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Evaluation of antidiabetic effect of *Spirulina* on blood of Alloxan Monohydrate induced mice

S. B. SHASHI, MANISHA* AND RAGHBENDRA PRATAP**

RB Jalan Bela College, Bela Darbhanga-846004 India,
*L. N. Mithila University, Darbhanga, India
**Murarka College, Sultanganj, India. raghbendrapratap@gmail.com

ABSTRACT

The effect of *Spirulina platensis* powder on blood profile in normal and diabetic mice was investigated and presented in present work. Diabetes was induced in Male mice (30 ± 5 g) by intra-peritoneal injection of alloxan monohydrate. Both normal and diabetic mice were fed with standard animal food containing 40% of *Spirulina platensis* powder for three weeks. In diabetic mice, reduction was recorded in Mean body weight from 30.64 ± 0.36 (gm) to 21.21 ± 1.259 (gm) after 28 day of treatment and in acute oral toxicity study, Spirulina was safe upto a dose level of 500 mg/kg of body weight. No lethality or any toxic reactions were found upto the end of the study period. In acute study, Spirulina (100,200 and 400 mg/kg) (Layam and Reddy, 2006).The onset of reduction of blood glucose of Spirulina (100, 200 and 400 mg/kg) was observed at 2h (76.79±0.436, 76.66±0.411 and 76.16±0.378 mg/dl respectively), peak effect at 24 h (118.82±3.042, 115.82±2.708 and 100.82±2. mg/dl respectively) .In the sub-acute study, repeated administration (once a day for 28 days) of the Spirulina. It Acts significantly ($P < 0.001$) reduction in the blood glucose level as compared with control group. Maximum reduction in blood glucose level was observed (233.6±16.539 to 85.65±3.881 mg/dl respectively) on 35th day in the diabetic mice treated with Spirulina (100, 200 and 400 mg/kg). Body weight of control treated (30.64±0.366, 30.68±0.358, 29.99±0.272, 29.72±0.29, 29.41±0.306 and 29.19±0.324 gram respectively) and Spirulina treated (100,200 and 400 mg/kg) diabetic mice weight increased during study period. The peak recovery (18.19±0.839 to 28.83±0.612 gram respectively)was obtained on 35th day. On the other hand, mice gained body weight (Table 3)which indicated beneficial effect of Spirulina In oral glucose tolerance test, Spirulina (400 mg/kg) produced significant ($P<0.001$) increase in glucose threshold, 60 min and 30 min post glucose loading in non-diabetic (Table 4) as well as diabetic (Table 5) mice respectively. A significant increase in the level of blood glucose, total haemoglobin and a decrease in body weight were observed in diabetic mice when compared to control mice. Administration of *Spirulina* to diabetic mice significantly decreased the level of blood glucose and increased body weight (Table 3) gain to near control level. The diabetic mice showed a significant decrease in the levels of total hemoglobin. Administration of *Spirulina* to diabetic mice restored the total haemoglobin to almost control level. So, *Spirulina platensis* powder may be of great value in managing the diabetic complications.

Keywords: *Spirulina platensis powder, Diabetes, blood glucose, Haemoglobin, Mean body weight , Diabetic complications, oral glucose tolerance test.*

INTRODUCTION

Diabetes is a metabolic disorder is becoming a major health problem. Due to its high prevalence and potential deleterious effects on a patient's physical and psychological state, diabetes mellitus, which can result in a morbid condition, is a major medical concern. (Halpern *et al*., 2000). According to the World Health Organization (WHO) the number of diabetics has doubled in the past few years and is expected to double once again by the year 2025. Today, there are 160,000 diabetics worldwide (Macedo *et al*., 2002). *Spirulina* is a microscopic blue-green aquatic plant and it is the nature's richest and plant and it is the nature's richest and most complete source of organic nutrition. *Spirulina* has economic

importance due to its nutritional value (Rafiqul *et al*., 2005) and is also important in the area of healthcare (Richmond, 1986 and Sasson, 1988). The concentrated nutritional profile of *Spirulina* occurs naturally, so it is ideal for those preferring a whole food supplement to artificial nutrient sources. *Spirulina,* the blue-green alga, has a unique blend of nutrients that no single source can provide. It contains a wide spectrum of nutrients that include B-complex vitamins, minerals, good quality proteins, gamma-linolenic acid and the super anti-oxidants, beta-carotene, vitamin E and trace elements. *Spirulina* is fast emerging as a whole answer to the varied demands due to its impressive nutrient composition which can be used for therapeutic uses (Venkataraman, 1998).*Spirulina*, a blue-green alga, is now becoming a health food worldwide. It is a multicellular, filamentous cyanobacterium belonging to algae of the class *Cyanophyta* (Kumari *et al*., 2015). Antidiabetic property of *Spirulina* as a food supplement (Kapoor and Mehta ,1993).The *Spirulina* ability as a potent anti-viral (Hayashi and Hayashi,1996), anti–cancer, (Lisheng,1991), hypocholesterolemic (Kato *et al*.,1984)and health improvement (Annapurna *et al*.,1991) agent is gaining attention as a nutraceutical and a source of potential pharmaceutical . Although there are number of drugs available in the market long time use may cause a number of side effects. Hence, a large number of studies are in progress to find natural sources, which are effective in reducing the intensity of diabetes.

MATERIALS AND METHODS

Experimental Animals:

Three month old male Swiss albino mice (Body weight: 30 ± 5 g) were obtained from CDRI Lucknow were maintained at the animal house of University Dept. of Zoology, R. B. J. B. College, Bela Darbhanga, Bihar. They were separated and kept in cage in a temperature and humidity controlled with 12 h light/dark cycle. Food and water were given to the animal according to their need. All the animals were kept as accepted principles for laboratory animal use and care as per the guidelines of CPCSEA. The mice were acclimatized for one week before the experiment and then used in experiment at about 12 weeks of age.

Powder Preparation:

Powder product of *Spirulina platensis* were purchased from Sunova *Spirulina*, Sanat Products Ltd., Sikandrabad, Buland Shahar, UP, India. This company sold product commercially for medicinal and nutritional purposes. It is a spray dried product in powder form, standard in quality and a part of bulk production by the industry.

Drugs and Chemicals:

The drug alloxan monohydrate (Loba Chemicals, Mumbai) was purchased from commercial sources. All other chemicals were analytical grade and used as such without further testing.

Induction of Diabetes:

Experimental animals were kept on fast for 18 h prior to induction of diabetes. Diabetes was induced by intra-peritoneal administration of alloxan monohydrate (Rodriguez *et al.*, 1999). The total dose of alloxan-monohydrate (450 mg/kg/bw) was administered in three injections at intervals of 48 h (150 mg/kg/bw each time).

The present work was undertaken to evaluate the antidiabetic effect of *Spirulina* on alloxan monohydrate induced.After a 48-hour fast, the mice were weighed and anesthetized by her inhalation in a glass dome. A solution of alloxan at 2% diluted in normal saline(0.9%)

was administered to the animals in a single dose corresponding to 40 mg of alloxan per kg of animal weight injected into their penial vein. Blood glucose levels were elevated (The level of blood glucose considered to be normal in *Mus musculus* ranges from 50 to 110 mg/100ml. In this study, mice with glucose levels above 200mg/dl were considered as having severe diabetes) in diabetic mice. The levels of blood were estimated using standard protocols.

RESULTS AND DISCUSSION

A significant increase in the level of blood glucose, total haemoglobin and a decrease in body weight were observed in diabetic mice when compared to control mice. Administration of *Spirulina* to diabetic mice significantly decreased the level of blood glucose and increased body weight gain to near control level. The diabetic mice showed a significant decrease in the levels of total hemoglobin. Administration of *Spirulina* to diabetic mice restored the total haemoglobin to almost control levels (Table 6 and Table 7). In acute oral toxicity study *Spirulina* was safe up to a dose level of 500 mg/kg of body weight. No lethality or any toxic reactions were found up to the end of the study period. In acute study (Layam and Reddy,2006) the onset of reduction of blood glucose of *Spirulina* (100, 200 and 400 mg/kg) was observed at 2h as 76.79±0.436, 76.66±0.411 and 76.16±0.378 mg/dl and at peak effect at 24 h ,118.82±3.042,115.82±2.708 and 100.82±2. mg/dl (Table 1 and Table 2). In the sub-acute study, repeated administration (once a day for 28 days) of the *Spirulina*. It acts significantly ($P < 0.001$) reduction in the blood glucose level as compared with control group. Maximum reduction in blood glucose level was observed (233.6±16.539, 174.32±1.215 and 85.65±3.881 mg/dl) on the 35th day in the diabetic mice treated with *Spirulina* (100, 200 and 400 mg/kg). Body weight of control treated (30.64±0.366, 30.68±0.358, 29.99±0.272, 29.72±0.29, 29.41±0.306 and 29.19±0.324 gram) and *Spirulina* treated (100,200 and 400 mg/kg) diabetic mice weight increased during study period. The peak recovery (18.19±0.839, 19.79±1.132 and 28.83±0.612 gram) was obtained on the 35th day in the diabetic mice treated with *Spirulina* (100, 200 and 400 mg/kg). On the other hand, mice gained body weight which indicated beneficial effect of *Spirulina* (Table 3). In oral glucose tolerance test *Spirulina* (400 mg/kg) produced significant ($P<0.001$) increase in glucose threshold, 60 min and 30 min post glucose loading in non-diabetic(Table 4) as well as diabetic (Table 5) mice respectively.These results suggest that *Spirulina* showed antihyperglycaemic activity in alloxan induced diabetic mice. In acute study *Spirulina* (100,200 and 400 mg/kg) total hemoglobin at 2, 4, 6 and 24 h. the onset of reduction of blood glucose of *Spirulina* (100, 200 and 400 mg/kg) was observed at 2h (10.28±0.166, 10.22±0.121and 10.18±0.166 gm/dl), peak effect at 24 h (10.82±0.161, 10.92±0.134 and10.82±0.161 gm/dl). Maximum reduction in blood glucose level was observed (233.6±16.539, 174.32±1.215 and 85.65±3.881 mg/dl) on 35th day in the diabetic mice treated with *Spirulina* (100, 200 and 400 mg/kg).

Table 1

Effect of *Spirulina* on Blood glucose level in alloxan-induced diabetic mice (acute study).

S.N	TREATMENT (mg/kg. p.o.)	Mean Fasting Glucose Level (mg/ dl) ± SEM				
		0-HOUR	2- HOUR	4 -HOUR	6 -HOUR	24 -HOUR
1	CONTROL	76.37±0.50	75.79±0.64	75.64±0.61	75.18±0.60	74.9±0.67
2	DIABETIC-CONTROL	76.55±0.52	81.79±2.14	97.04±0.47	115.18±2.35	129.82±2.72
3	CONTROL+SPIRULINA	76.37±0.50	75.75±0.65	75.62±0.61	75.15±0.56	74.15±0.50
4	DIABETIC+SPIRULINA-1	76.55±0.52	76.79±0.43	95.64±0.61	105.18±0.60	118.82±3.04
5	DIABETIC+SPIRULINA-2	76.51±0.53	76.66±0.41	95.37±0.58	103.78±0.64	115.82±2.70
6	DIABETIC+SPIRULINA-3	76.3±0.56	76.16±0.37	89.47±1.39	96.78±2.23	100.82±2.22

Values are mean ± S.E.M., n = 10 in each group, data were analyzed by two-way ANOVA , ns- not significant, *P<0.05,P<0.01.**

Table 2
Effect of *Spirulina* on Blood glucose level in alloxan- induced diabetic mice (subacute study).

S.N	TREATMENT (mg/kg. p.o.)	Mean Fasting Glucose Level (mg/ dl) ± SEM					
		DAY-0	DAY-7	DAY-14	DAY-21	DAY-28	AFTER REST DAY-7
1	CONTROL	76.37±0.50	76.18±0.69	75.79±0.64	75.64±0.61	75.18±0.60	74.71±0.60
2	DIABETIC-CONTROL	76.35±0.51	101.55±3.57	156.19±11.94	170.04±13.99	257.18±16.3	252.74±16.28
3	CONTROL+SPIRULINA	76.23±0.51	75.37±0.73	75.133±1.37	75.99±2.01	75.86±2.27	74.86±2.17
4	DIABETIC+SPIRULINA-1	75.35±0.57	89.67±2.27	142.67±11.25	150.51±7.01	235.92±16.4	233.6±16.53
5	DIABETIC+SPIRULINA-2	76.5±0.65	85.52±2.85	142.67±11.25	153.31±7.65	175.92±0.63	174.32±1.21
6	DIABETIC+SPIRULINA-3	76.45±0.57	76.98±0.65	79.23±2.54	83.67±2.25	86.08±3.45	85.65±3.88

Values are mean ± S.E.M., n = 10 in each group, data were analyzed by two-way ANOVA, ns- not significant, *P<0.05,**P<0.01.

Table 3
Effect of Spirulina on body weight in alloxan-induced diabetic mice.

S.N	TREATMENT (mg / kg. p.o.)	Mean Body Weight (gm) ± SEM					
		DAY-0	DAY-7	DAY-14	DAY-21	DAY-28	AFTER REST DAY-7
1	CONTROL	30.64±0.36	30.68±0.358	29.99±0.272	29.72±0.29	29.41±0.306	29.19±0.324
2	DIABETIC-CONTROL	30.52±0.33	29.78±0.326	24.39±0.52	21.58±0.36	18.41±1.601	17.19±1.091
3	CONTROL+SPIRULINA	30.58±0.10	30.45±0.345	29.82±0.264	29.43±0.288	29.32±0.334	28.99±0.3506
4	DIABETIC+SPIRULINA-1	30.64±0.34	29.88±0.316	25.29±0.272	23.28±0.414	19.41±1.344	18.19±0.839
5	DIABETIC+SPIRULINA-2	30.64±0.36	30.07±0.32	26.29±0.502	24.48±0.605	21.21±1.259	19.79±1.132
6	DIABETIC+SPIRULINA-3	30.64±0.36	30.46±0.129	29.76±0.633	29.68±0.445	29.08±0.541	28.83±0.612

Values are mean ± S.E.M., n = 10 in each group, data were analyzed by two-way ANOVA , ns- not significant *P<0.05,**P<0.01.

Table 4
Effect of *Spirulina* on oral glucose tolerance test (OGTT) in normal mice

S.N	TREATMENT (60 mg /kg. p.o.)	Mean Fasting Glucose Level (mg/ dl) ± SEM				
		BEFORE GLUCOSE	0-MINUTE	30-MINUTE	60-MINUTE	120-MINUTE
1	NORMAL	76.37±0.508	77.74±0.289	283.74±3.419	173.74±7.634	128.74±4.62
2	NORMAL+SPIRULINA-1	76.37±0.508	77.74±0.289	273.54±2.475	163.75±7.4	120.25±3.743
3	NORMAL+SPIRULINA-2	76.39±0.503	77.72±0.289	213.69±16.189	156.81±6.557	116.85±5.156
4	NORMAL+SPIRULINA-3	76.4±0.507	77.71±0.289	151.47±6.279	127.59±7.407	100.67±2.058

Values are mean ± S.E.M., n = 10 in each group, data were analyzed by two-way ANOVA , ns- not significant, *P<0.05,**P<0.01.

Table 5
Effect of *Spirulina* on oral glucose tolerance test (OGTT) in diabetic mice.

S. N	TREATMENT (60 mg /kg. p.o.)	Mean Fasting Glucose Level (mg/ dl) ± SEM				
		BEFORE GLUCOSE	0-MINUTE	30-MINUTE	60-MINUTE	120-MINUTE
1	CONTROL	76.37±0.508	77.74±0.289	282.42±3.05	172.24±7.246	117.87±3.317
2	DIABETIC-CONTROL	282.42±3.05	282.37±3.06	472.42±7.227	352.18±14.323	217.85±3.31
3	DIABETIC+SPIRULINA-1	282.32±3.044	281.41±2.356	406.42±3.399	268.18±16.813	188.01±12.279
4	DIABETIC+SPIRULINA-2	280.72±3.152	280.31±2.241	336.34±16.474	194.13±3.068	127.81±12.957
5	DIABETIC+SPIRULINA-3	270.72±7.058	270.31±7.818	138.62±15.86	129.05±7.914	101.43±2.366

Values are mean ± S.E.M., n = 10 in each group, data were analyzed by two-way ANOVA , ns- not significant *P<0.05,**P<0.01

Table 6
Effect of *Spirulina* on total haemoglobin level (acute study)

S. N	TREATMENT (mg/kg. p.o.)	PERCENT HAEMOGLOBIN LEVEL (Gram)± SEM				
		0-HOUR	2- HOUR	4 -HOUR	6 -HOUR	24 -HOUR
1	CONTROL	9.9±0.13	10.2±0.134	9.99±0.171	10.06±0.054	10±0.11
2	DIABETIC-CONTROL	10.08±0.13	10.08±0.12	10.97±0.101	11.1±0.155	11.13±0.156
3	CONTROL+SPIRULINA	9.9±0.13	10.39±0.146	10.29±0.132	10.2±0.139	10.56±0.093
4	DIABETIC+SPIRULINA-1	10.08±0.13	10.28±0.166	10.5±0.158	10.72±0.152	10.82±0.161
5	DIABETIC+SPIRULINA-2	10.08±0.117	10.22±0.121	10.63±0.061	10.78±0.121	10.92±0.134
6	DIABETIC+SPIRULINA-3	10.08±0.13	10.18±0.166	10.5±0.158	10.72±0.152	10.82±0.161

Values are mean ± S.E.M., n = 10 in each group, data were analyzed by two-way ANOVA , ns- not significant, *P<0.05,P<0.01.**

Table 7
Effect of *Spirulina* on total haemoglobin level (sub-acute study)

S. N	TREATMENT (mg/kg. p.o.)	PERCENT HAEMOGLOBIN LEVEL (Gram)± SEM					
		DAY-0	DAY-7	DAY-14	DAY-21	DAY-28	AFTER REST DAY-7
1	CONTROL	9.9±0.14	10±0.11	10.06±0.193	10.1±0.155	10.14±0.136	9.99±0.171
2	DIABETIC-CONTROL	10.62±0.075	10.62±0.075	11.14±0.133	11.38±0.147	12.88±0.196	11.78±0.062
3	CONTROL+SPIRULINA	9.9±0.13	10.1±0.133	10.14±0.142	10.35±0.136	10.36±0.117	10.02±0.1
4	DIABETIC+SPIRULINA-1	10.62±0.075	10.43±0.079	10.96±0.132	11.18±0.138	12.63±0.187	11.42±0.211
5	DIABETIC+SPIRULINA-2	10.62±0.075	10.61±0.045	10.69±0.144	10.62±0.105	10.33±0.081	10.23±0.096
6	DIABETIC+SPIRULINA-3	10.62±0.075	10.37±0.045	10.45±0.102	10.22±0.076	10.07±0.042	10.05±0.103

Diabetes is now recognized as one of the killer diseases with increasing incidence world-wide over. Oral hypoglycaemic agents especially the sulphonylureas and biguanides have been commonly used for the management of diabetes, especially the type 2, in spite of the associated adverse effects. Attention is now focused on the use of plants and herbal remedies that would be devoid of serious side effects encountered with sulphonylureas and biguanides so an alternatives treatment system is needed for proper health management of diabates.

Currently-available drug regimens for management of *Diabetes mellitus* have certain drawbacks and therefore, there is a need for safer and more effective antidiabetic drugs (Grover *et al*., 2002).Present study was undertaken to assess the antidiabetic effect of *Spirulina*. In the present study, the oral treatment of *Spirulina* decreased the blood glucose levels in diabetic mice. Venkataraman, (1998) reported that using medicinal *Spirulina* to treat alloxan-induced diabetic mice results in activation of *ß*-cells and insulinogenic effects. Alloxan is well known for its selective pancreatic islet *β*-cell cytotoxicity and has been extensively used to induce *Diabetes mellitus* in animals. It interferes with cellular metabolic oxidative mechanisms (Dunn and Mcletchie, 1943; Ahrén and Sundkvist, 1995). Intraperitoneal administration of Alloxan (40 mg/kg) effectively induced diabetes in normal mice, as reflected by glycosuria, hyperglycemia, polyphagia, polydipsia and body weight loss when compared with normal mice (Hyashi *et al.*, 1994). In the present study, it was observed and demonstrated that oral administration of *Spirulina* could reverse the above mentioned diabetic effects. The possible mechanism by which *Spirulina* brings about its antihyperglycemic action may be through potentiation of the pancreatic secretion of insulin from islet *β*-cell or due to enhanced transport of blood glucose to the peripheral tissue. This was clearly demonstrated by the increased levels of insulin and C-peptide in diabetic mice treated with spirulina. In this context, a number of other products have also been reported to

have an antihyperglycemic and insulin-release stimulatory effect (Prince *et al*., 1998 and Pari and Umamaheswari, 1999). It is also evident from Table 6 and 7 that there was an increase in total hemoglobin from normal to diabetic control albino mice, and this may be due to the formation of glycosylated hemoglobin. The increase in the level of hemoglobin in animals given spirulina may have been due to the decreased level of blood glucose that would automatically lead to a decrease in glycosylated hemoglobin. Another reason might be that *Spirulina*, which is a rich source of iron, contributed to the elevated levels of hemoglobin. The administration of *Spirulina* to alloxan dosed animals reversed their weight loss. The ability of *Spirulina* to recover body weight loss seems to be due to its anti-hyperglycemic effect. Diabetes mellitus is a metabolic disease associated with impaired glucose metabolism which in effect adversely alters intermediary metabolism of lipids and proteins. Formation of protein glycation products releases free radicals; subsequently causing oxidative stresses (Koto and Takemoto, 1984). Most of the complications of the diabetic state are initiated by the generation of free radicals: for instance LDH oxidative modification, leading to atherosclerosis (Felmenden *et al.,* 2003; Badole *et al.,* 2006 and Bhadki *et al.,* 2004) occurs only in the presence of free radicals. Basal metabolic rate, which represents energy expenditure at rest, is elevated (Nawata *et al.,* 2004). The rise in BMR is attributed to increased breakdown of lipids and proteins – as lipids have a higher concentrate of energy than do carbohydrates hence in their breakdown BMR is raised. *Spirulina* is used as medicine for the treatment of diabetes. (Venkataraman, 1998)The hypoglycemic properties of the *Spirulina* have been reported (Anuradha and Vidhya, 2001). *Spirulina* used as a source of dietary fibre, which exhibited more hypocholesterolemic activity than pure cellulose (Krishnamurthi, 2003). Some bioactive components from *Spirulina* reduced the blood glucose level in alloxan induced diabetic mice. *Spirulina* (100, 200 and 400 mg/kg) showed significant ($P<0.001$) decrease in blood glucose level at 2, 4 and 6 h. Continuous treatment with *Spirulina* (100, 200 and 400 mg/kg) for a period of 35 days showed a significant ($P<0.001$) decrease in the blood glucose level in diabetic mice. Maximum reduction of BLOOD glucose level in acute and sub-acute occurred at the dose of 200 mg/kg. The *Spirulina* showed short onset and short duration of anti-hyper glycaemic action. Sub-acute treatment for 35 days with the *Spirulina* in the treated doses brought about improvement in body weights indicating its beneficial effect in preventing loss of body weight in diabetic mice. The ability of *Spirulina* to prevent body weight loss seems to be due to its ability to reduced hyperglycaemia. *Spirulina* significantly enhanced glucose utilization in OGTT in both non diabetic and diabetic mice. From the data obtained OGTT, it is clear that administration of *Spirulina* effectively prevented the increase in blood glucose level without causing a hypoglycaemic state. The effect may be due to restoration of the delayed insulin response. In this context, other medicinal plants, such as *Pleurotus pulmonarius* (Badole *et al*.,2006), *Cassia auriculata* (Latha and Pari,2003) have been reported to possess similar effects. Steroid containing plants known to exhibit antidiabetic activity include the bark of various species of Ficus (Evans, 2002). β sitosterol was confirmed in the petroleum ether extract of fruits of *Ficus racemosa* by TLC (Harborne,1984).Flavonoids are potent antioxidant and known to modulate the activities of various enzyme due to their interaction with various biomolecules. Kameswararao *et al.,* 1997 reported that flavonoids, alkaloids, tannins and phenolics as bioactive antidiabetic principles (Catapano,1997).Early interest in *Spirulina* focused mainly on its rich content of protein, vitamins, essential amino acids, minerals and essential fatty acids. *Spirulina* is 60-70% protein by weight and contains a rich source of vitamins, especially vitamin B^{12} and provitamin A (β-carotene), and minerals, especially iron. One of the few sources of dietary γ-linolenic acid (GLA), it also contains a host of other phytochemicals that have potential health benefits. (Belay, 1993).

Phytochemical analysis indicated that, the extracts of *Spirulina* contain sterols, triterpenoids, flavonoids, glycosides, tannins and carbohydrates. The antihyperglycaemic activity of *Spirulina* may probably be due to the presence of several bioactive antidiabetic principals. It is thus apparent that *Spirulina* possesses antihyperglycaemic activity.

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