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Review

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Tomas Lafarga, José María Fernández-Sevilla, Cynthia González-López,
Francisco Gabriel Acién-Fernández

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***Spirulina* for the food and functional food industries**

Tomas Lafarga *, José María Fernández-Sevilla, Cynthia González-López, and Francisco Gabriel Acién-Fernández

Department of Chemical Engineering, University of Almeria, 04120, Almeria, Spain.

* lpt365@ual.es

Abstract

Humans are no strangers to the consumption of *Spirulina* as already in the sixteenth century *Spirulina* was harvested from Lake Texcoco and consumed in markets in Tenochtitlan (today Mexico City). Nowadays, microalgae are being incorporated into many food formulations. Most of these use microalgae as a marketing strategy or as a colouring agent. However, *Spirulina* (and compounds derived thereof) show potential for being used as ingredients in the development of novel foods, which are one of the top trends in the food industry. Several human intervention studies demonstrated the potential of *Spirulina* for being used in the prevention or treatment of disorders related to metabolic syndrome. The aim of the current paper was to review current and potential applications of this microalga in the food and functional food industries. Health benefits associated with consuming *Spirulina* and/or some of the most important compounds derived from *Spirulina* were also discussed.

Keywords: Microalgae, Cyanobacteria, alternative proteins, bioactive peptides, phycocyanin, marine biotechnology.

1. Introduction

Cyanobacteria, also known as blue-green algae, are a phylum of microorganisms that are related to bacteria but are capable of performing photosynthesis. For this reason, cyanobacteria are generally included into the group of microalgae - although the former are prokaryotes and the algae term should be restricted to eukaryotes. These microorganisms are generally unknown to the general public but humans owe life to the millions of years of photosynthetic activity by cyanobacteria: they were the first group of microorganisms that evolved to fix atmospheric carbon dioxide into organic carbon (Belay, 2008). Millions of years later, humans continue to take advantage of their ability to fix carbon dioxide and produce organic matter as microalgae are being mass cultured for a wide range of industrial applications (Spolaore, Joannis-Cassan, Duran, & Isambert, 2006).

The most well-known genus is *Spirulina*, which is a trade name given to describe mainly two species of cyanobacteria: *Arthrospira platensis* and *Arthrospira maxima*. *Spirulina* is the most cultivated microalga worldwide - over 30% of the world microalgal biomass production is from *Spirulina* (Costa et al., 2019). *Spirulina* is mainly known because of its high protein content, which is around 60% on a dry weight basis (Rosa, Moraes, Cardias, Souza, & Costa, 2015). However, this valuable resource is also a rich source of other high value-added compounds such as chlorophylls, carotenoids, and phycobiliproteins. All of these are coloured compounds that have potential applications in the food industry as pigments. Despite not being as stable as their synthetic counterparts, *Spirulina*-derived pigments have the added advantage of exerting potential health benefits upon ingestion as, for example, carotenoids possess provitamin A activity and their consumption has been associated with enhanced immune system and reduced risk of developing degenerative chronic diseases, cardiovascular diseases, and some types of cancer (Rodriguez-Concepcion et al., 2018).

Spirulina is one of the top trends in the food industry (Lafarga, 2019a). Humans are no strangers to the consumption of *Spirulina* as already in the sixteenth century *Spirulina* was harvested from Lake Texcoco and consumed in markets in Tenochtitlan (today Mexico City). It wasn't until 1967 that *Spirulina* was recognised as a source of food for the future by the International Association of Applied Microbiology (Costa et al., 2019). Nowadays, microalgae are being incorporated into many food formulations, leading to a significant increase in the number of food products containing microalgae that have been launched into the market – although most of these use microalgae as a colouring agent or as a marketing strategy (Lafarga, 2019a). Most of the biomass of *Spirulina* being produced today is consumed as a nutritional supplement promoted as a “superfood” and sold as a dried powder, flakes, or capsules (Lafarga, 2019a). *Spirulina* has been certified as Generally Recognised as Safe (GRAS) – GRN No. 127 - by the United States (US) Food and Drug Administration (FDA) and, because of its long history of use, it can also be commercialised in the European Union (EU) without the need to comply with Regulation (EU) 2015/2283 on novel foods (EU, 2015). Because of its composition and because of the health benefits associated with consuming *Spirulina* (or compounds derived thereof), *Spirulina* shows potential to become an important food in the future and to be used as an ingredient in the development of functional foods. The aim of the current paper was to review current and potential applications of the microalga *Spirulina* in the food and functional food industries. Health benefits associated with consuming *Spirulina* and/or some of the most important compounds derived from *Spirulina* are also discussed.

2. Chemistry and biochemistry of *Spirulina*: What makes *Spirulina* so valuable?

2.1 Macromolecular composition

Main microalgae photosynthetic products are proteins, carbohydrates, and lipids. While proteins are associated with functions of biosynthesis and cell division, carbohydrates and lipids serve mainly as intracellular reservoirs of carbon and energy (Dean, Estrada, Nicholson, & Sigeo, 2008). Although there are thousands of microalgae strains available in culture collections worldwide, only a few of them have been studied in detail (Garrido-Cardenas, Manzano-Agugliaro, Acien-Fernandez, & Molina-Grima, 2018). Within those that have been studied, there are significant differences in the main macromolecular pools (proteins, carbohydrates, and lipids) across the different phyla of microalgae (Figure 2). Thus, to calculate an average macromolecular composition for microalgae is not easy. In a very pioneer work by Parsons, Stephens, and Strickland (1961) on eleven species of microalgae, the authors established that protein is 17-57% (39% on average), carbohydrate is 4-37% (23% on average), and lipids is 2-18% (8% on average) of dry weight. Moreover, in a more recent publication by Finkel et al. (2016), the authors conducted a hierarchical Bayesian analysis of data compiled from 130 scientific publications found in the literature and reported the median macromolecular composition of nutrient-sufficient exponentially growing microalgae as 32.2% protein, 17.3% lipid, 15.0% carbohydrate, and 17.3% ash on a dry weight basis (Figure 2).

In the above-mentioned study by Finkel et al. (2016), the authors reported that when compared to eukaryotic microalgal phyla, cyanobacteria have higher protein and carbohydrate (43.1 and 21.8%, respectively) and lower lipid and ash (11.7 and 8.1%, respectively) as percent dry weight. As an example, the composition of a commercial *Spirulina* powder can be observed in Table 1. These values must be taken with caution as the composition of the microalgal biomass can be strongly affected not only by phyla but also by

environmental and cultivation conditions (temperature, irradiance, light-dark cycle, salinity, culture medium composition, etc.) – and consequently, it can be modulated (Lafarga, 2019b). Indeed, a large number of studies reported to date demonstrated that culturing microalgae under nutrient starvation/limitation causes important biomass composition alterations. Probably the most common manipulation strategy is related to the nitrogen nutrient limitation (Markou, 2012). Nitrogen starvation leads to an increase in lipids accumulation because of alterations in the metabolic pathways of microalgae (Li, Horsman, Wang, Wu, & Lan, 2008). This strategy has been studied mainly for the production of microalgae with high lipid content for its potential use in the production of biodiesel. Moreover, Markou, Chatzipavlidis, and Georgakakis (2012) described that phosphorous limitation in cultures of *S. platensis* leads to increased carbohydrate and lipid content. Not only lipid content but also the fatty acid composition of *Spirulina* is influenced by environmental or growth conditions (Mühling, Belay, & Whitton, 2005). Some of the most common lipids found in *Spirulina* include γ -linolenic acid (18:3, n-6) from omega-6 family and palmitic acid (16:0), shown in Figure 1 (Ljubic, Safafar, Holdt, & Jacobsen, 2018). The former has attracted attention worldwide because of its medicinal potential to prevent cardiovascular diseases, hypercholesterolaemia, and other disorders (Barron, Torres-Valencia, Chamorro-Cevallos, & Zuñiga-Estrada, 2008). Depending on the strain cultured, the content of linoleic and γ -linolenic acid varies within 13.1-31.5 and 12.9-39.4% of total fatty acids respectively (Mühling, Belay, & Whitton, 2005). Other valuable lipids present in *Spirulina* at lower concentrations include the polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA, 20:5, n-3) and docosahexaenoic acid (DHA, 22:6, n-3) (Matos et al., 2016). These are essential components of a healthy and balanced diet and have health benefits on development of the neural system and in mitigating a number of pathologies (Tocher, Betancor, Sprague, Olsen, & Napier, 2019).

In the above-mentioned study by Markou et al. (2012), the authors observed that although proteins contain similar calorific values than carbohydrates, as their synthesis is more energy/ATP consuming, the protein content of the biomass decreased as the phosphorous became limited. Similar results were observed by Dean et al. (2008). Cyanobacteria have an especially high protein content (Finkel et al., 2016). Indeed, it was their high protein content what made *Spirulina* the most well-known microalga, at least for an average consumer. Several food products enriched in *Spirulina*-derived proteins currently being commercialised have been reviewed by Lafarga (2019b). *Spirulina* has one of the highest protein contents ever found as well as a high content of essential amino acids based on the FAO and World Health Organization (WHO) composition of an “ideal” protein (Morist, Montesinos, Cusidó, & Gòdia, 2001). The amino acid composition of *Spirulina* proteins is shown in Table 1. The protein content of *Spirulina* can reach up to 70% on a dry weight basis when it is cultivated under conditions not limited by nitrogen (Danesi, Rangel-Yagui, De Carvalho, & Sato, 2002). However, Sassano et al. (2010) reported that the highest protein and lipid content in *A. platensis* was obtained by increasing the rate of nitrogen supply up to a maximum threshold level (10 mol/m³), beyond which the excess nitrogen became toxic. The most relevant proteins found in *Spirulina* are phycobiliproteins namely phycocyanin, allophycocyanin, and phycoerythrin shown in Figure 1. These are bright blue (phycocyanin and allophycoerythrin) and fuchsia (phycoerythrin) and, depending on their purity, these molecules can have high commercial value for their use in the nutraceutical, cosmetic, pharmaceutical, textile, or food industries. Because of their biological health-promoting properties and their potential for being used in the development of functional foods, these molecules will be described in more detail in the following sections of this manuscript.

2.2 Other compounds

Spirulina is also valued for the presence of several minerals and vitamins. Most commonly reported minerals include potassium, calcium, magnesium, selenium, iron, zinc, and many more (Carcea et al., 2015). Moreover, *Spirulina* is also a rich source of vitamins, especially of B vitamins. B vitamins are eight unique water-soluble coenzymes that play a key role in DNA repair, electron transfer, fatty acid synthesis, and one-carbon metabolism (Monteverde, Gómez-Consarnau, Suffridge, & Sañudo-Wilhelmy, 2017). Microalgae are unable to grow in aquatic environments only with light and inorganic nutrients and therefore they depend on the availability of some B vitamins. Apart from those listed in Table 1, vitamin B12 has also been detected in some algae - although the majority of cyanobacteria contain an inactive corrinoid known as pseudo-vitamin B12 (Watanabe, Yabuta, Tanioka, & Bito, 2013). Edelmann, Aalto, Chamlagain, Kariluoto, and Piironen (2019) recently assessed the vitamin B12 content of several microalgae-based dietary supplements and concluded that although most of the vitamin B12 in commercial *Spirulina* powders was in the non-active pseudo form, daily requirements could still be met by consuming 4 g of dried biomass.

Other compounds present in *Spirulina* that are strongly related to vitamins are carotenoids: certain carotenoids, which are a class of pigments naturally synthesized by microalgae, act as provitamins A. This means that some carotenoids may be converted *in vivo* by our bodies into vitamin A. Vitamin A is essential for general growth promotion, visual function, regulation of differentiation of epithelial tissues, and embryonic development (Tang, 2010). Carotenoids are key compounds in Western diets: approximately 30% of daily vitamin A intake derives from carotenoids (Tang, 2010). Carotenoids present in *Spirulina* include astaxanthin, zeaxanthin, and β -carotene. Ljubic et al. (2018) recently reported the zeaxanthin, β -carotene, and astaxanthin content of *A. platensis* as 1.46, 1.74, and 0.43 mg/g on a dry weight basis. Other carotenoids identified in *Spirulina* include canthaxanthin and lutein, although they are generally present at lower concentrations (Hynstova et al., 2018). Natural carotenoids are

preferred to synthetic compounds because the former are a mixture of trans and cis isomers while the latter are usually all-trans isomers (Cerón-García et al., 2018). Finally, another valuable pigment that can be obtained from *Spirulina* is chlorophyll, which is present at a concentration of approximately 6.0-20.0 mg/g of dry weight (Rangel-Yagui, Danesi, de Carvalho, & Sato, 2004). This pigment is green-coloured and can be used not only as a colourant but also as an ingredient with potential health benefits. Indeed, Zepka, Jacob-Lopes, and Roca (2019) recently reported antimutagenic, chemoprotective, antioxidant, anti-inflammatory, and antimicrobial properties as well as potential uses of chlorophyll as photosensitisers.

Overall, depending on the culturing conditions, *Spirulina* can be a valuable source of proteins, polyunsaturated fatty acids, minerals, and/or vitamins. Culturing conditions are important not only to promote biomass productivity or the content of these valuable molecules but also to prevent growth of unwanted microorganisms (Großhagauer, Kraemer, & Somoza, 2020).

3. *Spirulina* in traditional foods

Previous reports suggested that microalgae utilisation in the food industry faced some challenges including an intense (generally green) colour and flavour. In order to overcome these issues, strategies such as encapsulation have been studied. Recently, da Silva et al. (2019) evaluated the potential of *Spirulina* encapsulated using maltodextrin or maltodextrin crosslinked with citric acid for being used as an ingredient in yoghurt and concluded that the latter showed not only higher thermal stability and antioxidant and anti-inflammatory activity but also led to a more homogeneous appearance of the product. Chacón-Lee and González-Mariño (2010) suggested that a solution to these challenges could reside in incorporating microalgae into exotic-flavoured snacks and foods as well as in masking flavour using traditional Asian and Indian spices. This would promote consumption of microalgae by Western consumers which are not generally used to consume algae. *Spirulina* has been effectively incorporated into a large number of Indian foods by Iyer, Dhruv, and Mani (2008). The authors of that study concluded that the biomass of *Spirulina* can be effectively incorporated into Indian recipes (over 30 different products) obtaining both, sensorial attributes that were well accepted by consumers, and products with improved nutritional quality such as lower glycaemic and lipemic responses when compared to the same foods formulated without *Spirulina*. Nowadays, consumers demand for innovative and sophisticated products and *Spirulina* has positioned firmly in the food market (Lafarga, 2019a). The green colour of *Spirulina* could be an opportunity to innovate and satisfy consumer demands – many large food companies have gone “green” during the last decade and commercialise green-coloured foods and beverages. Moreover, previous studies suggested that the “fishy” aroma and flavour of some microalgae, mainly marine species, could be an opportunity to develop innovative fish-based culinary preparations (Mónica Fradique et al., 2013). Indeed, the Spanish company Fitoplancton Marino S.L. (Cadiz, Spain)

is commercialising the freeze-dried biomass of *Tetraselmis chunii* under the name *Plancton Marino Veta la Palma*[®] to accentuate the marine flavour of foods.

3.1 Food products containing *Spirulina*

There are numerous records of historical utilisation of *Spirulina* in the human diet. It has been used for centuries in Chad, known in the local language as *dihé*, for everyday food and Aztecs prepared dry *Spirulina* cakes known in the local language as *tecuitlatl* (Gantar & Svirčev, 2008). Several studies assessed the effect of incorporating microalgae into traditional food recipes. Most commonly used microalgae include *Chlorella* (Gouveia, Batista, Miranda, Empis, & Raymundo, 2007; Graça, Fradinho, Sousa, & Raymundo, 2018; Nunes et al., 2020; Uribe-Wandurraga, Igual, García-Segovia, & Martínez-Monzó, 2019), *Nannochloropsis* (Durmaz et al., 2020; Gheysen, Lagae, et al., 2019; Lafarga, Mayre, et al., 2019), *Tetraselmis* (Batista et al., 2019; García-Segovia, Pagán-Moreno, Lara, & Martínez-Monzó, 2017; Lafarga, Acién-Fernández, et al., 2019; Lafarga, Mayre, et al., 2019), *Porphyridium* (Durmaz et al., 2020), *Isochrysis* (Babuskin et al., 2015; Mónica Fradique et al., 2013; Gheysen, Demets, et al., 2019; Gouveia et al., 2008), and *Haematococcus* (Gouveia, Raymundo, Batista, Sousa, & Empis, 2006; Hossain et al., 2017) although only those foods formulated using *Spirulina* will be discussed in the current paper.

Most commonly studied food matrices include cereal-based products such as pasta, bread, or biscuits. Recently, Niccolai et al. (2019) assessed the potential of *Spirulina* for being used as an ingredient in the development of sourdough *crostini* (toasted bread). Concentrations evaluated ranged between 2 and 6%. Authors reported that although doughs reached a lower volume when compared to the control, the products containing microalgae showed no differences in the microorganism concentrations and an increased content of protein and polyphenols as well as a higher antioxidant capacity. Uribe-Wandurraga et al. (2019) enriched breadsticks in minerals and concluded that when *Spirulina* is incorporated at a

concentration of 1.5%, the product can be classified as “high in iron and selenium food”. Moreover, Batista et al. (2017) evaluated the effect of incorporating *A. platensis* into cookies at microalgae concentrations ranging between 2 and 6% and reported that besides obtaining an attractive and innovative appearance, which was well accepted by the consumers after a sensorial analysis, the biscuits showed higher content of polyphenols and an improved antioxidant capacity. In addition, incorporation of microalgae did not affect the digestibility of the products. Similar results were obtained by De Marco, Steffolani, Martínez, and León (2014) who obtained a similar glycaemic index together with higher phenolic and protein content in pasta after incorporating *Spirulina* at a concentration of 5-20% into the recipe. Monica Fradique et al. (2010) also developed *Spirulina*-enriched pasta at *Spirulina* concentrations of 0.5-2.0% and reported not only a higher sensorial acceptance when compared to the control product but also no effect on the techno-functional properties of the products. The potential of *Spirulina* for being used in gluten-free pasta was studied by Fradinho et al. (2020). In that study, the authors reported increased content of phenolic compounds, chlorophylls, and carotenoids as well as no textural modifications after incorporation of the microalgal biomass into the recipes. Microalgal concentrations evaluated ranged between 1 and 15%, although those containing *Spirulina* at a concentration of 2% were preferred by the panellists after a sensorial analysis. In that study, the authors observed that the drying method used for dehydration of the biomass had an effect on the overall nutritional value of the products. Future studies should consider the effect of biomass processing on the quality of the end products as, for example, Bernaerts et al. (2020) recently observed that a cell disruption step can improve the bioaccessibility of carotenoids after digestion. Similar results were observed by Cavonius, Albers, and Undeland (2016) who concluded that biomass processing is important to produce a product that has beneficial nutritional properties when applied as food.

Other common food group used as delivery vehicle of *Spirulina* includes snacks and dairy products. For example, Lucas, de Moraes, Santos, and Costa (2018) manufactured extruded snacks containing *Spirulina* at a concentration of 2.6% and reported high sensorial acceptance and a higher content of both, total protein and digestible protein. High microalgae concentrations can lead to reduced physicochemical quality parameters. Moreover, Barkallah et al. (2017) developed a yoghurt containing *Spirulina* at concentrations within the range 0.25-1.00%, which showed higher protein and fibre content together with better water holding capacity and lower whey syneresis during storage. Incorporating microalgae into yoghurt could have an added advantage as Beheshtipour, Mortazavian, Haratian, and Darani (2012) observed that yoghurt containing *Spirulina* at a concentrations of 0.5-1.0% showed slower pH decline and an increased and sustained viability of *Lactobacillus acidophilus* and *Bifidobacterium lactis* at the end of fermentation and refrigerated storage. Similar results were observed by Varga, Szigeti, Kovács, Földes, and Buti (2002) who reported that *A. platensis* had a beneficial effect on the survival of *L. acidophilus*, *Streptococcus thermophilus*, and bifidobacteria regardless of the storage temperature. Çelekli, Alslibi, and üseyin Bozkurt (2019) recently highlighted the potential of *Spirulina* for being used as an ingredient for the manufacture of *ayran*, a cold Turkish beverage containing yogurt. In that study, the authors reported an increased protein content and growth of probiotics after incorporation of *Spirulina* at a concentration of 1%. Similar results were reported by Patel et al. (2019) who also reported higher carotenoid and chlorophyll content in *Spirulina*-containing yoghurt. *Spirulina* was also effectively incorporated into other dairy products such as cheese (Golmakani, Soleimani-Zad, Alavi, Nazari, & Eskandari, 2019).

Because of their high protein content, *Spirulina* was also evaluated as a potential meat substitute, which is one of the top trends in the food industry. Marti-Quijal et al. (2019) recently assessed the potential of *Spirulina* on the physicochemical properties of fresh pork

sausages and concluded that although colour and texture were significantly affected, the nutritionally favourable amino acid content and composition could lead to their use as alternatives to soy protein. Similar results were observed by Marti-Quijal et al. (2019) and Thirumdas et al. (2018). Palanisamy, Töpfl, Berger, and Hertel (2019) manufactured lupin-based protein meat analogues containing *Spirulina* at a concentration of 15, 30, or 50% and reported that *Spirulina* increased the total phenolic and flavonoid content as well as the antioxidant capacity of the end products. *Spirulina* was also used to enrich vegetable-based foods, most commonly in naturally green products such as broccoli soup (Lafarga, Acién-Fernández, et al., 2019) and green smoothies (Castillejo et al., 2018). Microalgae-derived compounds such as protein concentrates (Lupatini Menegotto et al., 2019) have also been studied as food ingredients and suggest their potential utilisation in the development of novel foods.

All of these potential techno-functional, nutritional, and sensorial benefits or innovations gained after incorporating microalgae into foods led to a number of novel food products enriched in *Spirulina* launched into the market. These were recently reviewed by Lafarga (2019a), who concluded that most common food matrices were beverages and baked products such as crackers or biscuits. Examples include *Spirulina* filled crackers (Lee biscuits, Malaysia) and Extreme green smoothie (Happy Planet Foods, Canada). Overall, the amount of *Spirulina* generally being incorporated into foods depends on the food matrix used as delivery vehicle. High biomass concentrations can lead to technological limitations such as lower volume (O'Shea & Gallagher, 2019) or acceptance (Tańska, Konopka, & Ruszkowska, 2017).

4. *Spirulina* and the functional foods industry

Functional foods are a relatively new food category that promise health benefits after consuming the product that go beyond basic nutrition. The concept of functional foods started in Japan in 1984 with the launch of large-scale government-funded research projects on “Systematic analyses and development of functional foods” (Lafarga & Hayes, 2017). Since then, the functional foods market has been growing constantly and it is likely to continue to grow in the future. The development and marketing of functional food products can be, however, challenging when compared to other foods that conventionally have a high “healthy” image (Urala & Lähteenmäki, 2004). *Spirulina* has potential to be used in the development of functional foods because of the large number of health-promoting benefits associated to its consumption. Different studies support that *Spirulina* and compounds derived thereof have therapeutic applications in non-communicable disease such as diabetes mellitus, hyperlipidaemia, oxidative stress-induced diseases, inflammations, allergies, hypertension, and some types of cancer (Gershwin & Belay, 2008). However, scientifically proved substantiation about the health-promoting benefits of *Spirulina* will be required when manufacturers develop specific functional products containing *Spirulina*. Functional foods are regulated in Japan and in the US by the Japanese Ministry of Health and Welfare and by the FDA, respectively. In the EU, functional foods are controlled by the European Food Safety Authority (EFSA), which demands for a substantial scientific validation of the health benefits of consuming bioactive ingredients before a health claim can be made for EFSA approval.

4.1 *Spirulina* and metabolic syndrome

As highlighted previously, several scientific publications suggested positive health outcomes of *Spirulina* in hypertension, type-2 diabetes, some types of cancer, obesity, hyperglycaemia, or hypercholesterolemia (Gershwin & Belay, 2008). *Spirulina* consumption also shows

potential for disease prevention and, for example, had positive effects on upper respiratory infection morbidity prevention and motor milestone acquisition among Zambian infants (Masuda & Chitundu, 2019). The current manuscript will focus on those related to metabolic syndrome, a combination of medical disorders which increase the risk of suffering from cardiovascular disease, namely diabetes, obesity, hypertension, lipid disorders and alterations in the thrombotic potential related to insulin resistance and hyperinsulinemia (Fulop, Tessier, & Carpentier, 2006), and on those conducted on humans. Huang, Liao, Pu, and Cui (2018) recently summarised a number of human intervention studies published between 1996 and 2018 and concluded that, overall, the number of participants ranged between 20 and 169, the studied doses varied between 1 and 19 g of *Spirulina* per day, and the duration of the interventions varied from 2 to 24 weeks.

4.1.1 High blood pressure

Metabolic syndrome is a clustering of metabolic abnormalities such as obesity, hyperglycaemia, dyslipidaemia, and arterial hypertension. Hypertension, also known as high blood pressure, is considered to be one of the most relevant cardiovascular risk factors and is a major cause of premature death worldwide – according to the World Health Organization over a billion people suffer from this condition, 1 in 4 men and 1 in 5 women. *Spirulina* and compounds derived thereof have shown potential for being used in the treatment or prevention of hypertension and other disorders related to cardiovascular health. Most of the studies carried out to date were performed in animal models. Recently, Arthur-Ataam et al. (2019) reported that consumption of *Spirulina* attenuated arterial blood pressure of spontaneously hypertensive rats and improved vascular reactivity, both effects associated a reduction in arterial thickness and stiffness. Moreover, Miczke et al. (2016) conducted a randomised double-blind placebo-controlled trial with patients with hypertension and reported a significant reduction of the systolic blood pressure and in the stiffness index in the

group of patients who received 2 g of *Spirulina* per day during three months. The antihypertensive activity of *Spirulina* has been partially attributed to its high protein content and to the potential release of bioactive peptides with angiotensin-I-converting enzyme (ACE-I; EC 3.4.15.1) and/or renin (3.4.23.15) inhibitory activities. Bioactive peptides are short sequences of generally 2-30 amino acids in length, that are inactive within the sequence of the parent protein but have positive health outcomes on systems of the body once released (Lafarga, Álvarez, & Hayes, 2017). Several bioactive ACE-I or renin inhibitory peptides have been obtained from *Spirulina*. For example, Anekthanakul, Senachak, Hongsthong, Charoonratana, and Ruengjitchatchawalya (2019) used *in silico* and *in vitro* methods to identify an ACE-I inhibitory peptide sequenced as IRDLDY. This peptide showed an IC₅₀ value of 1.75 mM (concentration needed to inhibit the activity of an enzyme by half) and was reported to be non-toxic to human cells. The peptides IQP and VEP, with *in vitro* ACE-I inhibitory properties were demonstrated to lower blood pressure after oral administration in spontaneously hypertensive rats (Jun Lu et al., 2011; J Lu et al., 2011; Pan et al., 2015). These peptides were demonstrated to be absorbed intact through Caco-2 cell monolayers with Papp values of $7.48 \pm 0.58 \times 10^{-6}$ and $5.05 \pm 0.74 \times 10^{-6}$ cm/s for IQP and VEP respectively – Figure 3 (He et al., 2018). Caco-2 monolayer is widely used as a well-established model of the intestinal epithelium to assess transepithelial transport of peptides and other molecules. Moreover, Carrizzo et al. (2019) demonstrated that *A. platensis* induced direct endothelial nitric oxide-mediated vasorelaxation of resistance vessels in mice and attributed this effect to a peptide generated after a simulated gastrointestinal digestion and sequenced as GIVAGDVTPI. The peptide GIVAGDVTPI also showed antihypertensive effects after oral administration in mice.

Overall, bioactive peptides derived from *Spirulina* show potential for being used in the development of novel functional foods in the EU, as several functional foods containing

peptides are currently being commercialised in Japan. For example, Calpis sour milk (Calpis Food Industry Co. Ltd., Japan) which contains the antihypertensive peptides IPP and VPP is currently being commercialised as a functional beverage in Japan. However, despite the large number of scientific evidences suggesting their blood pressure-lowering effects *in vivo*, a review carried out by EFSA concluded that a cause and effect relationship between consumption of IPP and VPP and maintenance of normal blood pressure could not be established (Lafarga & Hayes, 2017). Thus, more efforts are needed together with scientific evidences in order to obtain an approved health claim for peptides in the EU.

4.1.2 Diabetes

Diabetes is a chronic metabolic disease characterised by elevated blood glucose levels and which leads to serious damage to the heart, blood vessels, eyes, and kidney. According to the World Health Organization, about 422 million people worldwide have diabetes and 1.6 million deaths per year can be directly attributed to diabetes. Hamedifard et al. (2019) recently performed a systematic review and a meta-analysis to evaluate the effect of *Spirulina* on glycaemic control in patients with metabolic syndrome and concluded that supplementation of diets with *Spirulina* can reduce fasting plasma glucose and insulin concentrations – weighted mean differences were found to be 10.31 and -0.53. Antidiabetic potential of *Spirulina* is caused by its potential to reduce the rise in blood glucose levels and lipid profile and has been attributed to their content of PUFAs as well as to the generation of peptides with dipeptidyl peptidase-IV (DPP-IV; EC 3.4.14.5) inhibitory activity. For example, Wan et al. (2019) reported an improvement in glucose tolerance as well as altered gut microbiota composition after an 8-week high-fat high-sucrose diet supplemented with water and ethanol extracts of *Spirulina*. The authors of that study attributed the observed effects to the high content of PUFAs found in the extracts. In addition, Hu, Fan, Qi, and Zhang (2019) identified three peptides from proteins extracted from *Spirulina* using

subcritical water coupled to sonication and one of them, the peptide LRSELAAWSR displayed high DPP-IV and α -glucosidase inhibitory activities with IC₅₀ values of 167.3 and 134.2 μ g/mL, respectively. The enzyme DPP-IV is relevant in the prevention or treatment of diabetes as it degrades and inactivates glucagon-like peptide-1 and gastric inhibitory peptide, two incretin hormones which contribute to the increase of glucose-induced insulin secretion (Lafarga, Aluko, Rai, O'Connor, & Hayes, 2016). Moreover, Oriquat et al. (2019) postulated that improving mitochondrial biogenesis could be the mechanism by which *Spirulina platensis* exerts its antidiabetic effect. Oriquat et al. (2019) orally fed diabetic rats with 200 mg/kg of metformin (a first line medication for the treatment of type-2 diabetes) or 250-750 mg/kg of *Spirulina* for 30 days and observed that *Spirulina* successfully ameliorated the induced elevation of fasting blood glucose, insulin, and hepatic enzymes. *Spirulina* also showed anti-inflammatory properties through hepatic sterol regulatory element binding protein-1c inhibition and hepatic mitochondrial biogenesis enhancement. Simon, Baskaran, Shallaudin, Ramalingam, and Prince (2018) reported that oral administration of *Spirulina* to streptozotocin-induced diabetic Wistar albino rats could normalise blood glucose, serum lipid profile, and serum renal markers as well as increase the antioxidant status and minimize the extent of tissue damage.

4.1.3 *Spirulina* and obesity

Moreover, the prevalence of overweight and obesity is rapidly increasing worldwide: according to the FAO, approximately 3.4 million adults die every year as a result of being overweight or obese and 44% of the diabetes burden, 23% of the ischaemic heart disease burden and 7-41% of certain cancer burdens are attributable to overweight and obesity. The potential of *Spirulina* for being used in the prevention and treatment of obesity has been evaluated. For example, Yousefi, Mottaghi, and Saidpour (2018) investigated the effect of consumption of *Spirulina platensis* tablets (4 \times 500 mg per day) on appetite and

anthropometric measures in obese and overweight individuals. Authors reported that body weight, waist circumference, body fat, and BMI were lower in the group consuming *Spirulina* when compared to the placebo control. Moreover, the appetite score was also lower suggesting the potential of *Spirulina* supplementation for losing weight. In addition, Shariat, Abbasalizad Farhangi, and Zeinalian (2019) investigated the effect of *A. platensis* in macrophage inhibitory cytokine-1 (MIC-1/GDF15), superoxide dismutase (SOD), glutathione peroxidase (GPX), appetite, and anthropometric features in obese patients. MIC-1/GDF15 is associated with cardiovascular disease, inflammation, body weight regulation, and cancer and its serum levels are a powerful tool to predict all-cause mortality (Breit et al., 2011). Fifty six obese individual aged between 20 and 50 years old participated in the study by Shariat et al. (2019). These were randomly allocated into two groups and received either *A. platensis* (500 mg twice a day) or a placebo for 12 weeks. Authors observed significantly reduced MIC/GDF15 concentrations and appetite in obese individuals consuming *Spirulina* whereas no change was observed in the placebo-treated group. Moreover, consumption of *Spirulina* also increased blood concentrations of SOD and attenuated anthropometric parameters. SOD is a group of enzymes that catalyse the dismutation of superoxide radicals and provide cellular defence against reactive oxygen species. Similar results were observed by Zeinalian, Farhangi, Shariat, and Saghafi-Asl (2017) who reported reduced appetite as well as body weight and body mass index (BMI) in 27 obese individuals aged 20-50 years old, who received 500 mg of *Spirulina* twice a day during 12 weeks. In a different study, Hernández-Lepe et al. (2018) evaluated the effect of *A. maxima* supplementation and systematic physical exercise program on the body composition and cardiorespiratory fitness of overweight and obese subjects (Figure 4). Consumption of *Spirulina* alone (4.5 g per day during six weeks) or in combination with exercise (twice weekly during six weeks) led not only to reduced body fat percentage but also increased weight loss and time to reach fatigue. *Spirulina* was

also suggested as a potential lipid-lowering functional ingredient by Chen et al. (2019). In that study, the authors observed that *Spirulina* could reduce body weight and serum lipids and even enhance the restoration of fatty liver in high-fat diet rats up to a certain extent. Overall, human intervention studies suggest that consumption of *Spirulina* can reduce appetite and promote weight loss. Moreover, it seems that *spirulina* supplementation synergistically improves the effect of systematic exercise on body composition and cardiorespiratory fitness parameters in individuals with overweight or obesity.

4.2 Phycobiliproteins and health

Phycobiliproteins are water-soluble auxiliary pigments that can be divided into three main classes depending on their composition and chromophores content: phycocyanins, phycoerythrins, and allophycocyanins (Noreña-Caro & Benton, 2018). However, phycobiliproteins are more than just a coloured molecule and have been associated with several potential positive health outcomes including antihypertensive effects. Ichimura et al. (2013) suggested that long-term administration of phycocyanin may ameliorate systemic blood pressure by enhancing nitric oxide synthase expression levels in aorta that is simulated by adiponectin and also prevent endothelial dysfunction-related diseases. That study was conducted using spontaneously hypertensive rats that were fed a normal diet with phycocyanin at a dosage of 2500, 5000, or 10000 mg/kg diet for 26 weeks. Phycobiliproteins could be a source of bioactive peptides with antihypertensive effects. Indeed, the above-mentioned ACE-I inhibitory peptide IRDLDYY was found within the sequence of phycocyanin (Anekthanakul et al., 2019). Moreover, both the biomass of *A. maxima* and phycocyanin prevented the progression and complications of chronic kidney disease and were suggested as potential treatments by Memije-Lazaro, Blas-Valdivia, Franco-Colín, and Cano-Europa (2018). In that study, the authors used a rat model and observed that administration of *Spirulina* or phycocyanin reduced chronic kidney disease-related causes of hypertension as

well as left ventricular hypertrophy, renal dysfunction, and oxidative stress. Although phycobiliproteins were suggested as antihypertensive or sources of antihypertensive molecules, the health benefits of these pigments are mainly attributed to their high antioxidant capacity. Antioxidant capacity of phycobiliproteins has been assessed both, *in vitro* and *in vivo* using animal models. Cano-Europa et al. (2010) obtained a phycobiliprotein-rich extract containing 2% phycocyanin, 9% allophycocyanin, and 89% phycoerythrin and demonstrated that all the studied doses (10-100 mg/kg of body weight, orally administered) prevented the increase of oxidative markers and partially protected cells of mice against HgCl₂-induced oxidative stress and cellular damage. In that study, phycobiliproteins were obtained from *Pseudoanabaena tenuis*. Similar results were obtained by Rodríguez-Sánchez, Ortiz-Butrón, Blas-Valdivia, Hernández-García, and Cano-Europa (2012) after oral administration of a phycobiliprotein-rich extract and phycocyanin (extracted from *A. maxima*) at a dosage of 100 mg/kg of body weight. Phycobiliproteins showed not only antioxidant but also other health-promoting bioactivities. For example, Guzmán-Gómez et al. (2018) recently suggested that phycobiliproteins extracted from *A. maxima* could show antiulcerogenic activity against ethanol-induced ulcers in a rat model. Guzmán-Gómez et al. (2018) evaluated the activity of antioxidant defence enzymes, level of lipid peroxidation, and histopathological changes of gastric mucosa of rats after intragastric administration of phycobiliproteins at a dosage of 100, 200, or 400 mg/kg of body weight. Authors reported lowered index values and inflammatory responses especially after administration especially at the concentration of 400 mg/kg of body weight. Phycobiliproteins reversed the ethanol-reduced increase in lipid peroxidation. Phycocyanin also showed potential for being used for the prevention of fibrotic diseases and cancer. Pattarayan, Rajarajan, Sivanantham, Palanichamy, and Rajasekaran (2017) concluded that phycocyanin suppresses transforming growth factor- β 1-induced epithelial mesenchymal transition (EMT) and EMT-associated

proliferation in human epithelial cell lines, which has been shown to contribute to the development of fibrotic disease. Moreover, An, Park, and Lee (2016) demonstrated that phycocyanin could lessen the over expression of connective tissue growth factor (CTGF) and α -smooth muscle actins (α -SMA), alleviating fibrotic contracture. Phycocyanin (6 nM) inhibited α -SMA expression by 70% and reduced collagen contraction by 29%. Moreover, Ivanova et al. (2010) analysed the effect of phycocyanin on the enzymatic antioxidant defence system in lymphocytes of nuclear-power workers and concluded that the modulating capacity of this phycobiliprotein at the molecular level could be of interest for protecting occupationally exposed people. In that study, the authors observed that phycocyanin at a concentration of 5 μ M selectively stimulated the lymphocyte antioxidant defence system of the subjects.

Conclusions

Spirulina shows potential to become an important food in the future. Several food products have been formulated using *Spirulina* and the amount of novel foods launched into the market incorporating this valuable resource is increasing every year. *Spirulina* is not only “trendy” but rich in several valuable and highly nutritional compounds namely proteins, polyunsaturated fatty acids, and bioactive pigments including chlorophylls, carotenoids, and phycobiliproteins. One of the main advantages of *Spirulina*-derived pigments, when compared to their synthetic counterparts, is that the former have several health-promoting properties upon consumption and could be used as ingredient in the development of novel functional foods. Moreover, *Spirulina*-derived proteins have been proved to be excellent sources of bioactive peptides with potential application in the functional foods industry as antihypertensive, antidiabetic, antiobesity, and antioxidant ingredients among other positive bioactivities.

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Table 1. Nutritional profile of *Spirulina* powder

Composition*	per 100 g	Composition*	per 100 g
<i>1. Macronutrients</i>		Vitamin B2, mg	3.7
Calories, kcal	290	Vitamin B3, mg	12.8
Water, g	4.7	Vitamin B6, mg	0.4
Total lipids, g	7.7	Vitamin E, mg	5.0
Total protein, g	57.5	<i>4. Amino acids</i>	
Carbohydrates, g	23.9	Tryptophan, g	0.93
Ash, g	6.2	Threonine, g	2.97
<i>2. Minerals</i>		Isoleucine, g	3.21
Calcium, mg	Vitamin C, mg	Leucine, g	4.95
Iron, mg	28.5	Lysine, g	3.02
Magnesium, mg	195.0	Methionine, g	1.15
Phosphorous, mg	118.0	Cysteine, g	0.66
Potassium, g	1.4	Phenylalanine, g	2.77
Sodium, g	1.0	Tyrosine, g	2.58
Zinc, mg	2.0	Valine, g	3.51
Copper, mg	6.1	Arginine, g	4.15
Manganese, mg	1.9	Histidine, g	1.08
Selenium, µg	7.2	Alanine, g	4.51
<i>3. Vitamins</i>		Aspartic acid, g	5.79
Vitamin A, IU	570	Glutamic acid, g	8.39
Vitamin K, µg	25.5	Glycine, g	3.09
Vitamin B1, mg	2.4	Proline, g	2.38

		Serine, g	2.99
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*Data accessed from the U.S. Department of Agriculture FoodData Central database available at <https://fdc.nal.usda.gov/>. Data accessed on March 2020 – FDC ID:170495.

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List of figures**Figure 1. Valuable molecules found in *Spirulina***

Main phycobiliproteins found in *Spirulina* include phycocyanin and allophycocyanin at a ratio of 10:1 (Patil, Chethana, Madhusudhan, & Raghavarao, 2008). Together with palmitic and linolenic acid, other valuable lipids found in *Spirulina* include EPA and DHA (Matos et al., 2016). Thiamin and riboflavin are known as vitamin B1 and vitamin B2, respectively. Other valuable compounds contained in *Spirulina* are listed in Table 1.

Figure 2. Median and 95% credible intervals for protein, lipid, and carbohydrate as percent dry weight.

Algae grown under nutrient-sufficient exponential growth. Data estimated using a hierarchical Bayesian analysis of data compiled from the literature. Figure reprinted from Finkel et al. (2016).

Figure 3. Effect of IQP and VEP concentrations on transport across Caco-2 cell monolayers.

Different concentrations of the peptides were added to the AP side and aliquots were collected from the BL side and analysed by RP-HPLC at 60 min.

Figure reprinted from He et al. (2018) with permission from Wiley.

Figure 4. Changes in body weight and body fat percentage by treatments - (A) Total body weight changes of subjects; (B) Body weight changes in overweight subjects; (C) Body weight changes in subjects with obesity; (D) Total body fat changes of subjects;

(E) Body fat changes in overweight subjects; and (F) Body fat changes in subjects with obesity.

Treatments: SE: *Spirulina* and exercise; Ex: Exercise and placebo; Sm: Spirulina without exercise; and C: Control (placebo).

Figure reprinted from Hernández-Lepe et al. (2018).

Figure 1

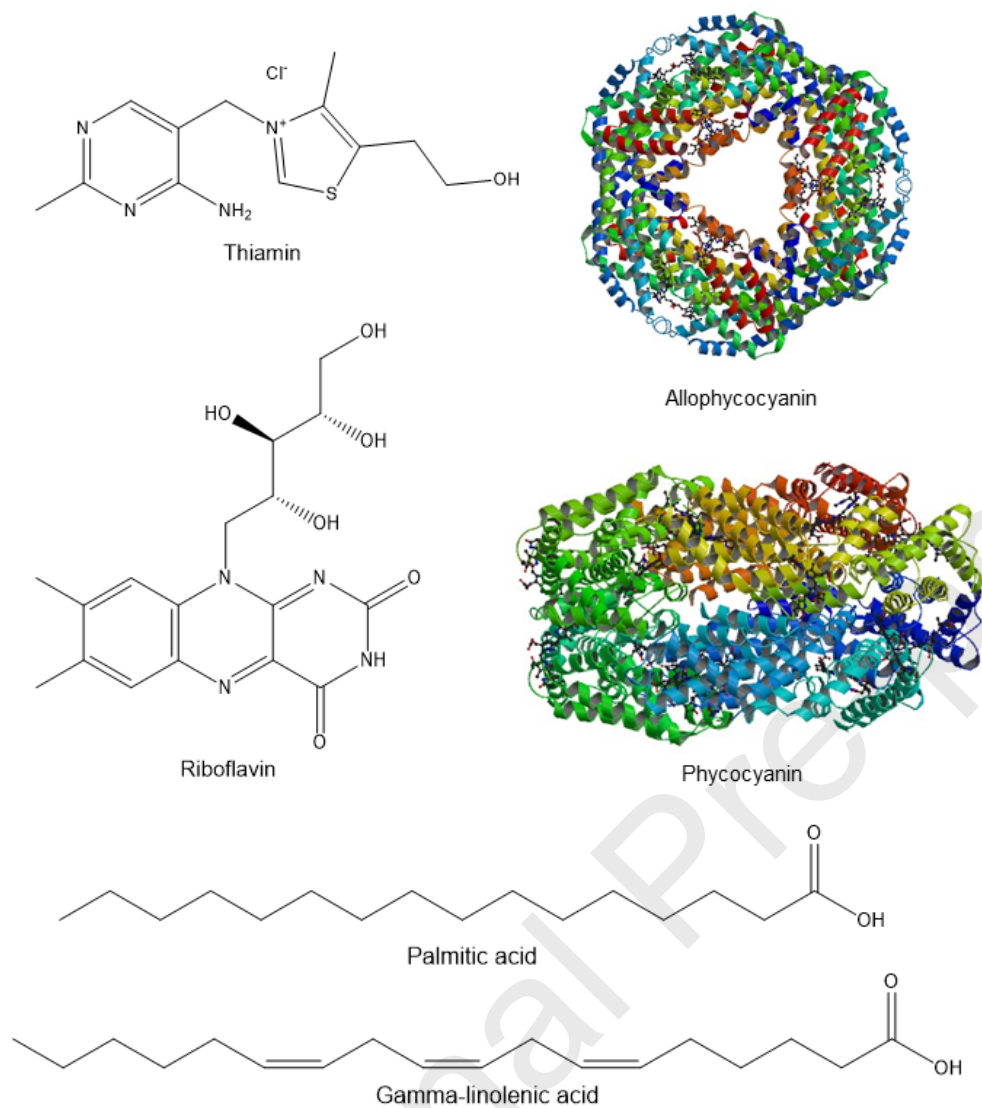
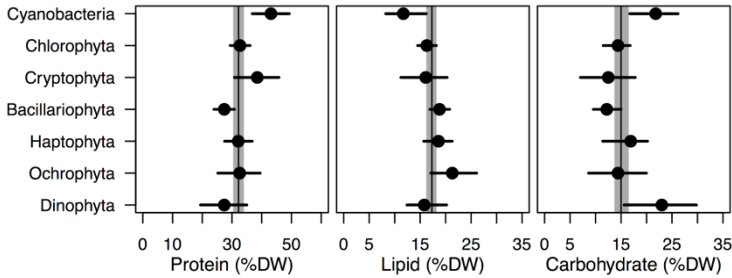


Figure 2b



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Figure 3.

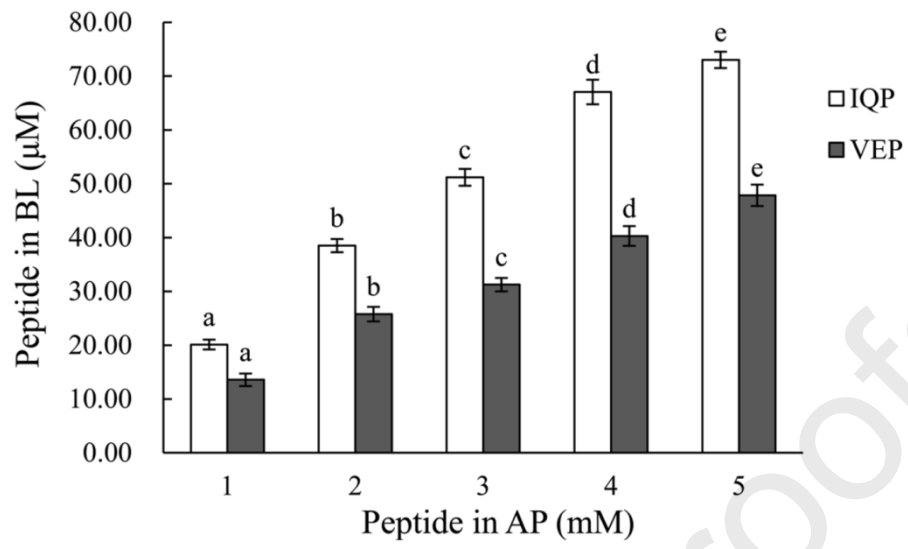
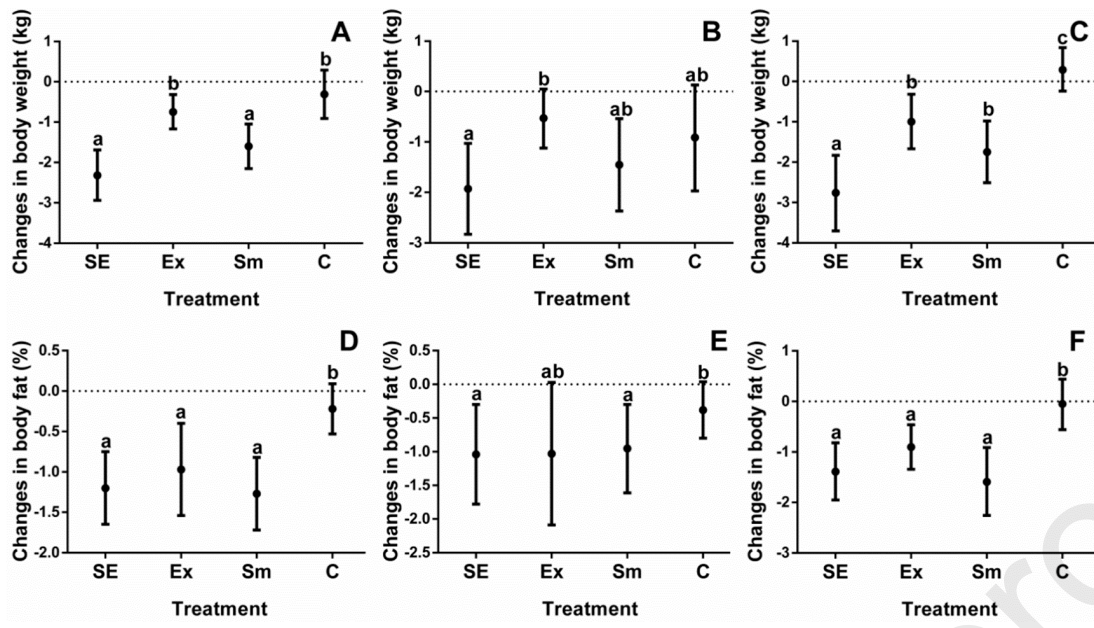


Figure 4.



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Conflict of interests

None



Spirulina
A. Platensis & A. maxima



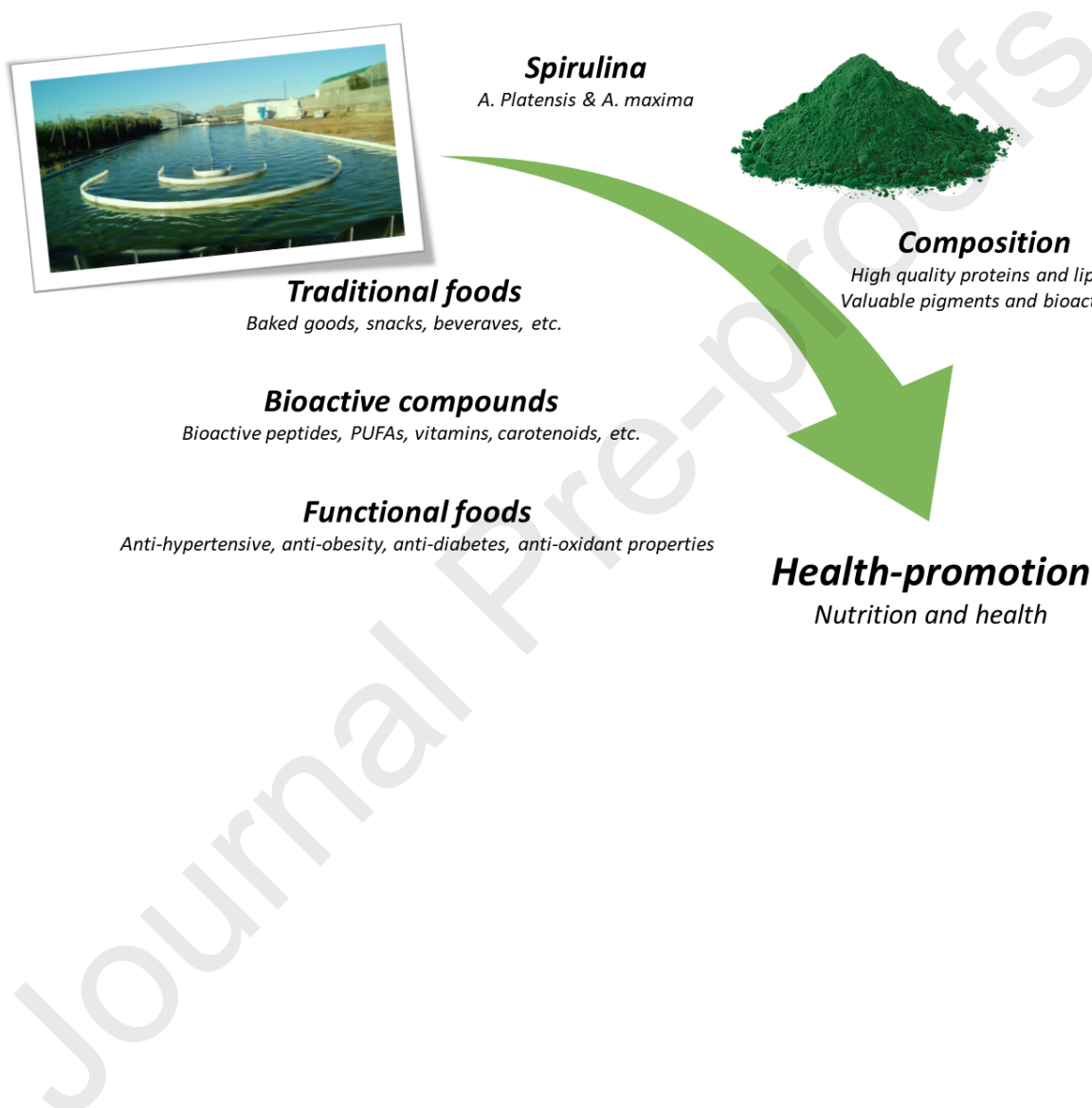
Composition
*High quality proteins and lipids
Valuable pigments and bioactives*

Traditional foods
Baked goods, snacks, beverages, etc.

Bioactive compounds
Bioactive peptides, PUFAs, vitamins, carotenoids, etc.

Functional foods
Anti-hypertensive, anti-obesity, anti-diabetes, anti-oxidant properties

Health-promotion
Nutrition and health



Highlights

- The molecular composition of *Spirulina* is discussed
- The effect of incorporating *Spirulina* into foods is reviewed
- *Spirulina* is being consumed mainly in cereal-based products and snacks
- Health-benefits of consuming *Spirulina* are revised and discussed
- *Spirulina* shows potential for prevent-treat metabolic syndrome