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Spirulina Platensis Microalgae as High Protein-Based Products for Diabetes Treatment

Mustofa Ahda[a,b], Suhendra[b,c], and Adi Permadi[c]

[a]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia; [b]Ahmad Dahlan Halal Center, Universitas Ahmad Dahlan, Yogyakarta, Indonesia; [c]Faculty of Chemical Engineering, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

ABSTRACT

Spirulina (Arthrospira platensis) is a protein-rich source because it contains approximately 60% protein. Therefore, it has positive impacts on human health, including anti-diabetes. The potential of *Spirulina platensis* as an anti-diabetic agent has been investigated in-vitro and in-vivo. Its extract is capable of inhibiting amylase, α-glucosidase, and DPP IV enzymes in a range of medium activities. Furthermore, spirulina at 250 mg/Kg body weight (BW) in mice can reduce blood glucose levels with similar outcomes to the positive controls (pioglitazone and glibenclamide). Protein groups (Phycocyanin), isolated peptides, and flavonoid groups such as Pinocembrin, Acacetin, and others have been predicted to be responsible for lowering glucose levels. In the market, several commercial products have been sold. Many commercial products have been sold in the market. However, these products are food supplements because a clinical study has not yet been undertaken to confirm their potency and safety. According to this analysis, there is a significant chance to produce anti-diabetic medications from spirulina sources in the future.

KEYWORDS

Spirulina platensis; antidiabetes; phycocyanin; acacetin; pinocembrin

Introduction

Diabetes cases should be reduced globally over the next 20 years. It is one of the hazardous metabolic disorders that have resulted in human death.[1] Therefore, many synthetic medications, such as acarbose, stimagnitol, and others, have been sold on the market to prevent it. In general, this disease is associated with an increase in blood glucose levels above normal. It can be caused by a problem with insulin secretion and sensitivity. However, long-term usage of synthetic medications could potentially result in adverse effects such as hypoglycemia, cancer, and other complications.[2] The use of herbs for diabetes therapy is a popular issue that has received a lot of attention.

China is one of the Asian countries that has produced traditional Chinese medicine (TCM) herbal medications for diabetes therapy. Over 30 TCM medicines have been approved as herbal diabetes medications.[3] Therefore, the high potency of natural resources from Indonesia, particularly microalgae, reveals a great chance to contribute to the creation of herbal medications. Generally, any four types of microalgae groups such as *Bacillariophyceae* (diatoms), *Chlorophyceae* (green algae), *Chrysophyceae* (golden algae), and *Cyanophyceae* (blue algae).

One of the microalgae types that will be reviewed is spirulina sp. It has many advantages in many industrial fields such as raw materials for herbal medicines, foodstuffs, beverages, etc. Many industrial applications from spirulina because it contains essential nutrients such as amino acids, minerals, vitamins, and fatty acids.[4] Lupatini et al.[5] reported that spirulina is rich in protein

CONTACT Mustofa Ahda mustofa_ahda@yahoo.com Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Ahmad Dahlan, Jl. Prof. Dr. Soepomo, Janturan, Campus 3, Yogyakarta, Indonesia

sources where the protein levels are almost the same as meat or soybean. Furthermore, spirulina is a renewable natural source that can be produced in a bioreactor, making production simple.[6,7] According to a previous study, the World Health Organization (WHO) declared spirulina as a future food for decreasing childhood malnutrition concerns in 1992.[8] Furthermore, spirulina at 400 mg/kg body weight rat significantly decreases blood glucose levels and lipid profile in streptozotocin-induced diabetic rats.[9]

Therefore, this review is now focused on therapeutic uses, specifically antidiabetes. However, spirulina has been widely used as a food supplement for people and animals due to its high protein, minerals, and vitamin content.[10] It is a fascinating subject because the existence of synthetic medications for diabetes results in long-term negative effects. The discovery of diabetic medications from natural resources is still under investigation. Therefore, this review will supply the last information on spirulina use as an anti-diabetes. Future studies will support spirulina applications in the medical industry.

Active compounds of spirulina microalgae

Chemical compounds of spirulina microalgae are an important part of supporting its biological activities. On the other hand, they should be mentioned and confirmed before spirulina use due to the lack of active compound levels decreasing its biological activities including antidiabetes. However, spirulina has been known as a natural superfood that contains several chemical compounds such as protein, vitamins, minerals, β-carotene, fatty acids, etc.[8] General information regarding the chemical compounds of spirulina is illustrated in Table 1.

Based on Table 1 depicts that the dominant chemical compounds are fatty acid groups and protein groups. These chemical compounds are responsible for repairing cells of the human body tissues and influence metabolism. The benefits of spirulina consumption are associated with its biological activities. The advantages of spirulina are modulating body immunes and inhibiting inflammation, cancer, and oxidation stress occur.[16,17] Even, the rich proteins and amino acids will increase the nutritional value.[17] Table 1 also shows that spirulina is a high mineral source. The dominant flavonoid groups are Pinocembrin and Acacetin where both active compounds are highly responsible for their biological activities including antioxidant, anti-diabetes, and anti-hyperlipidemia effects.[18] The total flavonoids and total phenolic of spirulina are around 15.60 ± 2.74 mg Rutin Equivalent/g dry weight and 4.19 ± 0.21 mg Gallic Acid Equivalent/g dry weight, respectively.[19] Therefore, El-Sayed et al.,[20] also predicted that both phenolic compounds and phycocyanin positively affect hypoglycemic and hypolipidemic conditions. Furthermore, several minerals such as calcium, phosphorous, zinc, etc supported the application of spirulina as a popular supplement.[21]

Potency of spirulina microalgae as an antidiabetes agent

The isolated chemical compound from spirulina is phycocyanin which is responsible for reducing blood glucose levels at a dose of 100 mg/kg BW mice for 3 weeks.[22] A previous study has reported that 3 peptide types of spirulina inhibited α-amylase, α-glucosidase, and DPP IV enzymes.[23] Therefore, these results depict that spirulina has big challenges as an antidiabetes agent. Food-based proteins and bioactive peptides are possible to decrease blood glucose levels through several mechanisms of action including α-amylase, α-glucosidase, and DPP IV.[24,25] Besides the presence of protein levels, several flavonoid groups also act as anti-diabetes.[18] Even though the isolated phycocyanin derived and phycocyanobilin can protect the oxidation process where both active compounds have a dose orally 300 mg/kg for 10 weeks and 15 mg/kg for 2 weeks, respectively.[26] In silico approach also showed any interaction between phycocyanin and the protein structures of α-amylase (PDB ID: 1HNY) and α-glucosidase (PDB ID: 2ZE0) with hydrogen bonding on their catalytic residue.[27] Furthermore, another compound including pinocembrin was grouped into a moderate α-

Table 1. Composition of chemical compounds from *Spirulina platensis*.

Compound classes	Compound types	Levels (mg/kg)	References
(1) Proteins	(a) Total Protein	88,800–618,000	[11–13]
	(b) Total amino acids	114.9–561.4	[14]
	(1) **Essential amino acids**		
	• Leucine (mg/kg)	291.1	[12,13]
	• Phenylalanine	237.8	
	• Lysine	191.0	
	• Valine	184.0	
	• Isoleucine	141.2	
	• Threonine	135.9	
	• Histidine	134.6	
	• Methionine	53.1	
	(2) **non-essential amino acids**		
	• - Glutamic acid	470.3	
	• - Arginine	449.1	
	• Aspartic	366.9	
	• Alanine	338	
	• Cysteine	33.0	
	• Tyrosine	197.4	
	• Serine	184.3	
	• Glycine	150	
	• Proline	148.8	
(2) Minerals	• Ca	3637–5000	
	• Na	2167	
	• P	1231–8000	
	• Fe	124–900	
	• Zn	25.01–150	
(3) Vitamins	• Beta carotene	700	
	• Vitamin E	600	
	• Niacin	122	
	• Riboflavin	37	
	• Thiamin B1	30	
(4) Fatty acids	(c) Total Fat	35,500–301,200	[11,15]
	• linoleic acid	6.8	[14]
	• γ-linolenic acid	5.95	
	• PUFA	42.5	
(5) Others	(d) 0Total Phenolic Levels	9971	[13]
	(e) Flavonoid levels	7111	

glucosidase activity which has IC_{50} of 0.35 ± 0.021 and 0.39 ± 0.020 mM from both maltase and sucrose, respectively.[28] The previous studies that explain the potential of this microalgae as antidiabetes as given in Table 2.

Table 2 showed that spirulina contains specific peptides and proteins acting as anti-diabetes based on the *in-vitro* and *in-vivo* evaluations. *In-vitro* testing elaborated that spirulina has moderate activity to inhibit α-amylase, α-glucosidase, and DPP-IV. These mechanisms of action are related significantly to decreasing blood glucose levels. However, *in-vivo* evaluation explained that spirulina and isolated compounds have a good ability for increasing insulin sensitivity and reducing glucose, cholesterol, and triglycerides.[18,20] He et al.,[31] reported that *Spirulina platensis* will affect and improve several biochemical parameters in reducing blood glucose levels such as the increase in short-chain fatty acid production. Besides, the use of spirulina will increase plasma insulin and hexokinase activity.[32]

Based on previous studies, spirulina powder can decrease blood glucose levels in mice at a dose ranging from 50–500 mg/kg BW for 3–6 weeks.[18,20,22] While the suspension form of spirulina also increases its biological activity as anti-diabetes compared with spirulina powder (Table 2). However, the suspension form of spirulina is a better activity than the powder form. Mathur[8] also recommended that the purification and isolation process should be performed to find the best spirulina that will be commercialised further. Based on previous studies, spirulina has a huge potency to be commercialised as an antidiabetes agent. Even though, the development of product forms of spirulina is also needed to increase its biological activity.

Table 2. Previous studies of S*pirulina platensis* testing as anti-diabetes.

Extract types	Doses	Testing Evaluations	Reports	References
The isolated peptides (LRSELAAWSR) from Spirulina water extract	-	In-vitro	It has inhibited α-amylase, α-glucosidase, and DPP-IV which results from IC_{50} are 313.6 µg/mL, 134.2 µg/mL, and 167.3 µg/mL, respectively	[23]
The isolated Pycocyanin from spirulina	100 mg/kg BW mice	In-vivo	It has increased insulin sensitivity and decreased glucose levels	[22]
Butanol fractions	250 mg/kg BW rats		Decrease blood glucose levels in rats	[29]
Spirulina Powder	50 mg/kg BW rats		Decrease glucose, triglyceride, and total cholesterol levels in the blood of rats (almost a quarter)	[18]
Spirulina Powder	500 mg/kg BW albino rats		This dose can decline almost half of glucose levels in diabetic rats	[30]
Spirulina Feeds	30 mg/kg BW rats		It can increase trace minerals and reduce glucose concentrations	[12]
Spirulina Platensis suspension and its bioactive including phycocyanin (PC), phycocyanopeptide (PCP), and phycocyanobilin (PCB)	50 mg/ml/kg−1 body weight		They reduced fasting serum glucose by more than half the glucose levels of diabetic rats	[20]

*BW= Body weight.

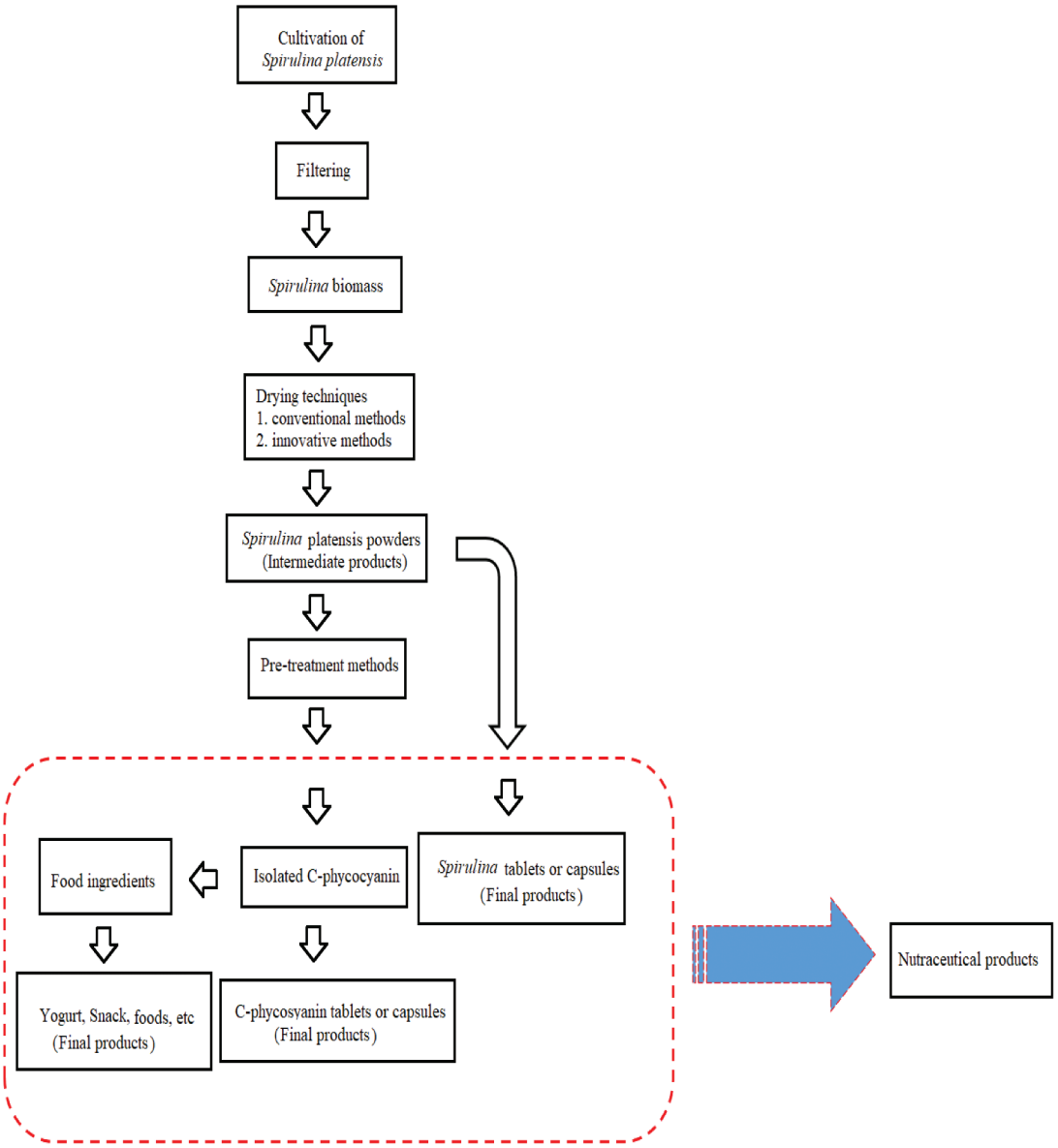

Figure 1. The steps of *Spirulina platensis* production: From farm to commercialised products.

Spirulina production process becomes commercial spirulina products

The Spirulina cultivation process is an important part to control its chemical compounds hence they significantly affect its biological activity. Narala et al.,[33] depicted that the low production of spirulina relatively depends on optimised cultivation conditions. However, the optimised spirulina cultivation will influence obtained biomass and spirulina nutrition contained. The increase in spirulina biomass will increase income and increase economic value due to spirulina powder also increasing. Suherman et al.,[34] observed that the mixture of Urea and TSP (Triple Super Phosphate) fertilizers can considerably change the protein content of spirulina, with the greatest protein levels reaching 34.33% with urea and TSP composition is about 0.6 g/l Urea +0.012 g/l TSP. Many factors influence spirulina production, including temperature, light, inoculation

Table 3. The *Spirulina platensis* products have been released to the market[14].

Product names	Forms	Companies and Origin Countries	Functions
Australian spirulina	Tablets	AAU Australia Pvt Ltd., NT (Australia)	Dietary supplements (60–63% proteins)
Sunfood; Spirulina whole plant powder	Tablets and Capsules	General Nutrition Corp., Pittsburgh (USA)	Superfoods and supplements
Spirulina micro-algae	Capsules	Nature's Way Products, Inc., Springville, Utah (USA)	Dietary supplements (Immune support)
Organic Spirulina	Tablets	Now Foods, Bloomingdale (USA)	Nutrien Rich superfoods
California spirulina	Tablets	Nature Pure, Inc., Larkspur, California (USA)	Superfood and Vegetarian
Spirulina	Tablets	Source Naturals, Inc., Santa Cruz, California (USA)	Dietary supplements
Spirulina Natural	Powder and Tablets	Earthrise Nutritionals LLC, Irvine, CA (USA)	Green superfoods
Pure Hawaiian Spirulina	Powder and Tablets	Nutrex Hawaii Inc., Kailua-Kona, Hawaii (USA)	Superfood supplements
Spirulina	Powder and Capsules	Pure Planet Products, Inc., Long Beach, CA (USA)	Nature perfect multivitamin
Spirulina	Tablets	Puritan's Pride, Inc., Oakdale, New York (USA)	Dietary supplements
Spirulina 1000 mg	Capsules	21st Century HealthCare, Inc., Arizona (USA)	Complete nutrition and good health
100% spirulina	Powder and Tablets	Japan Algae Co., Ltd., Tokyo (Japan)	Superfood supplements

quantity, stirring speed, solids dispersed, pH levels, the quality of the water, and the micronutrients supplied.[35]

Nowadays, the development of spirulina-based products is a good innovation to improve the added value of spirulina. The raw material of spirulina contains a narrow application such as feeding animal nutrition. Currently, many products including foods and beverages, cosmetics, and pharmaceutical products contain spirulina which is intentionally added to increase product quality. Grahl,[36] has blended spirulina into other foods to produce novel foods that can change eating habits and food culture. This purpose is a good idea due to the change in eating habits will open a big opportunity for new food development in the future, especially for non-animal meat-based foods. Rimkus and Simkus[37] have registered that the combination of spirulina and honey becomes a food supplement for the human diet. Fig. 1 illustrated the several steps of spirulina production from farm to industrial products.

To produce a spirulina powder, spirulina materials should be dried using traditional and innovative drying. This step is an integral part of controlling the chemical compounds of spirulina. Many chemical compounds of spirulina are degraded easily and will decline in spirulina quality. Demarco et al.,[38] said the use of traditional dryings such as air drying (at 40–60°C), freeze drying, and cast-type drying and innovative drying including vacuum cast-type drying (at 40–60°C) are suitable techniques for producing spirulina powders. Besides spirulina capsules and tablets, spirulina powder can be incorporated into food products as a natural ingredient. El-Hameed et al[39] have successfully added spirulina to Pasta products which contain an increase in fatty acid contents of raw and cooked pasta. Another study by Saharan and Jod[40] also reported that 6% of spirulina powder added to wheat flour is acceptable for consumers. However, high spirulina levels will change the flavor, appearance, and textures. However, sometimes 12.5% of spirulina powder added to foods is also acceptable because it depends on eating habbits each person.[41]

The spirulina products have been commercialised

In general, microalgae can be created become food supplements due to several active compounds of microalgae such as astaxanthin, polyunsaturated fatty acids (PUFA), β-carotene, Pinocembrin, Acacetin, etc., are responsible for biological activities.[8,18,42] The spirulina-based products can be widely applied such as food ingredients and supplements, cosmetic

ingredients, or alternative herbal drugs including antidiabetes. Nowadays, Slovenian markets provided several spirulina supplements in various forms such as tablets, powders, capsules, flakes, and fresh that are made in various origin regions such as Japan, Italy, China, India, Hawaii, etc.[4] The spirulina products were sold as food supplements because it is easier to distribute to the market. Several spirulina products have been released to the Market as given in Table 3.

All spirulina products sold in the market is not containing specific benefits. Many companies produce spirulina products as food supplements. However, the specific benefit of spirulina products should be performed through several steps before release. Thus, it is a big problem for the industrial market. However, the industry was focused on profit-oriented so it should release quickly its products. This problem can be removed after a clinical study has been performed completely on raw spirulina powder. At present, the clinical study of spirulina use is limited to small participants (<50 participants), especially an antidiabetic drug. For specific functions, however, spirulina products should be proven through a clinical study to ensure their biological activities, especially anti-diabetes agents.

Future studies and recommendations

Many spirulina products have been sold in the market in various forms such as tablets, powders, and capsules. However, It is only consumed as a food supplement due to the limitation of a clinical study that has been conducted to prove its potency. Therefore, the clinical study should be performed to support pre-clinic studies before. For diabetes treatment, *in-vitro* and *in-vivo* evaluations showed that it affects significantly the decreasing blood glucose levels. However, the evidence-based application of spirulina using clinical study is still limited. A previous study reported that the clinical studies of spirulina applications have been applied to several diseases such as chronic fatigue, inflammation (immunomodulators), diabetes (Cholesterol reduction), cancer, and melanosis and keratosis (chronic arsenic exposure).[16] Another study also explained that any different low-density lipoprotein and high-density lipoprotein ratio (LDL:HDL) is significant among 15 diabetic patients given spirulina.[43] The development of spirulina tablets containing hydroxypropyl cellulose has been registered as Paten in China with the number: CN 104382950A. Therefore, these results can be used as a good recommendation for clinical study phases I, II, etc. on diabetic patients in the future. Even, the production of spirulina-based foods should be applied due to the big potency of spirulina as anti-diabetes treatments have been evaluated using in-vitro and in-vivo testing.

Conclusion

This review spells out the putative active compounds from spirulina platensis that play significant a role in anti-diabetes. Proteins and isolated peptides positively affect to control of blood glucose levels. Besides, phenolic groups and flavonoid groups are also reducing significantly blood glucose levels. The spirulina forms will influence its biological activities whereas the suspensions form has better activity than the powder form and its extract. In future studies, the development of spirulina form should be considered to acquire the best spirulina products such as spirulina suspension, nano-emulsion spirulina, etc. This finding opens up a big opportunity to develop spirulina-based anti-diabetes drugs.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Mustofa Ahda http://orcid.org/0000-0002-2185-043X

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