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Review

Nutritional Composition and Functional Properties of *A. platensis*-Derived Peptides: A Green and Sustainable Protein-Rich Supplement

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Abstract: Among cyanobacterium, *Arthrospira platensis* (*A. platensis*) is a rich source of diverse bioactive compounds due to its high protein, essential amino acid, vitamin, and mineral content. *A. platensis* is one of the most abundant sources of protein (50–70%). In the food industry, *A. platensis* is being used as an ingredient for the development of food flavor, taste, and nutritional composition. Several in vitro and in vivo studies have revealed the potential use of *A. platensis* in the prevention and treatment of various metabolic diseases. Recently, extensive research has focused on the production and bioactivity of the *A. platensis-derived* bioactive peptides. A series of steps were used for the production of bioactive peptides including hydrolysis, ultrafiltration, and chromatographic techniques, coupled with an advanced detector. *A. platensis* peptides showed health benefits such as anti-hypertension, anti-diabetes, anti-microbial, antioxidant, anti-obesity, and anti-cancer activities. This review aims to present the main nutritional composition of *A. platensis*, the processes of purification, and the identification of bioactive peptides, and the potential health benefits such as antihypertensive, antidiabetic, anti-cancer, anti-obesity, antioxidant, and anti-microbial activities associated with the consumption of *A. platensis*-derived peptides are discussed. The originality of this review over the old review is that our review comprehensively studies the macro- and micronutrient composition and listed bioactive peptides to date, which can play an important role in the treatment of various diseases. Moreover, this review provides information related the research gaps of the various technologies that should be used for the development of the peptide as a pharmaceutical and functional food.

Keywords: *Arthrospira platensis*; protein; bioactive peptides; functional foods; chromatography; ultrafiltration

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1. Introduction

Although various food recognition methods and their safety are increasing sharply, algae have received minute attention, despite their abundant and wide availability. Several thousand algae species exist on earth, and algae is also one of the first life forms on earth. Various algal food supplements are used to upturn nutritional value and can be used as animal feed additives and be put to pharmaceutical uses [1]. Various bioactive compounds with bioactivity are present in marine organisms. The sea offers approximately one half of the global diversity of marine species and has vast resources of novel compounds [2].

A. platensis belongs to the group of "*cyanobacteria*", called blue-green algae, a photosynthetic bacterium. There are mainly two species of Spirulina which are commonly utilized, Spirulina maxima and Spirulina platensis. In some countries such as India, *Spirulina fusiformis* is also regarded as a source plant [3]. *A. platensis* belongs to the genus *Arthrospira* or *A. platensis*, and the most interesting and studied species of them is called *Spirulina platensis* (or *Arthrospira platensis)* [4]. Among microalgae, *A. platensis* is the most cultivated worldwide blue-green algae, and its production constitutes around 30% of the world's microalgae production [5]. *A. platensis* is found in freshwater, seawater, marshes, soil, and thermal springs. Alkaline water having a higher pH (8.5–11) is good for *A. platensis* production. Commercial production of *A. platensis* is usually carried out on shallow raceways in which paddle wheels are used. Microalgae of very small size cannot be harvested from the normal environment, therefore, they must be produced inland and in a controlled environment. There are several methods used for the cultivation of *A. platensis*. In the outdoor cultivation system method, an open pond/shallow tanks are used for the production, but in this method it is hard to control environmental factors, and a high risk of contamination exists. The other method is greenhouse cultivation—this method's yield is high compared to the aforementioned method, but the initial cost is high. The third method which is usually used is the closed cultivation system, which uses closed bioreactors for the production of *A. platensis*. This process involves the strict monitoring of environmental factors but it is quite expensive compared to the other two methods [6]. In the last two decades, the production of microalgae for food and feed has increased five-fold. *A. platensis* is is produced in a total of 22 countries. The highest consumption rate is in the European market (32%), while in Asia it is 15%. Spirulina (Arthrospira), and species such as S. platensis and S. maxima, are consumed as foods by humans because of their high content of protein. The nutritional supplements which are marketed for human use are mainly granulated and in powder form, or in tablets/capsules [5].

Among algae, *A. platensis* cyanobacterium (*Arthrospira platensis*) has become a nutritious and healthy food brand with a more secure food future. The nutritional composition includes a high level of protein (50–70%), lipids (3–10%), carbohydrates (10–20%), and other compounds such as fiber, pigments, fatty acids, minerals, and vitamins B [7]. Some polyphenolics and flavonoid compounds that act as natural antioxidants were also found in *A. platensis* [8]. The National Sanitary Surveillance Agency (ANVISA) and the Food and Drug Administration (FDA) recognized *A. platensis* as a safe food supplement (GRAS) [9].

Currently, microalgae are widely used in food industries, and the number of food products containing microalgae launched in the market has significantly increased. The biomass of *A. platensis* nowadays is consumed as a high nutritional supplement (superfood), and in the market it is available in the form of capsules, flakes, and dried powder [10]. *A. platensis* can be an important food in the upcoming days and is used as an essential ingredient for the development of functional food. In vivo and in vitro experimental studies of *A. platensis* reveal that it is effective in the treatment of immune system development in HIV, other viral diseases, several types of cancer, inflammatory processes, cardiovascular diseases, immunodeficiency, anemia, hyperlipidemia, hyperglycemia, and the reduction of cholesterol. According to the FDA (Food and Drug Administration), since 2003 *A. platensis* has been considered a safe ingredient. These qualities make *A. platensis* a good source for the research and production of bioactive peptides [11].

Currently, various diseases and morphological and physiological disorders such as cancer, cardiovascular diseases, diabetes, oxidative stress, severe infections, and obesity are at alarming stages and are distressing for life quality. Unbalanced diets, radiation exposure, powerful viruses, and synthetic additives are the major causes of these disorders. To fight against degenerative illnesses, the search for new functional foods and drugs has increased in the last few decades. In this context, research has mainly focused on natural sources [12]. *A. platensis* is a good source of protein, which allows it to be a good source for the generation of bioactive peptides that conduct various activities such as anti-cancer,

anti-proliferative, immune-strengthening, ACE inhibitory, and anti-inflammatory activities, and to have cardio-protective, antioxidant, antiviral, and anti-Bacterial properties [13].

Bioactive peptides are present in food/protein, and can be utilized in a biologically active form once released from the food matrix. These peptides are generally short sequences of amino acids (2–20) in length, most of them are too short (2–4 amino acids long), and have low molecular weight, i.e., <6000 Da. Due to low molecular weight, bioactive peptides can easily enter the intestinal system and show potent bioactivities. The composition of bioactive peptides is mostly hydrophobic amino acids [14]. Bioactive peptides can be used as important ingredients for functional food development such as cosmetics, functional foods, and nutraceutical products [15]. Bioactive peptides can be obtained by enzymatic hydrolysis or naturally. Commercial proteases of microbial origin or plant origin in a controlled environment are used to produce bioactive peptides, while naturally they are produced during gastrointestinal food digestion or food processing [16]. A large number of peptides are generated during hydrolysis, and among them a limited number of peptides have bioactive properties. Molecular weight cut-off filtration (MWCO) is generally used to fractionate the hydrolysate to obtain the desired peptides [17]. The majority of bioactive peptides and hydrolysates are obtained from fish and fish co-products, meat and animal co-products, milk and dairy products, and pulses [18]. Other sources such as cereals and algae have also been extensively studied. Bioactive peptides can affect the body system by various possible physiological functionalities such as the nervous system (opioid), immune system (immunomodulatory, cytomodulatory, and antimicrobial), gastrointestinal system (anti-appetizing, antimicrobial, and mineral binding), and the cardiovascular system (antioxidant, hypocholesterolemic, antithrombotic, and antihypertensive). Peptide activity mainly depends on the amino acid sequence and composition [19]. Bioactive peptides could act as hormones, antibiotics, and neurotransmitters, and they can modify the physiological function by binding with the receptor sites and interacting with the target cells [20].

A. platensis is considered the most cultivated microalgae, and worldwide microalgal biomass contains over 30% of *A. platensis* production. Moreover, *A. platensis* is gaining more interest in terms of the food supplement sector. *A. platensis* has nutritional value for humans and plays an important role in the management of various diseases. Publications about its nutritional composition and bioactive peptide and extraction is limited. Previous research [21–23] has mainly focused on the production methods of *A. platensis*, the use of *A. platensis* peptides in the cosmetic industry, and discussed some of the activities such as hypertensive and anti-cancer. This review comprehensively explains *A. platensis*'s nutritional composition, bioactive peptides' role in the management of various diseases, and the mechanism of action associated with their consumption.

2. Nutritional Composition of *A. platensis*

The word *A. platensis* is a Latin word meaning "spiral" or "helix". This name is due to the physical configuration which forms a swirling microscopic structure. It contains protein (55–70%), total lipids (5–6%), polysaccharides (15–25%), nucleic acid (6–13%), and minerals (2.2–4.8%). It contains important vitamins such as A, B, D, E, and K. Some important minerals such as calcium, zinc, selenium, iron, nickel, chromium, potassium, magnesium, manganese, copper, and sodium are also found in it. In addition to these macro- and micronutrients, it also contains carotenoids and essential fatty acids (eicosapentaenoic acid, stearidonic acid, 3,6-linolenic acid,-linolenic acid, docosahexaenoic acid, and arachidonic acid) which play an important role in a balanced diet and in human health. In terms of protein and amino acids, it contains all the essential amino acids required for the body, and the digestibility of protein is higher compared to other natural sources of protein. The content of digestible polysaccharides present in the cell wall of *A. platensis* is (86%), and due to this higher content the digestibility of protein is high [24]. *A. platensis* can be a good source of macronutrients such as polyunsaturated fatty acids, proteins, vitamins, and/or minerals, which are important for human health. The main macronutrient composition of *A. platensis* is shown in Table 1 and Figure 1. In addition to the macro- and micronutrients,

some other compounds with biological activities are also present. These compounds are phenolic compounds, carotenoids, and amino acids. The nutritional composition of food is important to maintain a healthy lifestyle and prevent chronic diseases [25]. For the analysis of food composition, various techniques such as HPLC (high-performance liquid chromatography) for lipid, amino acid, and carotenoid analysis, a spectrophotometer for the determination of pigments, and ICP-OES (inductively coupled plasma optical emission spectrometry) for heavy metals and micronutrients were used [26]. These compounds possess some biological activities such as neuroprotective, anticarcinogenic, and antioxidant functions [27].

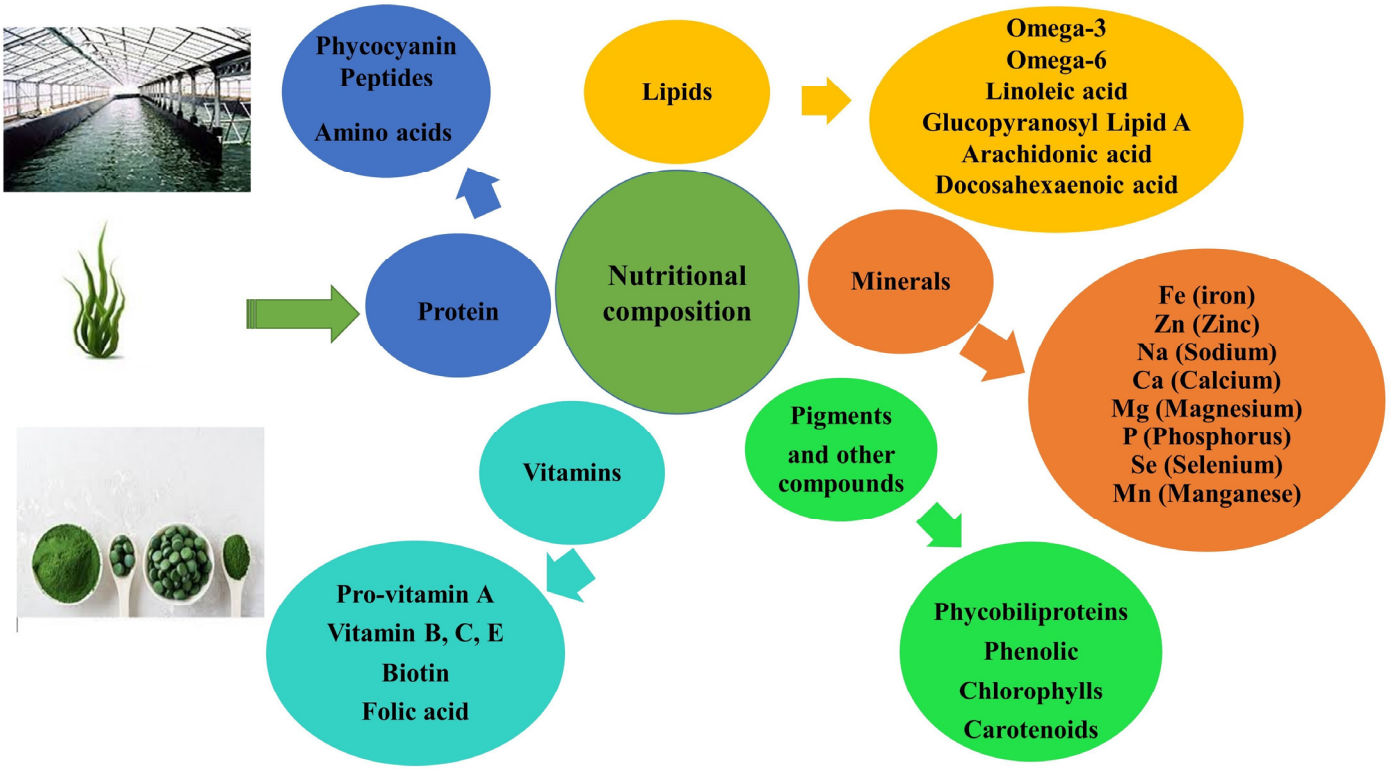

Figure 1. Nutritional composition (macro- and micronutrients) of *A. platensis*.

Table 1. Macronutrient composition of *A. platensis*.

Macronutrient	[28] Brazil	[29] Austria	[4] Spain	[1] Morocco	[30] Spain		[24] India	[31] India	[32] Egypt	[33] Luxembourg
	g/100 g (Fresh Weight)	(% Dry Matter)	g/100 g	(% Dry Matter)	g/100 g		(% Dry Matter)	(g/100 g)	(%)	g/100 g Dry Matter
					A. platensis	Commercial Variety				
Moisture	90.7	-	4.7	12.6	-	-	5.81	7.00	6.98	
Energy (Kcal)	-	1603	290	436.18	-	-	412.78	373.00	-	
Protein	5.92	62.7	57.5	76.5	58.1	53.3	65.71	63.00	56.79	81.9
Fat	0.39	8.1	7.7	2.45	8.1	4.4	6.94	5.60	8.33	3.77
Ash	0.6	-	6.2	14.56	8.2	10.5	8.34	9.00	10.50	6.3
Carbohydrate	2.42	15.6	23.9	6.46	25.6	30.7	21.87	20.5	13.60	8.16
Total dietary fiber	0.4	3.1	-	4.07		-	-	7.7	4.25	

2.1. Macronutrient Composition

2.1.1. Protein and Amino Acid Composition

The highest protein and essential amino acid contents have been found in *A. platensis*, which makes it an "ideal" protein based on the WHO (World Health Organization)'s and FAO's composition criteria [34]. *A. platensis* protein content varies between 50 and 70% of its dry weight. The quality of protein is better as compared to other sources. The taking of 10 g of *A. platensis* protein/day by a 60 kg person can fulfill around a quarter or one third of the daily protein requirement. According to Muy et al., the protein content varies between 48% and 67% in 11 *A. platensis* powders tested by two different methods (Markwell asssay) and (Kjeldahl) [35]. It can be concluded from the results that the protein content is overestimated by the later method. Essential amino acid index values indicate the values between 1.01 and 1.45, while the amount of sulfur-containing amino acids (cysteine and methionine) was 18 ± 5 mg/g protein, and histidine was 10 ± 3 mg/g protein. In general, deviation in the nutrient profile depends on the different cultivation environments, i.e., different culture media, nutrients, etc. [36]. The protein content of *A. platensis* is high compared to several plants and animal sources (beef, dairy products, pork), moreover, the amino acid content of all the essential amino acids is present in the protein concentrate [37,38]. A high amount of essential and non-essential amino acids are present in *A. platensis*. In a study carried out by Li and his team [39], the amino acid content included methionine (14 mg/g), methionine (14 mg/g), lysine (30 mg/g), phenylalanine (28 mg/g), valine (45 mg/g), lysine (30 mg/g), and isoleucine (36 mg/g). For all the biological processes, essential amino acids are very important. They cannot be produced by the body and must be included in the diet [40]. The amino acid composition found by various researchers is displayed in Table 2. *A. platensis* can be used as a supplement food for the provision of essential amino acids for daily needs. Non-essential amino acids are also important for the body, and they can help with the production of protein needed by the body's cells. In another form, they can be used as a source of fuel in the form of carbohydrates. The composition of the non-essential amino acids of *A. platensis* contains glutamate acid (92 mg/g), glycine (32 mg/g), alanine (47 mg/g), aspartic (60 mg/g), histidine (10 mg/g), tyrosine (30 mg/g), serine (33 mg/g), proline (27 mg/g), arginine (44 mg/g), and cysteine (7 mg/g) [41].

Table 2. Amino acid composition of *A. platensis*.

	[13]	[42]	[43]	[4]	[28]	[31]	[32]
	(mg/g Dry Sample)	**(mg/kg)**	**(mg/g)**	**(g/100 g)**	**(mg/g Dry Sample)**	**(g/100 g)**	**(mg/100 g)**
Aspartic acid	80.4	90.78	60	5.79	63.1	5.99	36.69
Glutamic acid	105.9	159.72	92	8.39	84.7	9.13	47.03
Histidine	14.8	41.25	10	1.08	11.3	1.00	13.46
Serine	42.7	40.52	33	2.99	30.9	2.76	18.43
Arginine	48.7	104.16	44	4.15	44.7	4.31	44.91
Glycine	44.8	119.62	32	3.09	34.3	3.13	15.0
Threonine	41.9	118.52	33	2.97	33.1	2.86	13.59
Alanine	66.1	118.55	47	4.51	50.2	4.59	33.80
Tyrosine	37.5	45.14	30	2.58	30.7	2.50	19.74
Methionine	13.7	35.84	14	1.15	17.1	1.17	5.31
Valine	48.2	30.51	45	3.51	42.2	3.94	18.40

Table 2. *Cont.*

	[13]	[42]	[43]	[4]	[28]	[31]	[32]
	(mg/g Dry Sample)	**(mg/kg)**	**(mg/g)**	**(g/100 g)**	**(mg/g Dry Sample)**	**(g/100 g)**	**(mg/100 g)**
Phenylalanine	42.3	29.47	28	2.77	33.3	2.75	23.78
Isoleucine	44.6	46.52	36	3.21	36.4	3.50	14.12
Leucine	73.1	99.41	55	4.95	61.7	5.38	29.11
Lysine	47.2	35.65	30	3.02	34	2.96	19.10
Tryptophan	5.3	-	10	0.93	8.5	1.09	12.88
Cystine	-	14.23	7	0.66	6.4	5.90	3.30

2.1.2. Lipids and Carbohydrates

A. platensis lipids mainly contain polyunsaturated fatty acids (PUFA), monounsaturated (MUFA) fatty acids, and saturated fatty acids (SFA). Moreover, a good and balanced composition of total fat in terms of PUFA and saturated fat characterizes it. For the human metabolic process, lipids are one of the main sources of energy. *A. platensis* lipids are composed of mainly γ-linoleic acid (30–35%), which is an essential PUFA required for both the functional and structural activity of cell membranes. Other lipids of *A. platensis* contain glycolipids and essential fatty acids (ω3 and ω6 families) [44]. From the omega-6 family, γ-linolenic acid (18:3, n-6) and palmitic acid (16:0) are widely studied due to their potential effects reducing the prevention of hypercholesterolemia, cardiovascular diseases, and other disorders. The contents of linoleic and γ-linolenic acids range from 13.1 to 31.5% and from 12.9 to 39.4% of the total fatty acid content. Polyunsaturated fatty acids (PUFAs) in the form of docosahexaenoic acid (DHA, 22:6, n-3) and eicosapentaenoic acid (EPA, 20:5, n-3) present in lower concentrations [4]. According to the study by Calla et al. [45], the lipid content of 11 *A. platensis* samples was 10%. In another study, the lipid content of five *A. platensis* powders from different origins was 1.5–8.1% [46]. An analysis of the fatty acid profile showed that the content of Omega-6 fatty acids ranged from 23.1 to 24.5%), while the omega-3 fatty acid (alpha-linolenic acid) content was very low. *A. platensis* fatty acids can be used in the diet for lipid metabolism disorder, especially polyunsaturated fatty acids [39]. The percentage of carbohydrates represents about 15–25% of the dry weight of *A. platensis*. Specific polysaccharides, such as sodium *A. platensis* (Na-SP) and calcium *A. platensis* (Ca-SP), have interesting antiviral, immunostimulant, and anticoagulant properties.

2.2. Micronutrients

Vitamins and Minerals

Vitamins such as E, B1, B2, and B12, minerals (magnesium, calcium, selenium, zinc, iron, and potassium), and some sulfolipids were also found in *A. platensis* and showed high activity against viral infections [47]. The minerals and vitamins of *A. platensis* found by various researchers are listed in Table 3. Among the vitamins, vitamin A in the form of carotenoids is a class of pigments naturally produced by microalgae. This pigment may be converted by our body into vitamin A. Important functions of vitamin A include embryonic development, general growth promotion, the regulation of differentiation of epithelial tissues, and visual function. In the Western diet, carotenoids are the key compounds, and around 30% of vitamin A daily intake is derived from carotenoids. Astaxanthin, β-carotene, zeaxanthin, lutein, and canthaxanthin are the identified carotenoids present in *A. platensis* [48].

Table 3. Mineral and vitamin composition.

Minerals	[43]	[4]	[1]	[29]	[28]	[31]	[37]
	(mg/g)	**(mg/100 g)**	**(mg/100 g) Dry Weight**	**(µg/100 g)**	**(mg/g) Fresh Weight**	**(g/100 g)**	**(mg/100 g)**
Potassium	16	1.4	2501.66	-	13.32–127	1.66	170.0
Calcium	15	30.3	6000	-	1.05–12	0.47	363.77
Phosphorus	10	118.0	10,088.33	-	11	0.96	123.1
Manganese	3	1.9	1.56	2.9–4.1	9.5	3.26	-
Zinc	70 (µg)	2.0	5	0.9–1.2	9.7	1.45	2.90
Magnesium	3.7	195	100.33	-	1.42–19	0.32	2.66
Sodium	2.5	1.0	14,004.397	-	11.50–98	0.64	216.77
Iron	1.7	28.5	80.66	48.9–82.9	0.15–2.79	0.09	12.44
Vitamins	(µg/g)	(mg/100 g)	-	(mg/100 g) dry weight	(mg/g) dry weight	(mg/100 g)	(mg/100 g)
Biotin	0.55	-	-	-	-	5.00	-
Folic acid	0.71	-	-	26.6–534.5 (µg)	7.3	0.33	-
Pantothenic acid	2	-	-	-	0.325	0.10	-
B12(cyanocobalamin)	3.6	-	-	127–244	-	0.36	-
B6 (pyridoxine)	8	0.4	-	-	90	0.96	-
B1 (thiamin)	48	2.4	-	-	48	0.51	3.0
B2 (riboflavin)	55	3.7	-	-	39	4.53	3.7
B3 (niacin)	0.15 (mg)	12.8	-	-	3.9	14.90	12.2
E (tocopherol)	0.41 (mg)	5	-	2.8–75	1.06	6.71	60.0
Inositol acid	0.7 (mg)	-	-	-	-	64.00	-
Pro vit A (beta carotene)	5.8 (mg)	570 (IU)	-	33.5–231.6	18	352,000 (IU)	70.0

Vitamin B is water-soluble and can act as coenzymes, required for fatty acids synthesis, DNA repair, electron transfer, and one-carbon metabolism [49]. Among B vitamins, B12 (Cyanocobalamin) levels range from 127 to 244 µg/100 g dry weight. Only animal-origin food contains vit-B12. In another study, the content of B12 was 3.6 µg/g. The majority of B12 present in cyanobacteria contains an inactive form known as pseudo-vitamin B12. A total of 83% can be classed as "pseudo-"B12, while the other 17% was found to be dimethylbenzimidalylcobamide, also known as vitamin B12. Dimethylbenzimidazol of B12 is replaced by adenine in "pseudo-" B12, which is inactive in humans and has very low affinity to intrinsic factors [50]. A daily intake of 3–9 g/day of *A. platensis* can cover the daily intake of B12—the human requirement for this vitamin is 1 mg/day [35]. Folate content presents a high variation (270–535 µg/100 g) dry weight of *A. platensis*. The variation may be due to the processing techniques. The content of folate was twice as high in the traditional method compared to in the improved processing method. The loss can be assumed to be due to the use of high thermal and light stress, as folate is sensitive to high temperature and light [51]. The vitamin E content of *A. platensis* ranges from 2.8 to 12.5 mg/100 g in the traditionally dried *A. platensis* method. A higher concentration of vitamin E was found in two varieties of *A. platensis* collected from Bodou Andja (30.9 mg/100 g to 75 mg/100 g) [52].

The content of macro-minerals of *A. platensis* was 32,694.32 ± 6175.08 mg/100 g dry weight, while the content of trace elements was 88.44 ± 3.2 mg/100 g dry weight [53]. Essential mineral content was: sodium (14,004 ± 397.55), calcium (6000 ± 4.66), phosphorus

(10,088.33 ± 5766.88), potassium (2501.66 ± 4.22), and magnesium Mg (100.33 ± 1.77) of mg/100 g of dry weight. Trace elements included manganese (1.56 ± 0.11), iron (80.66 ± 1.77), and copper (1.22 ± 0.66) mg/100 g of dry weight, respectively. The mineral content is slightly higher compared to the other land plants. However, in another study by [54], the content of sodium, potassium, and calcium were 0.7–12.3, 1.6–3.1, and 219–1290 mg/100, respectively. The contents of manganese, zinc, iron, and magnesium were also notable for meeting the daily requirements of the human body.

Plant-origin macro-minerals mainly contain phenolic compounds with a benzene ring and a hydroxyl substituent in their structure. These are the main bioactive compounds found in algae, tea, edible flowers, fruit, and vegetables [28]. The phenolic compounds ranged from 5.8 to 27.1 µg/100 g dry weight when *A. platensis* was dried in sandy hollows, while the phenolic content decreased (4.0–11.9 µg/100 g dry weight) when *A. platensis* was dried under solar dryers [54]. In another study, the content of polyphenols and flavonoids were 0.287 mg GAE/g DW and 0.166 mg QE/g DE, respectively. Functional food is a new category of food which has some beneficial effects on health beyond nutritional needs. Several health-promoting and therapeutic benefits such as allergies, oxidative stress-induced diseases, hypertension, hyperlipidemia, inflammations, diabetes mellitus, and some types of cancer have been linked with *A. platensis* and compounds derived from it.

3. Production of Bioactive Peptides/Process and Screening of Bioactive Peptides

In peptide identification, various steps are involved, including source selection, protein extraction, the selection of enzyme and hydrolysis conditions, potential bioactivity screening, fractionation, purification, sequence, and structural identification. The systematic overview of the steps involved in the production of bioactive peptides is summarized in Figure 2. Bioactive peptides are found in proteins of microorganisms, so the first step is the extraction of the protein which is present intracellularly. Mechanical and chemical methods are used for the cell lyses. Mechanical methods include freeze-thawing cycles in buffers or in liquid nitrogen, pulsed electric processing in French pressure cells, and sonication. In the freeze-thaw cycle method, repeated freezing and liquid cell suspension in a buffer or in liquid nitrogen results in the formation of ice crystals, which disrupts the cell membrane of the target protein. The second method, sonication, involves the use of high-frequency sound waves to create bubbles in the cell suspension. The cell membrane of the target cell is disrupted by the shock generated as a result of the bubbles' collapse. In the French press method, cells are forced through a narrow orifice under high pressure, and cell disruption is caused by the shear forces. The last method, homogenization, involves mechanically shearing by forcing cells through a narrow gap between a static tube and a rotating pestle [55].

The chemical methods listed use enzymes for cell wall degradation, as well as a buffer, surfactants, ionic liquids, a strong base, or acid [56]. *A. platensis*-derived peptides with anti-hypersensitive and antitumor activity were extracted through a freeze-drying and sonication process [57]. Another study reveals that the protein extraction for the peptide purification involved freezing at −20 °C in phosphate buffer solution, sonication, and centrifugation.

3.1. Enzyme Hydrolysis

In the food industry, the incorporation of protein hydrolysate into food has gained interest in recent years. This technology is beneficial for enhancing the human daily diet by adding beneficial compounds to the diet and promoting body function regulations. Protein hydrolysis (proteolysis) is usually carried out by enzymes for the production of bioactive peptides, which is considered more efficient for obtaining peptides with a target function. This method is considered more reliable and generally recognized as the safest (GRAS) method. Enzymatic hydrolysis is widely used in the food, pharmaceutical, and chemical industries [58].

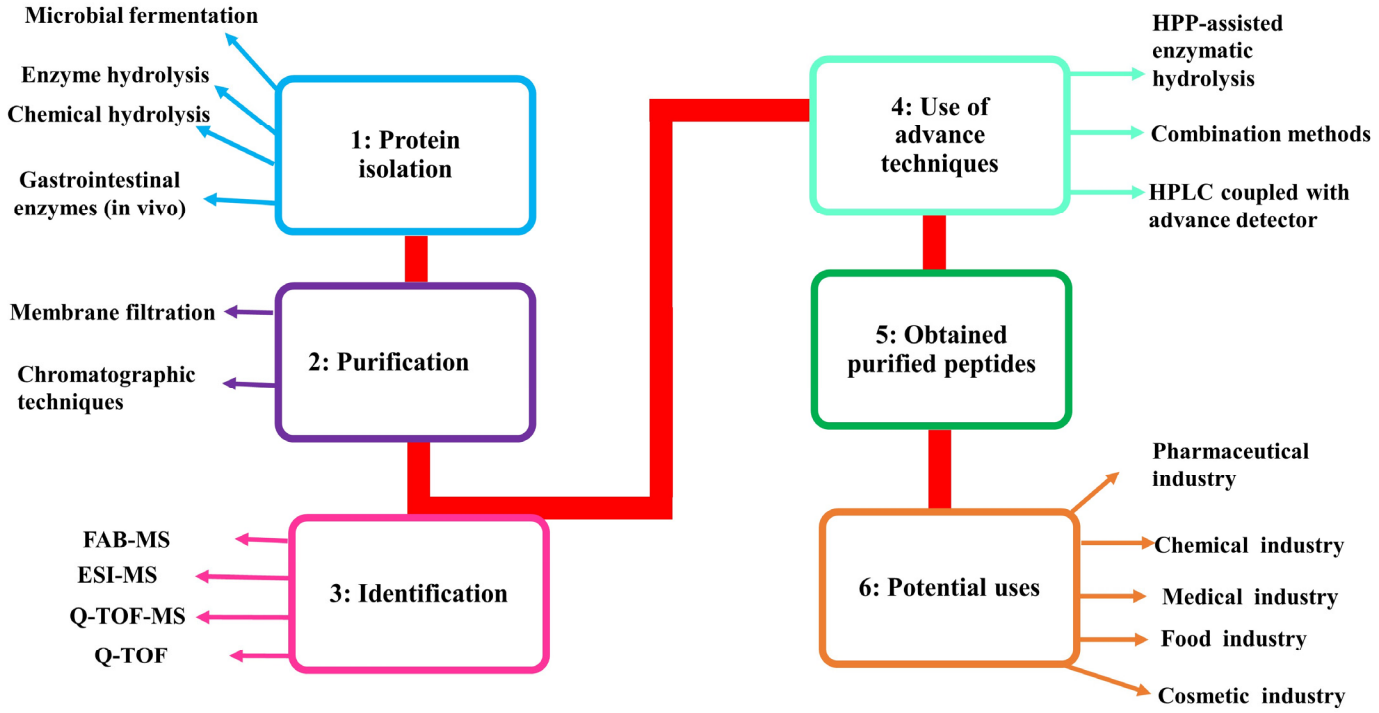

Figure 2. Systematic overview of the extraction, isolation, purification, and identification of bioactive peptides from *A. platensis*.

For the in vitro hydrolysis, mainly commercially available enzymes extracted from microbial, animal, or plant sources are used, while in vivo proteolysis uses gastrointestinal enzymes [59]. To gain a higher degree of hydrolysis (DH), and for the production of a target peptide, it is important to select the best enzyme and optimal conditions for the hydrolysis, i.e., temperature, time, enzyme/substrate ratio, and solvent [60]. Enzymes from plant sourced such as bromelain and pepsin, animal origin enzymes (trypsin, pepsin), bacterial enzymes (neutrase and alcalase), and fungal enzymes (fungal protease) are widely used for the production of peptides from *A. platensis*. Usually, a combination of endo- and exo-proteases are used for the production of a higher yield. Endo-protease breaks the peptide bond of the nonterminal amino acid (within the molecule), while exo-protease breaks the peptide bond from the end piece of terminal amino acids. For optimum activity, the temperature used for various enzymes is 40–50 °C, and the pH ranges from 4 to 7. For trypsin and pepsin, enzyme conditions used for the hydrolysis are pH = 8 and temperature 37 °C, and the reaction time is up to 120 min. For the purification of antidiabetic peptide, alkaline protease was used, and the conditions were: temperature set at 55 °C, pH of 7.0, and time of 160 min [61]. The lyophilized Spirulina proteins powder was first enzymatically hydrolyzed with alkaline protease. This was conducted with 4300 U/g enzyme added to *A. platensis* proteins at 55 °C, and with a pH of 7.0 for 160 min. Usually, digestive enzymes are helpful for obtaining a partial breakdown of proteins into peptides and for improving bio-accessibility. Various enzymes have different cleavage properties, and produce peptide sequences with different structural features which are responsible for single or multiple functional activities [62].

Hydrolysis conditions such as enzyme type, concentration, pH, protein source, and extraction conditions such as temperature and time highly affect the resultant hydrolysate. Hydrolysate with a higher concentration of peptide can be obtained by optimizing these conditions [63]. Hydrolysate from fish protein showed a variation in ACE inhibitory activity, depending on the hydrolysis time and type of enzyme (trypsin) [64,65]. For a higher yield, it is recommended to use two or more enzymes for sequential hydrolysis. Commonly used enzymes are pepsin, trypsin, alcalase, and flavorzyme [66].

3.2. Membrane Filtration

In membrane separation, a membrane system is used for the permeation and retenftion of the sample through various pressures. In food sources, this method is widely used for the isolation of bioactive peptides [58]. This process is mainly divided into four types (ultrafiltration, reverse osmosis, microfiltration, and nanofiltration) based on the pore size of the membrane. Among these methods, ultrafiltration is the most economical, eco-friendly, and fast method for peptide purification according to the molecular weight cut-off. Ultrafiltration was conducted with various molecular weight cutoff membranes including 1, 3, 5, and 10 kDa [67].

Wang and Zhang purified marine peptides by using membrane filtration with a molecular weight of <5 kDa and 3 kDa. Four peptide fractions with molecular weights of <3 kDa, 3–5 kDa, 5–10 kDa, and >10 kDa were purified by ultrafiltration from hairtail (*Trichiurus japonicus*) hydrolysate with MAO-A inhibitory activity [68]. Among all the fractions, <3 kDa showed the highest MAO-A inhibitory activity [69]. Several low-molecular-weight peptides from microalgae 1–10 kDa, seahorse <5 kDa, and round scad <5 kDa were obtained by using the ultrafiltration technique and exhibited improved biological activity [70]. Using membrane filtration entails some problems such as the interaction of hydrophobic peptides and semi-permeable membrane, the difficulty of obtaining pure peptides, the filtration of large-size molecules, the clogging and fouling of membranes, and the separation of large sample volumes. To resolve these problems, membrane filtration technology can be used with some other techniques such as a multistep recycling membrane reactor, electrodialysis, and chromatographic techniques to achieve more functional peptide separation with improved health benefits [58].

3.3. Chromatographic Techniques

The purification process involves a series of steps based on the chemical and physical characteristics of peptides, such as solubility, polarity, charge, molecular size, and specific covalent or non-covalent interactions [71]. Chromatography plays a vital role in the purification and separation of compounds from a mixture based on their retention and interaction with stationary and mobile phases. Based on the specific components and molecular characteristics, four main separation techniques are reported. 1: liquid–solid adsorption, 2: ion exchange, 3: liquid–liquid partition, 4: size exclusion. Chromatographic techniques are usually used along with other detectors such as MS (mass spectrometry detectors), UV, fluorescence, and diode-array for the identification of various compounds from protein sources. A column with silica-based material with a pH of 2–8 and UV range of <220 nm is used for the peptide selection. These techniques are time-consuming and costly, and proper resolution and selectivity make them appropriate for the identification of peptides [72].

For the separation of bioactive peptides, HPLC (high-performance liquid chromatography) is the common tool. Advanced technology like RP-HPLC separates the compounds through the specific column from the protein hydrolysate mixture. The normal HPLC is commonly used for the detection of hydrophilic peptides. CIEF (capillary iso-electric focusing), CE (capillary electrophoresis), and IEC (ion-exchange chromatography) used charge ability affinities based on negative or positive charges to separate bioactive peptides. GFC (gel filtration chromatography) is used to separate the aqueous solution according to the molecular weight [73].

For the identification of peptide structure and to measure the specific activity by various assays, purification is the main and important step. Analytical steps that are widely used for peptide purification are membrane filtration systems, chromatography techniques such as ultra-high-pressure liquid chromatography (UHPLC), SEC, reversed-phase high-performance liquid chromatography (RP-HPLC), hydrophilic interaction liquid chromatography (HILIC), and capillary electrophoresis (CE) [74]. For the peptide sequence identification, mass spectrometry (MS) methods are used such as fast atom bombardment mass spectrometry (FAB-MS), electrospray ionization–mass spectrometry (ESI-MS),

matrix-assisted laser deionization time-of-flight (MALDI-TOF), and matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) [75]. Recently, more advanced techniques such as MALDI-TOF, ESI-MS, and quadrupole-time-of-flight mass spectrometry (Q-TOF MS) have been widely used for protein and bioactive peptide characterization. The isolation, identification, and selection of bioactive peptide techniques depend on the projected peptides.

Antihypertensive peptides from *S. platensis* were isolated by gel filtration and ion exchange chromatography. Further purification was conducted by RP-HPLC (reverse phase liquid chromatography). A gas-phase automated sequencer was used for peptide sequence analysis [76]. Another study by [77] reported that S. platensis hydrolysate obtained by the alcalase enzyme was fractionated by ultrafiltration and gel filtration, and reverse-phase HPLC was used for peptide purification.

A. platensis peptide with iron-chelating activity was purified by ultra-filtration to obtain <3 kDa peptide. GPC (gel permeation chromatography) and anion exchange chromatography were used for isolation. Tandem mass spectrometry was used for peptide sequence analysis [78]. An antiallergic, anti-inflammatory, and anti-atherosclerotic peptide derived from S. maxima was obtained through ultrafiltration. The hydrolysates were fractionated by 3, 5, and 10 kDa molecular cutoff membranes. Chromatographic techniques for purification include FPLC (fast protein liquid chromatography), GPC (gel permeation chromatography), and RP-HPLC (reverse-phase high-performance liquid chromatography). Rotary evaporation and lyophilization were used between each step of purification. A Q-TOF mass spectrometer coupled with an electrospray ionization source were used for peptide amino acid sequence determination [56].

A. platensis peptides with antitumor activity were isolated by ultrafiltration and gel filtration chromatography. Molecular weight cutoffs of 3, 5, and 10 kDa were used in the ultrafiltration step. Nano-encapsulation of the peptide with chitosan was conducted to enhance the release in the intestine and absorption in the blood. Also, the spectrum was determined by infrared Fourier transform [57]. These studies suggest that, for the purification and isolation of bioactive peptides from marine sources, chromatography can be considered as the best technique. Moreover, the use of advanced detectors along with chromatography is a convenient way for the purification, separation, and identification of peptides on a large scale. It can be concluded from the above literature concerning isolation and purification that the most important techniques used for the production of bioactive peptide are membrane filtration (ultrafiltration), liquid chromatography (gel filtration, reverse-phase), nanofiltration, and ion-exchange chromatography. Peptides associated with potential health benefits, and their mechanism of action is displayed in Figure 3.

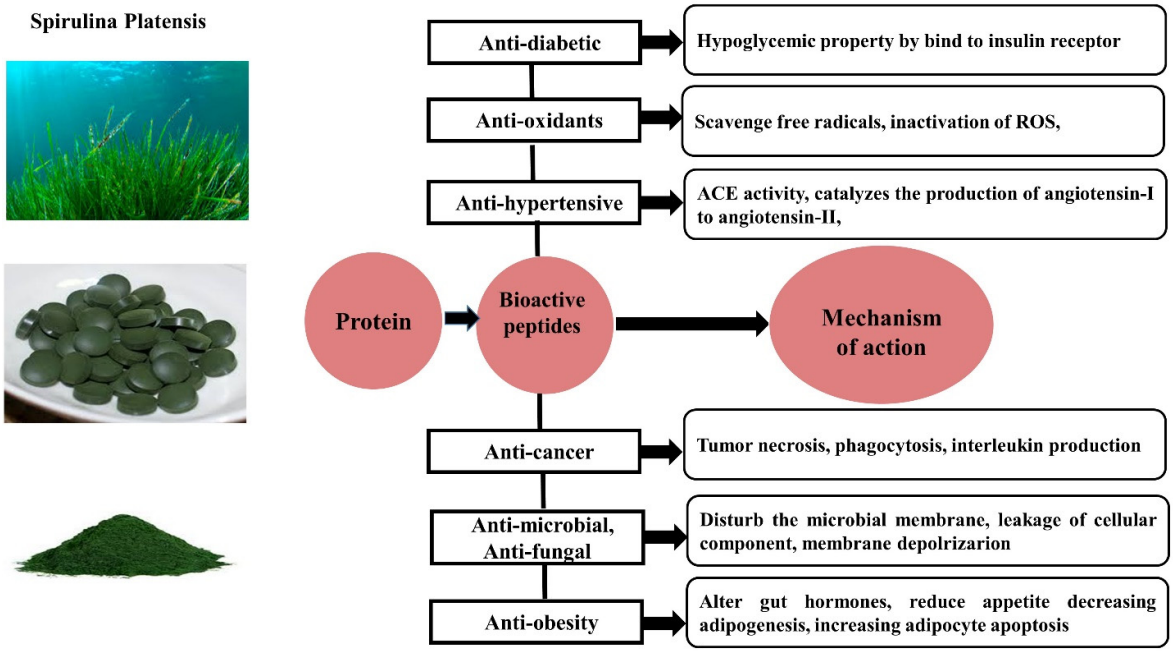

Figure 3. Potential health benefits and mechanism of action associated with *A. platensis*-derived peptides.

4. Health-Promoting Effect of *A. platensis*-Derived Peptides

4.1. Antihypertensive Activity

Hypertension is a major health problem worldwide, affecting nearly one third of adults. High blood pressure is also a risk factor for other diseases such as arteriosclerosis, stroke, myocardial infarction, and cardiovascular diseases [30]. In the regulation of blood pressure, Angiotensin-I-converting enzyme (ACE), a Zn-metallopeptidase, plays a vital role in blood pressure regulation in the renin–angiotensin system (RAS) and the kallikrein–kinin system (KKS). ACE changes angiotensin-I to angiotensin-II, which causes a rise in blood pressure. Therefore, the inhibition of ACE is a critical step in alleviating hypertension and stimulating cardiovascular function. Though anti-hypersensitive drugs have some side effects, the need for hypertensive peptides from natural sources (food) is increasing. Peptides associated with potential health benefits are listed in Table 4.

A. platensis contains much protein, and as a result has the ability to release bioactive peptides that have inhibitory activity due to the angiotensin-I-converting enzyme (ACE-I; EC 3.4.15.1) and/or renin (3.4.23.15) [79]. Anekthanakul and his team used in vitro and in silico methods to identify an ACE-I inhibitory peptide sequenced as IRDLDYY; this peptide showed a 1.75 mM IC_{50} value and was reported as being non-toxic for humans [80]. The peptides VEP and IQP showed ACE-I inhibitory in vitro properties when demonstrated orally in spontaneously hypertensive rats [81].

A significant decrease in systolic blood pressure (from 149 ± 7 mm Hg to 143 ± 9 mm Hg) was observed in a double-blind, placebo-controlled randomized trial when hypertensive and overweight Caucasians were administered with "*A. platensis maxima*" for three months. The stiffness index was also reduced by 5% in the target population [82]. Decreases in diastolic pressure and plasma triglycerides (5% and 21.7%) were also observed in Diabetic Korean patients through the administration of *A. platensis* powder with a dose of 8 g/12 weeks. Other health indices such as total insulin, cholesterol, and systolic blood pressure, as well as plasma levels of glycosylated hemoglobin A1C (HbA1c), High-Density Lipoprotein, and Low-Density Lipoprotein levels, remained unchanged [83].

According to He et al., two peptides VEP and IQP, showed in vitro and in vivo antihypertensive activity when absorbed by the human intestinal system. Tripeptides VPP and IPP are used in the development of functional foods in some countries and have the potential to show antihypertensive activity [84]. Low molecular weight peptide fractions (<10 kDa) are mainly responsible for the inhibition of ACE. The activity of peptides mainly depends on the structure of the peptides, and the amino acid sequence and composition, especially, are widely recognized for ACE inhibitory activity. Peptides with N-terminus and branched chain aliphatic residues (Leu, Ile, Ala, and Met) inhibit ACE by competitive effect, while peptides with positively charged residues (His, Arg, and Lys) and branched side chain (Leu, Ile, and Val), or with aromatic amino acids at c-terminal (Trp, Tyr, Pro, and Phe), inhibit ACE in a non-competitive manner [85,86]. Moreover, in the active site of ACE tetrahedrally, peptides also interact with the Zn(II) ion, which further decreases ACE activity. The peptide with ACE inhibitory activity primarily bonds with hydrogen bonds to form a stable structure [87].

A study carried out by [88] used two enzymes, pepsin and trypsin, for *A. platensis* protein hydrolysis. Dose–response in vitro ACE activity was measured for both of the hydrolysates. The IC_{50} values were 0.28 ± 0.03 mg/mL and 0.1 ± 0.04 mg/mL. These results showed that the protein hydrolysate with trypsin has three times less activity than hydrolysate from pepsin. This result is due to the various compositions of the hydrolysates, and both physical and chemical compositions may differ. Short-chain peptides with hydrophobic structures are more active and may present abundantly in pepsin hydrolysate. According to [80], a total of five peptides were obtained from *A. platensis* protein hydrolysate including (LIAGGTGPMDEY AGGTGPMDEYLI, IRDLDYY, LGTPGSSVAVG, and IAGGTGPMDEYL). All these peptides contain a high ratio of hydrophobic amino acids and show ACE inhibitory activity. These results are in line with the findings of Siaga et al., which reported that amino acids with branched side chains (V, L, I) or aromatic amino acids (W, F, I) retain a strong ACE inhibitory activity [89]. Two ACE inhibitory peptides, VEP and IQP, were obtained from *A. platensis* by the ultra-high-pressure (300 MPa)-assisted enzyme hydrolysis method, and the yields were 0.48% and 0.58%, respectively. These peptides were demonstrated to inhibit the ACE and lower the blood pressure of spontaneously hypertensive rats [90].

Table 4. Recent studies of bioactive peptides isolated from *A. platensis* and its hydrolysates.

Peptide Source	Preparation Method	Purification and Identification Method	Purified Peptide Sequence	Bioactivity	References
A. platensis platensis protein.	Hydrolysis by (trypsin, alcalase, pepsin, papain and protamex)	Ultrafiltration, gel column chromatography and MALDI-TOF-MS	1. Asn-Ala-Leu-Lys-Cys-Cys-His-Ser-Cys-Pro-Ala (NALKCCHSCPA) 2. Le-Asn-Asn-Pro-Ser-val-Cys-Asp-Cys-Asp-Met-Met-Lys-Ala-Ala-Arg(LNNPSVCDCDCMMKAAR), 3. Asn-Pro-Val-Trp-Lys-Arg-Lys (NPVWKRK) 4. Cys-Ala-Asn-Pro-His-Glu-LeuProAsn-Lys (CANPHELPNK)	Antiobesity activity	[91]
A. platensis platensis protein	Hydrolysis by thermolysin	Ultrafiltration (3 kDa), SEC-HPLC, ESI-Q-TOF	5. Val–Thr–Tyr (VTY) 6. Leu–Gly–Val–Pro (LGVP)	In-vitro ACE inhibitory activity	[92]
A. platensis maxima	Hydrolysis by Trypsin, α-chymotrypsin and pepsin	Ultrafiltration (10, 5, 3 kDa) Anion-exchange chromatography, Gel-permeation chromatography, RP-HPLC, Q-TOF/MS	7. Leu-Asp-Ala-Val-Asn-Arg	Anti-inflammatory	[56]
A. platensis maxima	Trypsin, α-chymotrypsin and pepsin	Ultrafiltration (<3 kDa), Gel-permeation chromatography, Q-TOF/MS	8. Met-Met-Leu-Asp-Phe	Anti-atherosclerotic Antiallergic	[56]
A. platensis platensis	Pepsin	Ion exchange chromatography and gel filtration.	9. Ile-Ala-Glu, Phe-Ala-Leu, 10. Ala-Glu-Leu	In-vivo ACE inhibitory activity	[93]
A. platensis platensis	Alcalase	Gel-permeation chromatography, RP-HPLC, (MALDI-TOF MS)	11. Ile-Ala-Pro-Gly, 12. Val-Ala-Phe, 13. Ile-Gln-Pro	In-vivo ACE inhibitory activity	[77]
A. platensis platensis	Papain	Gel-permeation chromatography, RP-HPLC, (MALDI-TOF MS)	14. Val-Glu-Pro	In-vitro ACE inhibitory activity	[90]
A. platensis platensis	Alcalase, flavourzyme	Ultrafiltration (<3 kDa), (SDS-PAGE), MALDI TOF/TOF	15. Thr-Asp-Pro-Leu-Ala-Ala-Cys-Ile(Leu)	Iron-chelating	[78]

Table 4. *Cont.*

Peptide Source	Preparation Method	Purification and Identification Method	Purified Peptide Sequence	Bioactivity	References
A. platensis platensis	Alcalse, papain, pepsin	-	-	In- vitro ACE inhibitory activity	[30]
Arthrospira platensis	-	MALDI-TOF MS	16. Gly-Gly-Thr-cys-Val-Ile-Arg-Gly-Cys-Val-Pro-Lys-Lys-Leu-Met(GGTCVIRGCVPKKLM)	Cytotoxicity Against cancer cell	[94]
A. platensis platensis	Thermolysin	LC/MS	Peptide sequence not identified	In- vitro ACE inhibitory activity	[80]
A. platensis platensis	Papain	Ultrafiltration (1 and 5 kDa)	17. Ile-Gln-Pro (IQP), 18. Val-Glu-Pro (VEP),	Invivo Antihypertensive activity	[81]
A. platensis platensis	Peptides produced during ultrasound-assisted protein extraction	LC-ESI-MS/MS	19. Leu-Arg-Ser-Glu-Leu-Ala-Ala-Trp-Ser-Arg(LRSELAAWSR)	In vitro: α-amylase, α-glucosidaseDPP-IV inhibition	[45]
A. platensis platensis	Hydrolysis by Pepsin	Ultrafiltration (3 kDa, 10 kDa), MALDI-TOF-MS	20. Phe-Phe-Glu-Phe-phe(FFEFF), 21. Glu-Tyr-Phe-Asp-Ala-Leu-Ala(EYFDALA), 22. Val-Thr-Ala-Pro-Ala-Ala-Ser-Val-Ala-Leu (VTAPAASVAL)	In vitro antioxidant activity	[95]
A. platensis Platensis protein	Hydrolysis by pepsin and trypsin	LC-ESI-MS/MS	Sequence of peptide was not identified	In vitro activity of Angiotension converting enzyme and DPP-IV	[88]
A. platensis Platensis	Alkaline protease and papain	Sephadex G-25 chromatography, (RP-HPLC), and Superdex 75 10/300 GL chromatography, (LC-MS/MS	23. Lys-Leu-Val-Asp-Ala-Ser-His-Arg-Leu-Ala-Thr-Gly-Val-Ala-Val-Arg-Ala (KLVDASHRLATGD VAVRA)	Antibacterial activity	[61]
A. platensis Platensis protein	Trypsin	Ultrafiltration (10, 5, 3 kDa), MALDI-TOF-TOF/MS	24. Gly-Met-Cys-Cys-SerArg (GMCCSR)	Anti-oxidant, Hemolysis inhibition, Collagen-stimulating activities	[96]

Table 4. *Cont.*

Peptide Source	Preparation Method	Purification and Identification Method	Purified Peptide Sequence	Bioactivity	References
A. platensis Platensis extract	Fermentation by Thermus thermophilus HB27, and Saccha romyces cerevisiae CH006	DEAE-52 cellulose column chromatography, UPLC-MS/MS,	25. Thr-Phe-Arg-Gly-Pro-Pro (TFRGPP) 26. Phe-Thr-Arg-Pro-Pro (FTRPP)	Antioxidant activity	[3]
A. platensis Platensis protein	Trypsin	Ultrafiltration	27. <3 kDa peptides	Bone regeneration/osteogenic	[97]
A. platensis Platensis protein	Trypsin, alcalase and papain	Ultrafiltration (10, 5, 3 kDa), gel filtration, MALDI-TOF-MS	28. Tyr-Gly-Phe-Val-met-Pro-Arg-Ser-Gly-leu-Trp-Phe-Arg (YGFVMPRSGLWFR)	Activity against cancer cells,	[98]
A. platensis platensis protein (SPP) and *A. platensis* platensis protein hydrolysate (SPPH)	Pepsin	Molecular weight by HPLC	Sequence of peptide was not identified	Anti-obesity activity	[99]
A. platensis platensis	-	UHPLC UV-MS/MS.	29. Gly-Ile-Val-Ala-Gly-Asp-Val-Thr-Pro-Ile(GIVAGDVTPI)	Ant-hypertensive acitivity	[100]
A. platensis platensis protein	Pepsin, trypsin, and chymotrypsin	Ultrafiltration (3, 5, 10 kDa), gel filtration chromatography, MALDI-TOF-MS	30. His-val-Leu-Ser-Arg-Ala-Pro-Arg (HVLSRAPR)	Inhibitory activity on HT-29 cancer cells	[68]
A. platensis maxima	Trypsin, a-chymotrypsin, and pepsin	Ultrafiltration (3, 5, 10 kDa), gel filtration chromatography, RP-HPLC	31. Leu-Asp-ala-Val-asn-Arg (LDAVNR), 32. Met-Met-Leu-Asp-Phe (MMLDF)	Anti-inflammatory activity	[56]
A. platensis platensis	Pepsin, α-chymotrypsin, and trypsin	Ultrafiltration (5,10 kDa), fast protein liquid, MALDI-TOF-TOF/MS chromatography, RP-HPLC	33. Thr-Met-Glu-Pro-Gly-Lys-Pro	ACE inhibitory activity	[101]

4.2. Antioxidant Peptides

ROS (reactive oxygen species) and free radicals (hydroxyl radicals, superoxide anion, single oxygen, and hydrogen peroxide) can negatively affect the body's important biological molecules including nucleic acids, lipids, and proteins, and can lead to the development of many chronic diseases such as including chronic inflammation, resulting in metabolic disorders, cancer, uncontrolled cell proliferation, and cell death and inflammation [102]. Similarly, diverse pathological incidents occur in biological systems by lipid peroxidation. Innate antioxidant compounds or enzymes retain the ability to scavenge ROS to maintain their proper level in the human body. Compounds responsible for antioxidant activity in microalgae are mainly phenolic compounds and short chain peptides. These compounds play a vital role in numerous physiological processes, e.g., stress response, allowing organisms to survive by interacting with their surrounding environment. These metabolites have antioxidant properties and help to regulate antimicrobial, anti-cancer, antitumor, anti-inflammatory processes, and the immune system [103].

In recent years, marine peptides have gained attention for their use as an antioxidant compound. The antioxidant activity of these peptides depends on the peptide sequence, length, and amino acid composition. Previous research has shown that peptides with hydrophobic amino acids such as Leu, Val, Trp, Ala, Phe, and Tyr in their structure exhibit higher free radical scavenging activity by helping the peptides pass through membrane lipid bilayers of target sites. Furthermore, acidic or basic amino acids (Glu, Asp, and, Lys) act as metal ion chelators, and aromatic amino acids (Tyr, Trp, and Phe) quench free radicals through the direct transfer of electrons [104]. The enzymatic hydrolysate of *A. platensis* through the trypsin enzyme exhibits ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) scavenging activity of the 1371 μM Trolox equivalent. While the hydrolysate by papain and pepsin showed the highest DPPH activity [105].

In another study, three peptides P1 (FFEFF), P2 (EYFDALA), and P3 (VTAPAASVAL) were purified from *S. platensis*. Among the three peptides, P2 exhibits higher antioxidant activity compared to P1 and P3. The higher activity is due to its secondary structure and amino acid composition. P2 also showed strong activity against AAPH-induced oxidative hemolysis and increased GSH-Px, SOD, and Cat activities by inhibiting MDA formation and protecting erythrocytes [95]. A previous study reported a hexapeptide (GMCCSR) from S. platensis hydrolysate through the trypsin enzyme, showing high antioxidant activity [96]. A recent study carried out by Villaro and his team [30] used different enzymes (Alcalase, papain, ficin, and pepsin) to generate hydrolysate from *A. platensis* protein. Hydrolysate from ficin and papain enzymes release peptides with the highest antihypertensive, antidiabetic, and antioxidant activity. A higher inhibitory activity against myeloperoxidase (MPO) was found by two peptides (Thr-Phe-Arg-Gly-Pro-Pro (TFRGPP) and Phe-Thr-Arg-Pro-Pro (FTRPP)) purified from *A. platensis* microbial fermentation. In peptide structure, Pro-Pro might play a vital role for antioxidant activity [3]. Another peptide (EYFDALA) from the enzymatic hydrolysate of *A. platensis* through pepsin exhibits excellent DPPH and ABTS activity [95].

4.3. Anti-Diabetic Peptides

Diabetes is a chronic metabolic disorder caused by elevated levels of glucose in the blood which harms the kidneys, eyes, blood vessels, and heart. The World Health Organization (WHO) reported that >400 million people worldwide are diagnosed with diabetes, and by 2045 approximately seven hundred million adults may be the victims of diabetes. A total of 1.6 million deaths/year can be directly caused by this disease [106]. According to different etiology, diabetes can be classified into two types: type 1 diabetes and type 2 diabetes. The former type is also called insulin-dependent diabetes, caused by the destruction of pancreatic β-cells due to cellular-mediated autoimmune disease and insufficient insulin secretion. Conversely, the latter is due to insulin resistance and insulin secretion, a total of 90–95% of cases of diabetes are type 2 [107]. Lifestyle and diet play an important role in the development of chronic diseases. For the management of type 2

diabetes, drugs can be used to reduce blood glucose levels and reduce insulin resistance. However, existing therapies are often associated with unwanted side effects, so there is increasing interest in the development of antidiabetic drugs without negative effects, and the use of natural products for pharmacological use. Several studies have shown that dietary ingredients such as protein hydrolysates and peptides could be effective in the management of diabetes [108,109]. Recent research has revealed the anti-diabetic activity of *A. platensis* and its protein and peptides. According to [110], *A. platensis* can prevent hyperglycemia in rats by apoptosis and gluconeogenesis, while another study indicated a reduction of blood glucose levels by 79% compared to the control [111].

Inhibitors with diverse chemical structures can inhibit the DPP-IV activity due to quick access to its long cavity active site [105]. Peptides with DPP-IV inhibitory activity are short-chain (2–5) amino acids in their structure, and the position of amino acids in peptide sequence is also important. Peptides with Pro at the *N*-terminus position, followed by Leu, Gly, Val, Phe, Ala, and ultimate *C*-terminal position, retain high DPP-IV inhibitory activity [85]. Hydrophobic amino acids (Ala, Val, Pro, Leu, Met, Ile, Gly, Trp, and Phe) also promote the specificity of the substrate [112].

Previous research has suggested that type II diabetes can be treated by targeting key enzymes such as dipeptidyl peptidase-4 (DPP-IV), α-glucosidase, and α-amylase. 1,4 glycosidic linkages of polysaccharides can be broken down by α-amylase to disaccharides, and α-glucosidase further converts disaccharides to monosaccharides, which leads to hyperglycemia. The prime target of glycemic control is DPP-IV, which helps in the inactivation of glucagon inhibitory peptide, incretin hormones, and peptide (GLP-1), which help to lower the post-prandial glucose level [113]. Hu et al., 2019 identified 11 peptides from *A. platensis* hydrolysate, and these three peptides showed in vitro anti-diabetic activities. After LC/MS and in silico identification, three peptides (LRSELAAWSR, RNPFVFAPTLLTVAAR, and GVPMPNK) were synthesized. The peptide LRSELAAWSR exhibits the best activity on DPP-IV and α-glucosidase (IC_{50} = 1167.3 µg/mL and IC50 = 313.6 µg/mL), respectively, while medium activity of α-amylase (IC50 = 313.6 µg/mL) was reported. Phycocyanin from *A. platensis* was purified and in vitro, anti-diabetic activity was evaluated by β-glucosidase and α-amylase inhibition assays [45]. Phycocyanin administration at the concentration of 250 µg/mL could inhibit the activity of β-glucosidase and α-amylase by 65% and 72%, respectively [114]. However, bioactive peptides identified from *A. platensis* with antidiabetic activity still need human trials to be used in the future as a functional food ingredient.

4.4. Anti-Cancer Peptides

Cancer is one of the leading causes of death worldwide, and its occurrence continues to rise due to various factors such as unhealthy lifestyle choices, poor diet, and elevated environmental pollution. Cancer can be characterized by improper cell function and abnormal cell growth. Chemotherapy, targeted therapy, immunotherapy, radiotherapy, and surgery are the conventional treatment methods. These methods have some adverse side effects, and the chance of tumor recurrence is also high. Therefore, it is important to search for more therapeutic approaches for the prevention and treatment of cancer [115]. In contrast, bioactive peptides can be used to control the growth of cancer cells, and peptides possessing effective antibody-related antigens for cancer, and cell bioactive peptides from various sources, have shown potential anti-cancer effects by entering into the cell membrane's lipid bilayer [116].

The anti-tumor effect of *A. platensis* protein hydrolysates and purified protein has been investigated by several researchers. A study carried out by Wang and Zhang uses single and sequential hydrolysis of *A. platensis* protein by trypsin, alcalase, and papain enzymes. At the concentration of 0.5 mg/mL, all the hydrolysates exhibited high anti-cancer activity against breast cancer cells (MCF-7), gastric cancer cells (SGC-7901), colon cancer cells (HT-29), lung cancer cells (A549), and liver cancer cells (HepG2) compared to the control 5-flurouracil (5-FU). Among all the hydrolysates, a peptide (YGFVMPRSGLWFR) was purified from papain hydrolysate and showed the highest antitumor activity on A549

cancer cells with IC50 = 104.1 µg/mL [2]. Sequential hydrolysis by alcalase/papain, three peptides (AGGASLLLLR, KFLVLCLR, LAGHVGVR), and one short peptide (LCLR) were identified. Peptide (LCLR) exhibits high anti-cancer activity against HepG2, HT-29, and A549 cancer cells. In vivo experiment results showed that a dosage of 200 mg/kg/d of the peptide fraction inhibits solid tumor growth in HepG2-bearing nude mice. The other novel peptide (HVLSRAPR) from the sequential hydrolysis of pepsin/trypsin/chymotrypsin showed inhibitory activity (IC50 = 99.9 µg/mL) against HT-29 cancer cells [95]. According to Wang and Zhang (2016), peptide fraction and its nano-encapsulation fraction from *A. platensis* were tested for antitumor activity by MTT assay in human liver and breast cancer cells. The chemotherapeutic drug 5-flurouracil was used as a standard and positive control. Both the peptide fractions (peptide fraction before encapsulation and fraction after encapsulation) showed high antitumor activity [98]. In another study, peptide phycocyanin isolated from *A. platensis* revealed anti-cancer activity against H1299 and HepG2 (liver and lung cancer cells) at the concentration of 500 µg/mL [114]. Sannasimuthu's research team identified a short-chain peptide (GGTCVIRGCVPKKLM) from *A. platensis* at the concentration of 25 µM, and the chemically synthesized peptide exhibited activity against the caspase-9-mediated apoptosis of oral cancer cells, membrane disruption, and DNA degradation [94].

4.5. Anti-Microbial and Antifungal Peptides

A significant reduction in the stability and shelf life of food products is due to lipid oxidation and microbial spoilage. It is important to produce natural preservatives and antibacterial compounds to protect food products. Antimicrobial peptides (AMPs) are natural sources of compounds that show antimicrobial activity against a variety of microorganism infections (parasites, protozoa, viruses, bacteria, and fungi) [58]. AMPs are generally small in size (<100 amino acids in their structure). Peptide characteristics such as flexibility, hydrophobicity, cationic charge, size, and amino acid composition play an important role in the interaction with the plasma membrane/cell wall of pathogenic microorganisms. The antimicrobial activity of peptides varies from peptide to peptide, depending on the method of obtaining the peptide, its source, its isolation, and purification techniques. Antimicrobial peptides can be divided into three categories based on their structure: (1) helical linear peptides, (2) open-ended cyclic peptides, and (3) disulfide-bridged cyclic peptides, with high amounts of proline/histidine and glycine in primary structures [116]. Several peptides can enter the cell wall of microorganisms to kill them by modulating the immune system through phagocytosis, disrupting cytoplasmic membranes, and interfering with nucleic acid synthesis [117]. Seghiri et al. investigated *A. platensis* and its hydrolysate effect on the growth inhibition of *B. cereus* (B.C.) and *E. coli* (E.C.), and compared it with the control sample. Among the hydrolysates, alcalase hydrolysate exhibited high activity against B.C. (11.6 mm) and E.C. (14.7 mm) [1]. The antimicrobial function of hydrolysates and peptides can depend on the amino acid composition, such as histidine, glycine, arginine, and proline, and hydrophobic amino acids. Bacterial growth can be inhibited by positively charged peptides and hydrophobic amino acids by the penetration and reaction with the cell membrane [118]. Enzymatic hydrolysis by papain and the alkaline protease of *A. platensis* were investigated for antimicrobial peptide identification. A series of chromatographic techniques (RP-HPLC, GPC, Superdex 75 10/300 GLC) was used for peptide purification. The amino acid sequence of the peptide was identified by LC-MS/MS. The identified peptide KLVDASHRLATGDVAVRA with a molecular weight of 1878.97 Da and a total of 18 amino acid residues was present in the structure. Inhibitory activity against *Staphylococcus aureus* was 16 mg/mL and 8 mg/mL for *Escherichia coli.* Due to the effective defense system and broad-spectrum characteristics of the *A. platensis* peptides against fungal and bacterial infections, it can be used as an active candidate for the development of antimicrobial drugs in the future [61].

4.6. Anti-Obesity

Obesity is caused by the abnormal accumulation of adipocytes, due to an imbalance between energy intake and expenditure. The increment in global obesity has tripled since 1975, affecting 13% of adults in 2016. Worldwide, 4.7 million deaths are linked to obesity, and life expectancy is reduced by 5–20 years [44]. The development of major human metabolic diseases such as cardiovascular diseases, non-alcoholic fatty liver, hypertension, insulin resistance, osteoarthritis, and hyperlipidemia are associated with obesity. A low energy diet supplemented with functional food has been used to reduce body mass index (BMI), body weight (BW), waist circumference (WC), cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBS).

In vitro obesity evaluation is the most important method for obesity inhibition, and the major key enzyme (pancreatic lipase) inhibition is most important. This enzyme is very important in the course of lipid metabolism. The accumulation of adipocytes originating from fibroblastic pre-adipocytes in adipose tissues is responsible for obesity at the cellular level [119]. For the reduction of obesity, the inhibition of lipogenesis, and the differentiation and proliferation of pre-adipocytes or lipolysis stimulation, is very necessary. Previous research accounts for the role of food-derived bioactive peptides in the reduction of body fat and fat metabolism. A significant reduction in BMI, WC, BW, and body fat was observed in obese patients by the administration of *A. platensis*. A significant increase in HDL-C (high-density lipoprotein cholesterol) and a reduction in LDL-C (low-density lipoprotein cholesterol), TC, FBS, and insulin was noted in metabolic syndrome patients [120].

A double-blinded placebo study revealed the effect of 1 g of *A. platensis* powder/day for 12 weeks, and a significant reduction in appetite and body weight (89.6–88.0 kg) was noted [99]. A study demonstrated that the *A. platensis* protein was hydrolyzed by five enzymes (alcalase, papain, trypsin, protamex, and pepsin). For purification of the peptides, hydrolysates were subjected to ultrafiltration and gel column chromatography. The ultrafiltration fraction (3–5 kDa) from pepsin hydrolysate possesses high inhibitory activity against lipase (72%). Its chromatographic results showed high activity (72.7–88.1%) against 3T3-L1 pre-adipocytes. The identification by mass spectrometry of four novel peptides (NPVWKRK, NALKCCHSCPA, CANPHELPNK, and LNNPSVCDCDCMMKAAR) were identified. These peptides inhibit pre-adipocyte proliferation by 32.29–60.08% [91]. Furthermore, CANPHELPNK and NPVWKRK inhibit triglyceride accumulation by up to 19.5% and 23.7%) at 600 µg/mL. *A. platensis* protein hydrolyzed by pepsin exhibits an anti-obesity effect by reducing weight by 39.80%, while decreasing the cholesterol level by 20.8% and serum glucose level by 23.8% [121].

5. Conclusions

Among the Cyanobacteria, *A. platensis* has the potential to become a superfood in the future. This review summarized important information about *A. platensis*'s nutritional composition, bioactive peptide production, isolation, purification identification of potential health benefits, and its role in health improvement. Overall, the research reveals that *A. platensis* is a valuable source of protein, minerals (potassium, calcium, selenium), omega-6 fatty acids, and vitamins (Vit E, A, C, B), and can be used as an important ingredient for the development of functional and fresh foods, dietary supplements, and be put to pharmaceutical use to obtain specific health outcomes. Although *A. platensis* is being used in many food products such ice cream, cookies, snacks, sauces, and pasta, *A. platensis* also contains a high amount of protein, and to use this protein the extraction of protein is needed first. For the release of bioactive peptides, enzymatic hydrolysis (pepsin, papain, trypsin, alcalase, flavorzyme) and fermentation are mainly used. Several studies show the bioactivities of released peptides such as hypoglycemic properties, and immunostimulant, anti-inflammatory, antiobesity, antitumor, and antioxidant activities. Important cost-effective methods need to be developed for the production, purification, isolation, identification, and stabilization of these peptides at the market level and to minimize the production of toxic compounds. Several in vitro and in vivo studies have shown the bioac-

tivity of peptides, however, human trials and molecular studies are needed to investigate the mechanism by which peptides exhibit their action at the cell level.

Future Trends

Although *Spirulina*-derived bioactive peptides have potential health benefits, further in vivo and clinical trials need to be conducted for validation and to transfer technology from bench to bedside. The demand of the new drug and functional food from natural sources is appealing. Therefore, *Spirulina*-derived peptides can play an important role in the nutraceutical, cosmeceutical, and pharmaceutical industries.

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Abbreviations

A. platensis, Arthrospira platensis; ANVISA, National Sanitary Surveillance Agency; FDA, Food and Drug Administration; GRAS, Generally Recognized as Safe; ACE, Angiotensin converting enzyme; MWCO, Molecular weight cut-off filtration; WHO, World Health Organization; FAO, Food and Agriculture Organization; DNA, Deoxyribonucleic acid; PUFA, Polyunsaturated fatty acids; MUFA, Monounsaturated; SFA, Saturated fatty acids; DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; DW, Dry Weight; GAE, Gallic acid equivalents; QE, Quercetin equivalents; DH, Degree of hydrolysis; MAO-A, Monoamine oxidase-A; IC_{50}, Half maximal inhibitory concentration; UV, Ultraviolet; MS, Mass spectrometry detectors; HPLC, high-performance liquid Chromatography; ICP-OES, Inductively coupled plasma optical emission spectrometry; LC-MS, Liquid chromatography–mass spectrometry; LC-MS/MS, Liquid chromatography with tandem mass spectrometry; RP-HPLC, Reversed phase high-performance liquid chromatography; CIEF, Capillary iso-electric focusing; CE, capillary electrophoresis; IEC Ion-exchange chromatography; GFC, Gel filtration chromatography; UHPLC, Ultra-high-pressure liquid chromatography; HILIC, Hydrophilic interaction liquid chromatography;

CE, Capillary electrophoresis; FAB-MS, Fast atom bombardment mass spectrometry; ESI-MS, Electrospray ionization–mass spectrometry; MALDI-MS, Matrix-assisted laser desorption/ionization mass spectrometry; MALDI-TOF, Matrix-assisted laser deionization time-of-flight; FPLC, Fast protein liquid chromatography; RAS, Renin-angiotensin system; KKS, Kallikrein-kinin system; HbA1c, Glycosylated hemoglobin A1C; MTT, 3-(4, 5-dimethylthiazole-2-yl)-2,5-diphenyltetrazoliumbromide; MDA, Malondialdehyde; ROS, Reactive oxygen species; SOD, Superoxide dismutase; ABTS, 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid; DPPH, 1,1-diphenyl-2-picrylhydrazyl; DPP-IV, Dipeptidyl peptidase-IV; BMI, Body mass index; BW, Body weight; WC, Waist circumference; TC, Cholesterol; TG, Triglyceride; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; FBS, Fasting blood glucose.

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