found after administration of 7.5 g day^{-1} of *Arthrospira*. Johnson et al. (2016) reported an anti-fatigue effect with short- and long-term *Arthrospira* intake.

Immune response Another important health outcome identified was immune response. The immune system has evolved to protect us from a universe of pathogenic microbes and toxins using a complex array of protective mechanisms to control and usually eliminate them (Chaplin 2006), as seen in the role of cytokines to control the behaviour of immune cells. Once activated, cytokines trigger other cells in the immune system, leading to a whole cascade of immune reactions. In healthy individuals, the immune system is self-regulated and once the threat disappears, the immune cells stop the inflammatory response via apoptosis. If this does not occur, chronic inflammation and even cancer may develop. In certain situations, such as advanced age or immunosuppressant diseases, numerous changes occur in the immune system, contributing to a decreased immune response (Ginaldi et al. 1999; McMichael et al. 2010).

Two of the three studies found in this field met the quality criteria for systematic review. Park and Lee (2016) studied the effect of *Arthrospira* supplementation on obese elderly people and found that a dosage of 8 g day^{-1} for 12 weeks decreased lipid parameters and increased interleukin-2 (IL-2) and total antioxidant status level. They also reported a decrease in TBARS. Park et al. (2008) determined the antioxidant capacity, immunomodulatory and lipid-lowering effects of *Arthrospira* in healthy older people to examine the effectiveness of *Arthrospira* as a functional food in this stage of life. They reported that after 4 months of supplementation with 8 g day^{-1} of *Arthrospira*, significant increases in IL-2 levels and superoxide dismutase activities occurred in female participants. Plasma levels of TBARS decreased 29% in males and SOD activity increased in females. With regard to immune variables, a significant rise in plasma IL-2 concentrations and a significant reduction in IL-6 levels were found in males. Plasma TC levels also decreased in both genders.

Interleukin-2 is an anti-inflammatory cytokine essential in the regulation of chronic inflammation which, together with lipid peroxidation and dysregulated lipid metabolism, is a major characteristic of age-related changes. Although Park et al. (2008) did not find a significant reduction in the levels of proinflammatory cytokines such as tumour necrosis factor (TNF-α), monocyte chemoattractant protein (MCP-1) or C3, it is likely that the sum of the downregulating effect of proinflammatory cytokines and improvement in other parameters improved the health of the population studied.

Inflammation and precancerous lesions Cancer prevention is another field in which *Arthrospira* could be beneficial. Reactive species damage DNA and its repair mechanism in a process that enhances ageing and carcinogenesis. Cancer cells exhibit accelerated metabolism and demand high ROS concentrations to maintain their high proliferation rate (Sosa et al. 2013). As the present review shows, the antioxidant compounds present in *Arthrospira* could be used to treat oral submucous fibrosis, a high-risk premalignant condition and reverse oral leukoplakias, both of which are well-known precancerous lesions. Animal studies have demonstrated the potential of *Arthrospira* in co-treatment of a range of malignant conditions. More studies in humans are needed, although conducting clinical trials on cancer treatment with natural products remains a sensitive issue. According to Paller et al. (2016), a likely explanation is that manufacturers of dietary supplements do not submit their products to the rigour and expense of a randomised, placebo-controlled phase 3 trial, which is required for therapy approval.

Six studies analysing the role of dietary *Arthrospira* in inflammation and precancerous lesions were retrieved, but only four met the quality criteria. All of them addressed the preventive effect of *Arthrospira* in oral precancerous conditions such as oral leukoplakias and oral submucous fibrosis. Patil et al. (2015) found that 0.5 g day^{-1} of *Arthrospira* for 3 months improved certain symptoms (mouth opening and ulcers/erosions/vesicles). Zwiri et al. (2015) similarly administered 0.5 g day^{-1} of *Arthrospira* for 3 months and compared the results with pentoxifylline administration. They observed improvements in all parameters for both groups, with clinical improvements in mouth opening and subjective symptoms of pain and burning sensation significantly higher in the *Arthrospira* group, while those treated with pentoxifylline had significant improvement in their ulcers, erosions and vesicles. In a similar study, Mulk et al. (2013) found significant improvements in mouth opening, burning sensation and tongue protrusion for both compounds after 3 months of treatment (0.8 g day^{-1} pentoxifylline plus 1 g day^{-1} *Arthrospira*). Comparing the effect of the two compounds, burning sensation was significantly improved after

pentoxifylline administration than with *Arthrospira*, but side effects such as stomach bloating, nausea and gastritis were reported to a greater extent after pentoxifylline treatment. Mathew et al. (1995) administered *Arthrospira* to participants with oral leukoplakia at a dosage of 1 g day^{-1} for 1 year and found 45% complete regression of lesions compared to 7% in the placebo-treated group. They also observed a greater response in homogeneous than in nonhomogeneous lesions (erythroplakia, nodular/ulcerated and verrucous leukoplakia).

Allergy Allergic rhinitis is a worldwide affection. Between 10 and 30% of the population suffer this disorder and, according to the American Academy of Allergy, Asthma and Immunology, its prevalence is increasing globally due to several factors. Allergic rhinitis exerts a major impact on the quality of life of sufferers. Pharmacotherapeutic options include oral antihistamines and topical antihistamines that can be administered in the nose (Mullol et al. 2005), but the long-term effects of these medications cannot be declared completely safe (Paakkari 2002). Natural products could be useful to treat allergy while caring for the organism. Two studies analysing the role of dietary *Arthrospira* in allergy were retrieved and both met the quality criteria.

Cingi et al. (2008) evaluated the effectiveness of 2 g day^{-1} of *Arthrospira* for 6 months in treating patients with allergic rhinitis. The symptoms evaluated were nasal discharge, sneezing, nasal congestion and itching. *Arthrospira* consumption significantly improved the evolution of symptoms and physical findings compared with placebo. Mao et al. (2005) found that at the same dosage, *Arthrospira* reduced production of IL-4, a cytokine involved in the induction of type I hypersensitivity that leads to the release of inflammatory mediators.

Arthrospira consumption and viral infections

In the field of antiviral activity, many studies have used *Arthrospira* extracts. Hernández-Corona et al. (2002) assessed 50% effective inhibition doses (ED_{50}) of *Arthrospira maxima* hot water extract against viruses such as herpes simplex virus type 2 (HSV-2), pseudorabies virus (PRV), human cytomegalovirus (HCMV) and HSV-1 (0.069, 0.103, 0.142, and 0.333 mg mL^{-1}, respectively). For adenovirus, inhibition was less than 20%, and no inhibition was found for measles virus, subacute sclerosing panencephalitis virus (SSPE), vesicular stomatitis virus (VSV), poliovirus 1 or rotavirus SA-11. El-Baz et al. (2013) reported the antibacterial and antiviral effect of ethanol extract of *S. platensis* against non-enveloped RNA and DNA enteric viruses. Gustafson et al. (1989) observed remarkable in vitro activity of the sulfonic acid-containing glycolipids fraction of *Arthrospira* against HIV-1 virus. However, in the present study, antiviral activity is perhaps the field with the poorest results, because supplementation with whole dried biomass was unable to reduce the viral load of HIV or hepatitis C in any of the clinical studies carried out in humans. Bioactive compounds may be found in higher concentrations in the extract than in whole biomass, explaining the difference in efficacy between the types of products. In the case of HIV-1, the mean level of CD38 on CD8+ cells is typically higher in HIV-positive untreated patients than in those on antiviral therapy and control because the level of CD8+ CD38+ T lymphocytes in blood correlates with disease progression in HIV-infected individuals, independently of the CD4 count (Benito et al. 2004).

Three of the four studies retrieved met the quality criteria. Two examined the role of *Arthrospira* consumption in HIV infections. Ngo-Matip et al. (2015) reported a significant increase in CD4 cell count and a significant decrease in viral load levels after 6 months of treatment with 10 g day^{-1} *Arthrospira* supplementation plus usual diet during a 12-month study. Haemoglobin level was significantly higher in this same treatment group and fasting blood glucose concentration decreased after 12 months compared to control. Winter et al. (2014) studied the effect of 5 g day^{-1} *Arthrospira* supplementation for 3 months on the viral load of people living with HIV/AIDS (PLHIV). They reported no difference between the immunological (CD4-T cell count) and virus markers (CD8 antigen expression) between the placebo group and the group supplemented with *Arthrospira*, although longer intervention periods could make a difference. Antioxidant capacity measured with the TAOS indicator (total antioxidant capacity of the serum) increased significantly in the *Arthrospira* supplemented group and decreased significantly in the placebo group. However, the intervention appeared to reduce the prevalence of concomitant events and opportunistic infections in both cases and showed a positive effect on patients' quality of life. Baicus and Tanasescu (2002) treated chronic viral liver disease or child A cirrhosis patients with 3.2 g day^{-1} *Arthrospira* for 30 days. A greater decrease in aminotransferases occurred in the control than in the treated group. Although *Arthrospira* appears to improve markers of antioxidant capacity, no positive effects were found. These authors also assessed potentially toxic effects of *Arthrospira*, but found no significant modifications in haemoglobin, white bold cells, platelets, renal function or urinary sediments.

Arthrospira consumption and nutritional status

Belay (2002) attributed initial interest in *Arthrospira* to its rich content of protein, vitamins, essential amino acids, minerals and essential fatty acids. Siva et al. (2015) found that significant studies have been done on *Arthrospira* to establish its potential use as a food supplement and food additive and to combat all forms of protein energy malnutrition (PEM) and protein energy wasting (PEW). Only three of the clinical trials retrieved met the quality criteria. Two of these were by Simpore et al. The first, published in 2005, assessed the

Table 3 Pigments found in *Arhrospira* (extracted from Herrera et al. 1989)

Phytopigments	% dry weight
Phycocyanin	7.71
Chlorophyll-*a*	0.67
Carotenes	0.57

impact of an alimentary integrator composed of *Arthrospira* on the nutritional status of undernourished HIV-infected and HIV-negative children. They observed a decrease in the level of anaemia during the study in all children, although the level of recovery was less efficient among HIV-infected children (81.8% recovery in HIV-negative undernourished children compared to 63.6% in HIV-infected children). The second study, in 2006, assessed the impact of another alimentary integrator on the nutritional status of undernourished children in Burkina Faso. To test the effect of their proposed diet, anthropometrics and haematological parameters were compared after children aged less than 5 years old were given different meal combinations. The results revealed differences in weight increase: children in the group given Misola (millet, soya, peanut) plus *Arthrospira* showed faster weight correction. Li et al. (2012) studied the effect of *Arthrospira* as a dietary source of nutrients and found an increase in serum β-carotene and total-body vitamin A in children after 10 weeks of intervention supplemented with 2 or 4 g day^{-1}. The studies that did not meet the quality criteria showed a significant improvement in children's HAZ after an intake of 10 g day^{-1} of *Arthrospira* (Masuda et al. 2014); gains in height, weight, proteinograms and other biochemical parameters such as blood haemoglobin, serum ferritin, serum zinc and serum protein, and an increase in albumin levels in girls who took *Arthrospira* in India (Ramesh et al. 2013); and a greater increase in anthropometry and biochemical parameters such as leukocyte and lymphocyte number in HIV-positive children supplemented with *Arthrospira* than in HIV-negative children fed with traditional meals only (Simpore et al. 2005).

Effect of size, dosage, gender, age and drop-out rate

Clinical trials must be carefully planned. According to Sakpal (2010), the basic rules for establishing the size of a clinical trial are level of significance, typically 5%; power, usually ≥ 80%; clinically meaningful differences (smaller differences need a larger sample size); and a search for equivalence or equality. Small clinical trials should be carried out only in cases of rare disorders, unique patient populations or studies requiring participation of patients with terminal, severely debilitating or incapacitating disorders (Evans and Ildstad 2001). Because few studies were eligible for this systematic review, the sample size cut-off was established as $n = 10$, although smaller studies were also retrieved from the databases. Future clinical trials should pay particular attention to this parameter, because it establishes the level of significance and the power of the study.

With regard to dosage, most of the health outcomes targeted in the clinical trials selected show significant benefits in daily consumption of *Arthrospira* biomass for a period varying from 1 to 12 months, with a mode of 2–3 months and a mean of 3.85 months with doses ranging from 0.5 to 20 g day^{-1} with a mode of 1 g day^{-1} and a mean of 7.5 g day^{-1} (Table 2). Dosage was low in most of the works reviewed. Studies on diabetes, hypertension and nutrition applied the highest dosages. Two studies on nutritional status used dosages of 10 and 20 g day^{-1} for children under 5 years, exceeding the ratio of *Arthrospira* intake (g)/weight (kg). The World Health Organisation (WHO) defined a safe level of protein intake for adults of 0.83 g kg^{-1} day^{-1}, irrespective of gender or age. The level is different for children and adolescents, varying from 1.31 to 0.89 g kg^{-1} day^{-1} from birth to adulthood depending on age, weight and height (WHO/FAO/UNU 2007). One gram of optimum quality *Arthrospira* would render 0.7 g of protein, which supports the theory of the current use of *Arthrospira* as a source of antioxidants rather than proteins. More studies are needed to assess the effect of dosage on outcomes.

Some studies included in the review found that *Arthrospira* bioactivity is gender- and age-dependent (Table 2). Improvements in the design and scope of studies would help to determine the correct dosage for a given health condition, gender and age group.

The drop-out rate was not excessively high in the studies. No adverse effects were recorded, which is not surprising given that the Dietary Supplements Information Expert Committee (DSI-EC) of the United States Pharmacopeial Convention (USP) assigned a class A safety rating for *A. maxima* and *A. platensis* after analysing 31 adverse event reports of *Arthrospira* to evaluate potential health concerns (Marles et al. 2011). The main concern expressed by patients was poor palatability.

Quality, the key factor

i. Quality in clinical practice

Arthrospira is a safe and promising dietary supplement to prevent and even treat a range of health conditions, as demonstrated by many of the studies included in this review. However, much work is needed before this organism can occupy the position it deserves and be gainfully applied in nutrition and medicine. Laboratory findings must be translated into scientifically validated health claims to fill the gaps between scientific knowledge, medical practice and consumption habits. This can only be achieved through high quality, controlled clinical trials. The methodology exists, but consistent clinical trials are costly. The quality and scope of most of

the studies found was lower than expected. Only 25 of the 42 studies targeted were eligible for inclusion in the systematic review (Table 1, Fig. 4). The Jadad scale is one of the simplest quality scales in clinical practice (Berger and Alperson 2009), even though more than half the studies retrieved could not be used in the review (Table 1). The Jadad quality criteria (randomisation, blinding and control inclusion) should be the minimum requirements of future studies to ensure irrefutable scientific proof about the benefits of *Arthrospira*, because these results will become the health claims demanded by the food industry. The result of any systematic review is susceptible to selection bias, detection bias, implementation bias and publication bias. The trials included in this study are all randomised control trials but the variety of conditions addressed made a pooled analysis impossible. More accurate results could be obtained through a pooled analysis based on disease progress, course of medication and control group dosage.

ii. Quality of *Arthrospira* biomass used as a supplement

Because the results of this review highlight the antioxidant capacity of *Arthrospira* as its major attribute in the treatment of various health conditions and diseases, the quality of the biomass is a key issue. Dosage is directly related to biomass quality. *Arthrospira* composition, as in all cyanobacteria and microalgae, is strongly affected by the production conditions (Colla et al. 2004; Mühling et al. 2005; Markou 2012; Kepekçi and Saygideger 2012; Kim et al. 2012) and processing (Morist et al. 2001, Tiburcio et al. 2007; Oliveira et al. 2010). Protein content in *Arthrospira* can be as much as 70% of dry weight (Uslu et al. 2009; Falquet 1997). C-phycocyanin and allophycocyanin, the main antioxidants in *Arthrospira*, account for 20% of the protein fraction when this microorganism is cultured under optimum conditions (Avila-Leon et al. 2012). Mass production, dehydration and storage probably reduce the antioxidant content (Torzillo et al. 1984). The safety of *Arthrospira* has been a major concern for authorities. Now that safety guidelines have been established, the scientific and medical community and manufacturers and suppliers need to make a considerable effort to define biochemical quality standards for *Arthrospira* biomass used for therapy.

Conclusion

To our knowledge, this study is the first systematic review to examine the effect of dietary supplementation with *Arthrospira* in various fields of human health. It reveals a variety of health outcomes that benefit from *Arthrospira* consumption. Most of the health outcomes targeted in the clinical trials selected showed significant benefits in daily consumption of *Arthrospira* biomass during a period varying from 1 to 12 months and doses of 0.5–20 g day^{-1}. Some diseases, such as dyslipidaemia, improved by directly recovering proper values, while others such as diabetes and viral infections benefitted from a reduced prevalence of concomitant effects or increased immunity. Our findings also support the theory that the main benefit of *Arthrospira* consumption could be associated with the high antioxidant capacity of this organism, even though manufacturers and suppliers commercialise it as a protein source.

Large randomised, double-blind, placebo-controlled trials are needed before firm, unequivocal conclusions can be drawn about the suitability of *Arthrospira* to improve health conditions. Many variables must be taken into account, including biomass quality, dosage, gender and age. Achieving this will pave the way for more thorough studies that are essential to validate *Arthrospira* health claims.

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References

Abdulqader G, Barsanti L, Tredici MR (2000) Harvest of *Arthrospira platensis* from Lake Kossorom (Chad) and its household usage among the Kanembu. J Appl Phycol 12:493–498

Anitha L, Chandralekha K (2010) Effect of supplementation of *Spirulina* on blood glucose, glycosylated hemoglobin and lipid profile of male non-insulin dependent diabetics. Asian J Exp Biol Sci 1:36–46

Avila-Leon I, Matsudo MC, Sato S, de Carvalho JCM (2012) *Arthrospira platensis* biomass with high protein content cultivated in continuous process using urea as nitrogen source. J Appl Microbiol 112:1086–1094

Ayehunie S, Belay A, Baba TW, Ruprecht RM (1998) Inhibition of HIV-1 replication by an aqueous extract of *Spirulina platensis* (*Arthrospira platensis*). J Acquir Immune Defic Syndr Hum Retrovirol 18:7–12

Baicus C, Tanasescu C (2002) Chronic viral hepatitis, the treatment with spiruline for one month has no effect on the aminotransferases. Rom J Intern Med 40:89–94

Belay A (2002) The potential application of *Spirulina* (*Arthrospira*) as a nutritional and therapeutic supplement in health management. J Amer Neutraceut Assoc 5:27–48

Belay A (2008) Spirulina (Arthrospira): production and quality assurance. In: Gershwin ME, Belay A (eds) *Spirulina* in human nutrition and health. CRC Press, Boca Raton, pp 1–25

Benito JM, López M, Lozano S, Martinez P, González-Lahoz J, Soriano V (2004) CD38 expression on CD8 T lymphocytes as a marker of residual virus replication in chronically HIV-infected patients receiving antiretroviral therapy. AIDS Res Hum Retrovir 20:227–233

Berger VW, Alperson SY (2009) A general framework for the evaluation of clinical trial quality. Rev Recent Clin Trials 4:79–88

Chaplin DD (2006) Overview of the human immune response. J Allergy Clin Immunol 117 (2 Suppl Mini-Primer): S430-S435

Chitsaz M, Mozaffari-Khosravi H, Salman-Roghani H, Zavar-Reza J, Lotfi M (2016) Effect of *Chlorella vulgaris* vs *Spirulina* supplementation on lipid profile and liver function in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Int J Probiotics Prebiotics 11:127–136

Chu W-L, Lim Y-W, Radhakrishnan AK, Lim P-E (2010) Protective effect of aqueous extract from *Spirulina platensis* against cell death induced by free radicals. BMC Complement Altern Med 10:53

Ciferri O (1983) *Spirulina*, the edible microorganism. Microbiol Rev 47: 551–578

Cingi C, Conk-Dalay M, Cakli H, Bal C (2008) The effects of *Spirulina* on allergic rhinitis. Eur Arch Otorhinolaryngol 265:1219–1223

Colla LM, Bertolin TE, Costa JAV (2004) Fatty acids profile of *Spirulina platensis* grown under different temperatures and nitrogen concentrations. Z Naturforsch C 59:55–59

Davies KJ (1995) Oxidative stress: the paradox of aerobic life. Biochem Soc Symp 61:1–31

de la Jara A, Assunção P, Portillo E, Freijanes K, Mendoza H (2016) Evolution of microalgal biotechnology: a survey of the European Patent Office database. J Appl Phycol 28:2727–2740

Deng R, Chow TJ (2010) Hypolipidemic, antioxidant and antiinflammatory activities of microalgae *Spirulina*. Cardiovasc Ther 28(4):e33–e45

Dillon JC, Phuc AP, Dubacq JP (1995) Nutritional value of the alga *Spirulina*. World Rev Nutr Diet 77:32–46

Durand-Chastel H (1980) Production and use of *Spirulina* in Mexico. In: Shelef G, Soeder CJ (eds) Algae biomass. Elsevier/North Holland Biomedical Press, Amsterdam, pp 51–64

El-Baz FK, El-Senousy WM, El-Sayed AB, Kamel MM (2013) In vitro antiviral and antimicrobial activities of *Spirulina platensis* extract. J Appl Pharm Sci 3:052–056

Evans CH, Ildstad ST eds (2001) Small clinical trials: issues and challenges. Committee on Strategies for Small-Number-Participant Clinical Research Trials, Board on Health Sciences Policy, Institute of Medicine. Washington, D.C.: National Academy Press

Falquet J (1997) The Nutritional Aspects of *Spirulina*. Antenna Technologies. http://antenna.ch/en/documents/AspectNut-UK.pdf. Accessed June 2017

Fan YY, Chapkin RS (1998) Importance of dietary γ-linolenic acid in human health and nutrition. J Nutr 128:1411–1414

Ferrari CKB (2012) Effects of xenobiotics on total antioxidant capacity. Interdiscip Toxicol 5:117–122

Ferruzzi MG, Blakeslee J (2007) Digestion, absorption, and cancer preventative activity of dietary chlorophyll derivatives. Nutr Res 27:1–12

Giacco F, Brownlee M (2010) Oxidative stress and diabetic complications. Circ Res 107:1058–1070

Ginaldi L, De Martinis M, D'Ostilio A, Marini L, Loreto MF, Martorelli V, Quaglino D (1999) The immune system in the elderly: II. Specific cellular immunity. Immunol Res 20:109–115

Grobbelaar JU (2003) Quality control and assurance: crucial for the sustainability of the applied phycology industry. J Appl Phycol 15:209–215

Gustafson KR, John H, Cardellina JH, Fuller RW, Weislow OW, Kiser RF, Snader KM, Patterson GML, Boyd MR (1989) AIDS-antiviral sulfolipids from cyanobacteria (blue-green algae). JNCI J Natl Cancer Inst 81:1254–1258

Halpern SH, Douglas MJ, (eds.) (2005) Appendix: Jadad scale for reporting randomized controlled trials. In: Evidence-based obstetric anesthesia. pp: 237–238. Blackwell Publishing Ltd., Oxford, UK

Hayashi K, Hayashi T, Morita N, Kojima I (1993) An extract from *Spirulina* is a selective inhibitor of herpes simplex virus type 1 penetration into HeLa cells. Phytother Res 7:76–80

Hayashi T, Hayashi K, Maeda M, Kojima I (1996) Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga *Spirulina platensis*. J Nat Prod 59:83–87

Hernández-Corona A, Nieves I, Meckes M, Chamorro G, Barron BL (2002) Antiviral activity of *Spirulina maxima* against herpes simplex virus type 2. Antivir Res 56:279–285

Herrera A, Boussiba S, Napoleone V, Hohlberg (1989) Recovery of C-phycocyanin from the cyanobacterium *Spirulina maxima*. J Appl Phycol 1:325–331

Hooijmans CR, Ritskes-Hoitinga M (2013) Progress in using systematic reviews of animal studies to improve translational research. PLoS Med 10(7):e1001482

Horrobin DF (1992) Nutritional and medical importance of gamma-linolenic acid. Prog Lipid Res 31:163–194

Huang Y, Gao L, Xie X (2014) Tan SC (2014) epidemiology of dyslipidaemia in Chinese adults: meta-analysis of prevalence, awareness, treatment, and control. Popul Health Metr 12:28

Ichimura M, Kato S, Tsuneyama K, Matsutake S, Kamogawa M, Hirao E, Miyata A, Mori S, Yamaguchi N, Suruga K, Omagari K (2013) Phycocyanin prevents hypertension and low serum adiponectin level in a rat model of metabolic syndrome. Nut Res 33:397–404

Karkos, PD, Leong SC, Karkos CD, Sivaji N, Assimakopoulos DA (2011) *Spirulina* in clinical practice: evidence-based human applications. Evidence-Based Complement Alternat Med Volume 2011, Article ID 531053, 4 pages

Johnson M, Hassinger L, Davis J, Devor ST, DiSilvestro RA (2016) A randomized, double blind, placebo controlled study of spirulina supplementation on indices of mental and physical fatigue in men. Int J Food Sci Nutr 67(2):203–206

Juárez-Oropeza MA, Mascher D, Torres-Durán PV, Farias JM, Paredes-Carbajal MC (2009) Effects of dietary Spirulina on vascular reactivity. J Med Food 12(1):15–20

Kaur K, Sachdeva R, Grover K (2008) Effect of supplementation of *Spirulina* on blood glucose and lipid profile of the non-insulin dependent diabetic male subjects. J Dairy Foods Home Sci 27: 202–208

Kepekçi RA, Saygideger SD (2012) Enhancement of phenolic compound production in *Spirulina platensis* by two-step batch mode cultivation. J Appl Phycol 24:897–905

Kim E-K, Choi G-G, Kim H-S, Ahn C-Y, Oh H-M (2012) Increasing γ-linolenic acid content in *Spirulina platensis* using fatty acid supplement and light–dark illumination. J Appl Phycol 24:743–750

Kumar P, Desai N, Dwivedi M (2015) Multiple potential roles of *Spirulina* in human health: a critical review. Malaysian J Nutr 21(3):375–387

Labhe RU, Mani UV, Iyer UM, Mishra M, Jani K, Bhattacharya A (2001) The effect of *Spirulina* in the treatment of bronchial asthma. J Nutraceut Funct Med Foods 3:53–60

Lee EH, Park JE, Choi YJ, Huh KB, Kim WY (2008) A randomized study to establish the effects of *Spirulina* in type 2 diabetes mellitus patients. Nutr Res Pract 2:295–300

Li L, Zhao X, Wang J, Muzhingi T, Suter PM, Tang G, Yin S-A (2012) *Spirulina* can increase total-body vitamin A stores of Chinese school-age children as determined by a paired isotope dilution technique. J Nutr Sci 1:1–7

Li XL, Wong YS, Xu G, Chan JC (2015) Selenium-enriched *Spirulina* protects INS-1 pancreatic beta cells from human islet amyloid polypeptide-induced apoptosis through suppression of ROS-mediated mitochondrial dysfunction and PI3/AK pathway. Eur J Nutr 54:509–522

Lobo V, Patil A, Phatak A, Chandra N (2010) Free radicals, antioxidants and functional foods: impact on human health. Pharmacogn Rev 4: 118–126

Lu HK, Hsieh CC, Hsu JJ, Yang YK, Chou HN (2006) Preventive effects of *Spirulina platensis* on skeletal muscle damage under exercise-induced oxidative stress. Eur J Appl Physiol 98:220–226

Mani UV, Desai S, Iyer U (2000) Studies on the long-term effect of *Spirulina* supplementation on serum lipid profile and glycated proteins in NIDDM patients. J Funct Med Foods 2(3):25–32

Mao TK, Van de Water J, Gershwin ME (2005) Effects of a *Spirulina*-based dietary supplement on cytokine production from allergic rhinitis patients. J Med Food 8:27–30

Marcel AK, Ekali LG, Eugene S, Arnold OE, Sandrine ED, von der Weid D, Gbaguidi E, Ngogang J, Mbanya JC (2011) The effect of *Spirulina platensis* versus soybean on insulin resistance in HIV-infected patients: a randomized pilot study. Nutrients 3:712–724

Maritim AC, Sanders RA, Watkins JB (2003) Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol 17:24–38

Markou G (2012) Alteration of the biomass composition of *Arthrospira* (*Spirulina*) *platensis* under various amounts of limited phosphorus. Bioresour Technol 116:533–535

Marles RJ, Barrett ML, Barnes J, Chavez ML, Gardiner P, Ko R, Mahady GB, Dog TL, Sarma ND, Giancaspro GI, Sharaf M, Griffiths J (2011) United States Pharmacopeia safety evaluation of *Spirulina*. Crit Rev Food Sci Nutr 51:593–604

Masuda K, Inoue Y, Inoue R, Nakamura A, Chitundu M, Murakami J, Ota Y, Matsugami J (2014) *Spirulina* effectiveness study on child malnutrition in Zambia. Institute of Development Studies, Brighton, UK

Mathew B, Sankaranarayanan R, Nair PP, Varghese C, Somanathan T, Amma BP, Amma NS, Nair MK (1995) Evaluation of chemoprevention of oral cancer with *Spirulina fusiformis*. Nutr Cancer 24: 197–202

Matondo FK, Takaisi K, Nkuadiolandu AB, Kazadi Lukusa AK, Aloni MN (2016) Spirulina supplements improved the nutritional status of undernourished children quickly and significantly: experience from kisantu, the Democratic Republic of the Congo. Int J Pediatr

Mazokopakis EE, Papadomanolaki MG, Fousteris AA, Kotsiris DA, Lampadakis IM, Ganotakis ES (2014) The hepatoprotective and hypolipidemic effects of Spirulina (Arthrospira platensis) supplementation in a Cretan population with non-alcoholic fatty liver disease: a prospective pilot study. Ann Gastroenterol 27:387–394

McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF (2010) The immune response during acute HIV-1 infection: clues for vaccine development. Nat Rev Immunol 10:11–23

Miczke A, Szulinska M, Hansdorfer-Korzon R, Kregielska-Narozna M, Suliburska J, Walkowiak J, Bogdanski P (2016) Effects of *Spirulina* consumption on body weight, blood pressure, and endothelial function in overweight hypertensive Caucasians: a doubleblind, placebo-controlled, randomized trial. Eur Rev Med Pharmacol Sci 20:150–156

Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S (1995) Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. Control Clin Trials 16(1):62–73

Morist A, Montesinos JL, Cusidó JA, Gòdia F (2001) Recovery and treatment of *Spirulina platensis* cells cultured in a continuous photobioreactor to be used as food. Process Biochem 37:535–547

Mühling M, Belay A, Whitton BA (2005) Variation in fatty acid composition of *Arthrospira* (*Spirulina*) strains. J Appl Phycol 17:137–146

Mulk BS, Deshpande P, Velpula N, Chappidi V, Chintamaneni RL, Goyal S (2013) *Spirulina* and pentoxyfilline—a novel approach for treatment of oral submucous fibrosis. J Clin Diagn Res 7:3048–3050

Mullol J, Bachert C, Bousquet J (2005) Management of persistent allergic rhinitis: evidence-based treatment with levocetirizine. Ther Clin Risk Manag 1:265–271

Ngo-Matip ME, Pieme CA, Azabji-Kenfack M, Biapa PC, Germaine N, Heike E, Moukette BM, Emmanuel K, Philippe S, Mbofung CM, Ngogang JY (2014) Effects of *Spirulina platensis* supplementation on lipid profile in HIV-infected antiretroviral naïve patients in Yaounde-Cameroon: a randomized trial study. Lipids Health Dis 13:191

Ngo-Matip ME, Pieme CA, Azabji-Kenfack M, Moukette BM, Korosky E, Stefanini P, Ngogang JY, Mbofung CM (2015) Impact of daily supplementation of *Spirulina platensis* on the immune system of naïve HIV-1 patients in Cameroon: a 12-months single blind, randomized, multicenter trial. Nutr J 14:70

Oliveira EG, Duarte JH, Moraes K, Crexi VT, Pinto LAA (2010) Optimisation of *Spirulina platensis* convective drying: evaluation of phycocyanin loss and lipid oxidation. Int J Food Sci Technol 45:1572–1578

Ouedraogo HG, Kouanda S, Bationo F, Doulougou B, Ouedraogo/Nikiema L, Lanou H, Tiendrebeogo S, Konseimbo AG, Liestman B, Simpore J, Nikiema J-B, Sondo B (2013) Effects of *Spirulina* supplementation on selected anthropometric, biochemical, and hematological parameters of HIV-infected adults in Ouagadougou, Burkina Faso. Int J Biol Chem Sci 7:607–617

Paakkari I (2002) Cardiotoxicity of new antihistamines and cisapride. Toxicol Lett 127:279–284

Paller CJ, Denmeade SR, Michael A, Carducci MA (2016) Challenges of conducting clinical trials of natural products to combat cancer. Clin Adv Hematol Oncol 14:447–455

Parikh P, Mani U, Iyer U (2001) Role of *Spirulina* in the control of glycemia and lipidemia in type 2 diabetes mellitus. J Med Food 4: 193–199

Park H-J, Lee H-S (2016) The influence of obesity on the effects of *Spirulina* supplementation in the human metabolic response of Korean elderly. Nutr Res Pract 10:418–423

Park HJ, Lee YJ, Ryu HK, Kim MH, Chung HW, Kim WY (2008) A randomized double-blind, placebo-controlled study to establish the effects of *Spirulina* in elderly Koreans. Ann Nutr Metab 52:322–328

Patil S, Al-Zarea BK, Maheshwari S, Sahu R (2015) Comparative evaluation of natural antioxidants *Spirulina* and aloe vera for the treatment of oral submucous. J Oral Biol Craniofac Res 5(1):11–15

Powers SK, Jackson MJ (2008) Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev 88:1243–1276

Ramamoorthy A, Premakumari S (1996) Effect of supplementation of *Spirulina* on hypercholesterolemic patients. J Food Sci Technol 33:124–128

Ramesh S, Manivasgam M, Sethupathy S, Shantha K (2013) Effect of *Spirulina* on antrophometry and bio-chemical parameters in school children. IOSR J Dental Med Sci (IOSR-JDMS) 7(5):11–15

Rizzo M, Kotur-Stevulkevic J, Berneis K, Spinas G, Rini GB, Jelic-Ivanovic Z, Spasojevic-Kalimanowska V, Vekic J (2009) Atherogenic dyslipidaemia and oxidative stress: a new look. Transl Res 153:217–223

Rzymski P, Jaśkiewicz M (2017) Microalgal food supplements from the perspective of Polish consumers: patterns of use, adverse events, and beneficial effects. J Appl Phycol 29:1841–1850

Sakpal TV (2010) Sample size estimation in clinical trial. Perspect Clin Res 1:67–69

Samuels R, Mani UV, Iyer UM, Nayak US (2002) Hypocholesterolemic effect of *Spirulina* in patients with hyperlipidemic nephrotic syndrome. J Med Food 5:91–95

Sekar S, Chandramohan M (2008) Phycobiliproteins as a commodity: trends in applied research, patents and commercialization. J Appl Phycol 20:113–136

Selmi C, Leung PS, Fischer L, German B, Yang CY, Kenny TP, Cysewski GR, Gershwin ME (2011) The effects of *Spirulina* on anemia and immune function in senior citizens. Cell Mol Immunol 8:248–254

Serban MC, Stoichescu-Hogea G, Gurban C, Petcu F, Jeyakumar D, Andrica F, Munteanu C, Dragan S (2015) The role of *Spirulina platensis* in the control of type 2 diabetes mellitus. Physiology 86: 27–31

Serban MC, Sahebkar A, Dragan S, Stoichescu-Hogea G, Ursoniu S, Andrica F, Banach M (2016) A systematic review and meta-analysis of the impact of *Spirulina* supplementation on plasma lipid concentrations. Clin Nutr 35:842–851

Shetty P, Shenai P, Chatra L, Rao PK (2013) Efficacy of *Spirulina* as an antioxidant adjuvant to corticosteroid injection in management of oral submucous fibrosis. Indian J Dent Res 24:347–350

Shi L, Hu J, Zhu K, Fu Y, Xia R, Hu X (2014) Changes of prevalence of dyslipidaemia among adults: a cross-sectional study with a 2-year follow-up in urban southeast China. Clin Lipidol 9:33–47

Shimamatsu H (2004) Mass production of *Spirulina*, an edible microalga. Hydrobiologia 512:39–44

Shin D-H, Martinez SS, Parsons M, Jayaweera DT, Campa A, Baum MK (2012) Relationship of oxidative stress with HIV disease progression in HIV/HCV co-infected and HIV mono-infected adults in Miami. Int J Biosci Biochem Bioinformat 2:217–223

Simpore J, Zongo F, Kabore F, Dansou D, Bere A, Nikiema J-B, Pignatelli S, Biondi DM, Ruberto G, Musumeci S (2005) Nutrition rehabilitation of HIV-infected and HIV-negative undernourished children utilizing *Spirulina*. Ann Nutr Metab 49:373–380

Simpore J, Kabore F, Zongo F, Dansou D, Bere A, Pignatelli S, Biondi DM, Ruberto G, Musumeci S (2006) Nutrition rehabilitation of undernourished children utilizing Spiruline and Misola. J Nutr 5:3

Siva Kiran RR, Madhu GM, Satyanarayana SV (2015) *Spirulina* in combating protein energy malnutrition (PEM) and protein energy wasting (PEW)—a review. J Nut Res 3:62–79

Soni A, Dubey M, Verma M, Dhankhar R, Kaushal V, Atri R, Sabharwal R (2015) Revisiting the role of phycocyanin in current clinical practice. Int J Pharm Sci Res 6:4588–4600

Sosa V, Moliné T, Somoza R, Paciucci R, Kondoh H, Lleonart ME (2013) Oxidative stress and cancer: an overview. Ageing Res Rev 12:376–390

Teas J, Irhimeh MR (2012) Dietary algae and HIV/AIDS: proof of concept clinical data. Appl Phycol 24:575–582

Tiburcio PC, Galvez FCF, Cruz LJ, Gavino VC (2007) Optimization of low-cost drying methods to minimize lipid peroxidation in *Spirulina platensis* grown in the Philippines. J Appl Phycol 19:719–726

Tomaselli L (1997) Morphology, ultrastructure and taxonomy of *Arthrospira* (*Spirulina*) *maxima* and *Arthrospira* (*Spirulina*) *platensis*. In: Vonshak A (ed) *Spirulina platensis* (*Arthrospira*): physiology, cell-biology and biochemistry. Taylor & Francis, London, pp 1–15

Torres-Duran PV, Aldo Ferreira-Hermosillo A, Juarez-Oropeza MA (2007) Antihyperlipemic and antihypertensive effects of Spirulina maxima in an open sample of mexican population: a preliminary report. Lipids Health Dis 6:33

Torres-Durán PV, Ferreira-Hermosillo A, Ramos-Jimenez A, Hernandez-Torres RP, Juarez-Oropeza MA (2012) Effect of *Spirulina maxima* on postprandial lipemia in young runners: a preliminary report. J Med Food 15:753–757

Torzillo G, Giovannetti L, Bocci F, Materassi R (1984) Effect of oxygen concentration on the protein content of *Spirulina* biomass. Biotechnol Bioeng 26:1134–1135

Tóth PP, Potter D, Ming EE (2012) Prevalence of lipid abnormalities in the United States: the National Health and Nutrition Examination Survey 2003–2006. J Clin Lipidol. 6(4):325–30

Uslu LH, Işık O, Sayın S, Durmaz Y, Göksan T, Gökpınar S (2009) The effect of temperature on protein and amino acid composition of *Spirulina platensis*. EU J Fish Aquat Sci 26:139–142

Wells ML, Potin P, Craigie JS, Raven JA, Sabeeha S, Merchant SS, Helliwell KE, Smith AG, Camire ME, Brawley SH (2017) Algae as nutritional and functional food sources: revisiting our understanding. J Appl Phycol 29:949–982

Winter FS, Emakam F, Kfutwah A, Hermann J, Azabji-Kenfack M, Krawinkel MB (2014) The effect of *Arthrospira platensis* capsules on CD4 T-cells and antioxidative capacity in a randomized pilot study of adult women infected with human immunodeficiency virus not under HAART in Yaoundé, Cameroon. Nutrients 6:2973–2986

World Health Organization, Food and Agriculture Organization, United Nations University. Protein and amino acid requirements in human nutrition: Report of a Joint WHO/FAO/UNU Expert Consultation. Geneva, Switzerland: World Health Organization; 2007. WHO Technical Report Series 935

Yan S-G, Zhu L-P, Su H-N, Zhang X-Y, Chen X-L, Zhou B-C, Zhang Y-Z (2011) Single-step chromatography for simultaneous purification of C-phycocyanin and allophycocyanin with high purity and recovery from *Spirulina* (*Arthrospira*) *platensis*. J Appl Phycol 23:1–6

Yu B, Wang J, Suter PM, Russell RM, Grusak MA, Wang Y, Wang Z, Yin S, Tang G (2012) *Spirulina* is an effective dietary source of zeaxanthin to humans. Br J Nutr 108:611–619

Zeinalian R, Farhangi MA, Shariat A, Saghafi-Asl M (2017) The effects of *Spirulina platensis* on anthropometric indices, appetite, lipid profile and serum vascular endothelial growth factor (VEGF) in obese individuals: a randomized double blinded placebo controlled trial. BMC Complement Altern Med 17:225

Zwiri AMA, Patil S, Yadav N (2015) Comparative evaluation of newer drugs Pentoxifylline and Spirulina in the management of OSMF. Int J Pharmacol Toxicol 5(3):141–145