

## ANTIHYPERGLYCEMIC POTENTIAL OF *SESAMUM INDICUM* (LINN) SEEDS IN STREPTOZOTOCIN INDUCED DIABETIC RATS

P.BHUVANESWARI AND S.KRISHNAKUMARI\*

Department of Biochemistry, Kongunadu Arts and Science College, Coimbatore 641029, Tamilnadu, India.

Email: krishnashanmugambc@gmail.com

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### ABSTRACT

**Background:** In the present study, we have evaluated the hypoglycaemic effects of ethanolic extract of *Sesamum indicum* (Lin) seeds by analyzing the glucose, insulin, haemoglobin, glycosylated haemoglobin and hepatic glycogen levels.

**Methods:** Twenty four Wistar albino rats of 200-250 g each were grouped into 4 groups with six rats in each group (control, diabetic, diabetic treated and standard drug -glibenclamide treated). After treatment for 8 weeks, the animals were sacrificed and the biochemical parameters like blood glucose, serum insulin, hemoglobin, glycosylated hemoglobin, liver glycogen levels were measured.

**Results:** Blood glucose and glycosylated hemoglobin levels were significantly increased whereas the serum insulin and hemoglobin levels were significantly decreased in diabetic rats and reverted to near normal in treated groups. The liver glycogen level was significantly decreased in diabetic rats and reverted to near normal in treated groups.

**Conclusion:** The above results shows that the ethanolic extract of *Sesamum indicum* seeds has a potential effect to control hyperglycemia in streptozotocin induced diabetic rats.

**Keywords:** Glycosylated hemoglobin, Streptozotocin, *Sesamum Indicum*

### INTRODUCTION

Diabetes a global public health problem associated with its devastating consequences has assumed epidemic proportion in developing countries of the world (Jali *et al.*, 2009). It is a condition primarily defined by the level of hyperglycaemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy) (WHO, 2006). This disease has become one of the most challenging health problems of the 21st century. Diabetes mellitus (DM) can be divided primarily into two types: type 1 or insulin dependent diabetes mellitus and type 2 or non-insulin dependant diabetes mellitus. Type 1 DM is due to autoimmune destruction of  $\beta$ -cells especially in childhood. On the other hand, type 2 DM is mainly due to hereditary factors, affluent lifestyles and obesity (Kumar & Clark, 2002). Both types of DM are associated with common long term complications including cardiomyopathy, nephropathy and digestive insufficiency, especially if the disease is not diagnosed and treated early (Jullien, 1999).

It has been estimated that the global burden of type 2 diabetes mellitus (T2DM) for 2010 would be 285 million people (2010) which is projected to increase to 438 million in 2030; a 65 % increase. Similarly, for India this increase is estimated to be 58%, from 51 million people in 2010 to 87 million in 2030 (Snehalatha and Ramachandran, 2009). The impacts of T2DM are considerable: as a lifelong disease, it increases morbidity and mortality and decreases the quality of life. At the same time, the disease and its complications cause a heavy economic burden for diabetic patients themselves, their families and society. A better understanding about the cause of a predisposition of Indians to get T2DM is necessary for future planning of healthcare, policy and delivery in order to ensure that the burdens of disease are addressed (Hoskote and Joshi, 2008).

India, the world's second most populous country, now has more people with type-2 diabetes (more than 50 million) than any other nation. The problem has been well documented in a battery of recent papers (Shaw *et al.*, 2010). There is considerable evidence that chronic hyperglycemia is the proximate cause of retinopathy, kidney failure, neuropathies, and macrovascular diseases in diabetes. In addition, it has been demonstrated that  $\beta$  cells are particularly susceptible to oxidative damage. Therefore, as hyperglycemia worsens,  $\beta$  cells steadily deteriorate, secrete less insulin, and

participate in a downward spiral of loss of pancreatic functions (Coskun *et al.*, 2005).

Diabetes mellitus often referred to simply as diabetes-is a condition in which the body either does not produce enough, or does not properly respond to, insulin, a hormone produced in the pancreas. Insulin enables cells to absorb glucose in order to turn it into energy. In diabetes, the body either fails to properly respond to its own insulin, does not make enough insulin, or both. This causes glucose to accumulate in the blood, often leading to various complications. Symptoms include frequent urination, lethargy, excessive thirst, and hunger. The treatment includes changes in diet, oral medications, and in some cases, daily injections of insulin (Sood *et al.*, 2005 & Kirkman, 2009). The enormous costs of modern medicines indicate that alternative strategies are required for better management of diabetes. Traditional plant medicines are used throughout the world for a range of diabetic complications. The study of such medicines might offer a natural key to unlock a diabetologist's pharmacy for the future.

Medicinal plants have been used for centuries and have become part of complementary medicine world wide because of their potential health benefits. There is an increasing interest among diabetic patients and health professionals in using medicinal herbs. These natural products are available in abundance. A scientific investigation of traditional herbal remedies for diabetes may provide valuable leads for the development of alternative drugs and strategies. Alternatives are clearly needed for better management of diabetes because of high cost and poor availability of current therapies for many rural populations, particularly in developing countries. In Ayurveda, large numbers of herbs are mentioned which possess hypoglycemic or antidiabetic, but their use in the modern therapy needs the evaluation of activity by using recent methods/techniques.

*Sesamum indicum* (Linn.) belongs to the family - Pedaliaceae is a flowering plant in the genus *Sesamum*. The precise origin of the species is unknown, although numerous wild relatives occur in Africa and a smaller number in India. It is one of the most important oil seed crops cultivated in Asia. Sesame seeds and oil have long been categorized as traditional health food in India and other East Asian countries. It is a pharmaceutically important plant specially its seeds, which accumulates a variety of secondary metabolites

including phenolic compounds, terpenes, limonoids and steroids for which it is used traditionally as herbal medication for many years both for the benefits of the whole body and also in cosmetic preparations as free-radical scavenger (Ghani, 2003).

Scientifically, most pharmacological studies on *Sesamum indicum* seed is reported hypoglycemic effect in genetically diabetes, antitumor effect, antiestrogenic activity, benefits in the parkinsonism disease, antihypertensive effect and increases vitamin E concentration without use of vitamin E supplements. The aqueous defatted seed extraction of *Sesamum indicum* already has shown Hypoglycemic and Hypolipidemic activity (Hu et al., 2007). To our knowledge, no detailed investigations had been carried out to shed light on the effect of *Sesamum indicum* seeds on diabetic complications of diabetic rats injected with STZ (60 mg/kg body weight). Thus, the present investigation envisages studying the effect of *Sesamum indicum* seeds extract on control and STZ-diabetic rats. The effects produced by *Sesamum indicum* seeds were compared with the standard drug glibenclamide.

## MATERIAL AND METHODS

### Collection of plant material and preparation of plant extract

*Sesamum indicum* (Linn.) (Family- Pedaliaceae) seeds were collected from Tirupur district, Tamilnadu, India. Taxonomic authentication was done by Dr.V.S.Ramachandran, Department of Botany, Bharathiar University, Coimbatore, Tamilnadu, India. The seeds were shade dried and powdered using mixer grinder. The powdered material (50g) was extracted with 250ml of ethanol using Soxhlet apparatus and filtered. The filtrate was concentrated and dried under reduced pressure and controlled temperature.

### Chemicals

Streptozotocin was obtained from Himedia Laboratory Limited, Mumbai, India. The chemicals and solvents used in the study were of highest purity and analytical reagents grade.

### Selection of animals

Male Albino Wistar rats (250-300 g) of about two and half months were obtained from the National Institute for Mental Health and Neuro Sciences, Bangalore, India. The institutional ethical committee (IAEC) approved the research. Animals were acclimatized under standard laboratory conditions at (25 ± 2°C) and normal photoperiod (12 h light:dark cycle) for a week. The animals were fed with commercial rat pellet diet (AVM feeds, Coimbatore) and water *Ad libitum*. The animal care and handling were done according to the regulations of Council Directive CPCSEA no: 659/02/a about Good Laboratory Practice (GLP) on animal experimentation. All animal experiments were performed in the laboratory according to the ethical guidelines suggested by the Institutional Animal Ethics Committee (IAEC).

After one week of acclimatization period, the animals were divided into four groups with six animals in each.

Group I: Control rats fed with standard pellet diet and water.

Group II: Rats induced with Nicotinamide (110 mg/kg body weight) followed by

Streptozotocin (60 mg/kg body weight) intraperitoneally

Group III: Diabetic rats treated with ethanolic extract of *Sesamum indicum* seeds orally

(500 mg/kg body weight for 8 weeks)

Group IV: Rats treated with standard drug glibenclamide orally

(600 µg/kg body weight for 8 weeks)

### Sample Collection

After the experimental regimen, the animals were sacrificed by cervical dislocation under mild chloroform anesthesia. Blood was collected by an incision made in the jugular veins and the serum was separated by centrifugation at 2000 rpm for 20 minutes. The liver

was excised immediately and thoroughly washed in ice cold physiological saline. A 10% homogenate of the washed tissue was prepared in 0.1M Tris HCl buffer (pH 7.4) in a potter homogenizer filled with a Teflon plunger at 600 rpm for 3 minutes.

## Methods

Blood glucose was estimated by the method of Beach & Turner (1958), serum insulin by the method of Anderson (1993), hemoglobin by the method of Drabkin and Austin (1932), glycosylated hemoglobin by the method of Sudhakar & Pattabiraman (1981), liver glycogen by the method of Morales et al. (1973) were estimated. Statistical analysis was performed using SPSS package, version 15.0. The values were analyzed by one - way analysis of variance (ANOVA) followed by Least Significant Difference (LSD). All the results were expressed as mean ± SD for six rats in each group p<0.05 were considered as significant.

## RESULTS

The levels of blood glucose, serum insulin and liver glycogen of the control and experimental animals were shown in the Table 1. It is evident from the table 1 that the blood glucose, serum insulin and liver glycogen levels of the control group remained at normal level. However, a significant increase in glucose level and decrease in insulin and glycogen were observed in the diabetic group. The treatment with the plant extract caused a significant decrease in the elevated blood glucose and increase in the lowered insulin and glycogen levels. Rats treated with the standard drug glibenclamide showed significant decrease in glucose level and increase in serum insulin and liver glycogen levels.

**Table 1: Effect of *Sesamum indicum* extract on blood glucose and serum insulin and liver glycogen levels in control and experimental rats**

Groups	Glucose (mg/dl)	Insulin (µu/ml)	Glycogen (mg/g wet tissue)
Group I	113.00±1.78	15.14±0.20	40.41±3.99
Group II	272.50±2.94a*	6.40±0.25 a*	25.00±2.76 a*
Group III	203.66±0.81b*	12.84±0.38 b*	34.12±1.11 b*
Group IV	192.00±3.34c*d <sup>ns</sup>	13.13±0.03c*d <sup>ns</sup>	36.90±1.16 c*d <sup>ns</sup>

Values are expressed as Mean±SD (n=6) (p<0.05)

### Statistical comparison

a : Group I and Group II;

b : Group II and Group III;

c : Group II and Group IV;

d : Group III and Group IV;

\* indicates P<0.05; ns : non significant.

The levels of total hemoglobin and HbA<sub>1c</sub> in control and experimental animals are depicted in Table 2. The diabetic rats showed a significant decrease in the level of total hemoglobin and increase in the level of HbA<sub>1c</sub> when compared with normal control rats. The level of total hemoglobin was significantly increased and HbA<sub>1c</sub> was significantly decreased by the administration of plant extract in diabetic rats and the standard drug glibenclamide treated rats showed significant increase in total hemoglobin level and significant decrease in HbA<sub>1c</sub> level.

**Table 2: Effect of *Sesamum indicum* extract on Hemoglobin and Glycosylated hemoglobin in control and experimental rats**

Groups (mg/dl)	Hemoglobin (g/dl)	Glycosylated hemoglobin
Group I	12.48±0.43	0.46±0.01
Group II	6.67±0.30 a*	1.29±0.02 a*
Group III	10.25±0.20 b*	0.64±0.00 b*
Group IV	10.38±0.21 c*d <sup>ns</sup>	0.63±0.01 c*d <sup>ns</sup>

Values are expressed as Mean±SD (n=6) (p<0.05)

**Statistical comparison**

a : Group I and Group II;      b : Group II and Group III;

c : Group II and Group IV;      d : Group III and Group IV;

\* indicates P&lt;0.05; ns : non significant.

**DISCUSSION**

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history. Herbal medicine, also called botanical medicine or phytomedicine, refers to the use of a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Long practiced outside of conventional medicine, herbalism is becoming more main stream as improvements in analysis and quality control along with advances in clinical research show their value in the treatment and prevention of disease (Collin *et al.*, 2007).

For the study of antidiabetic agents, STZ-induced hyperglycemia in rats is considered to be a good preliminary screening model (Hussain, 2002). STZ is a potent methylating agent for DNA and acts as nitric oxide donor in pancreatic cells.  $\beta$ -cells are particularly sensitive to damage by nitric oxide and free radicals because of their low levels of free radical scavenging enzymes. Diabetes mellitus is a metabolic abnormality in which there is a failure to utilize glucose and hence a state of hyperglycaemia can occur. If hyperglycaemia continues uncontrolled over time, it will lead to significant and widespread pathological changes, including involvement of the retina, brain and kidney (Viswanath & Mc Gavin, 2003). Glibenclamide is derivatives of sulphonylurea used as a standard drug to produce hypoglycaemia by increasing the secretion of insulin from pancreas and by increasing the glycogen deposition in the liver (Grodsky *et al.*, 1971; Yallow *et al.*, 1960).

Glucose processing uses a variety of diverse metabolic pathways, hence chronic hyperglycemia can induce multiple cellular changes leading to complications. Effective blood glucose control is the key for preventing or reversing diabetic complications and improving quality of life in patients with diabetes. The plant extract exhibited a significant activity and effectively reduced the blood sugar level compared to control group. The activities of all the plants tested were well established and they act through different mechanisms (Joy & Kuttan, 1999; Vats *et al.*, 2002 & Grover *et al.*, 2002).

The increased glucose level in the diabetic animals might be due to the destruction of the pancreatic cells caused by the streptozotocin induction and the glucose level was found to be near normal in the extract treated animals which may be due to the insulin like activity of *Sesamum indicum* extract by activating the glucose uptake by the cells. Lowered blood glucose levels in the treated diabetic rats might be due to increasing glycogenesis, inhibiting gluconeogenesis in the liver or inhibiting the absorption of glucose from the intestine. From the results of clinical studies by Knekt *et al.* (2002), it is evident that the reduction of hyperglycaemia is the most important factor in the prevention of chronic microvascular complications of diabetes mellitus (retinopathy, nephropathy, neuropathy and diabetic foot) as well as in the prevention of the accelerated atherosclerosis-related conditions (myocardial infarction, stroke).

This significant change to near normal glycemic concentration in streptozotocin induced diabetic rats, which is an essential trigger for the liver to revert its normal homeostasis during experimental diabetes. The fundamental mechanism underlying hyperglycemia involves over-production (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues (Nadkarni, 2004). Persistent hyperglycemia, the common characteristic of diabetes can cause most diabetic complications. In our investigation, the glycaemic studies revealed that the ethanolic extract of *Sesamum indicum* seeds has the capacity to lower blood glucose levels. Ramesh *et al.* (2005) found that diabetic rats which were fed with sesame oil, when compared with controls (diabetic rats not receiving sesame oil), showed a significant reduction in the levels of blood glucose. In another study, it has been suggested by the researchers that hot-water extract of defatted sesame delayed glucose absorption which had a reductive effect on the plasma

glucose concentration of genetically diabetic mice (Takeuchi *et al.*, 2001). Daily administration of various crude extracts of *Terminalia bellerica* fruits produced gradual decrease in the blood glucose level and significant inhibition if STZ induced diabetes and its complications in albino rats (Latha and Daisy, 2010).

Insulin plays a key role in glucose homeostasis along the side of a counter regulatory hormone, glucagon, which raises serum glucose. Carrier proteins (GLUT 1- 5) are essential for glucose uptake into cells. The mode of action of the active compound(s) of the plant material is probably mediated through enhanced secretion of insulin from the  $\beta$ -cells of Langerhans or through extrapancreatic mechanism (Akhtar *et al.*, 2007). Previous data shows that, ferulic acid a phenolic compound increases insulin release in clonal  $\beta$ - cells RIN-5F (Nomura *et al.*, 2003). The lowered insulin level in the diabetic rat plays an important role in the pathogenesis of diabetes and its complication thereby increasing glucose level in blood.

The possible mechanism by which the plant extract brings about a decrease in blood sugar level may be by potentiating the insulin effect of plasma by increasing either the pancreatic secretion of insulin from  $\beta$ -cells of the islets of langerhans or its release from the bound form. A number of other plants have been reported to exert hypoglycaemic activity through insulin release-stimulatory effects (Sarkar *et al.*, 2011). Bioactive molecules present in *Sesamum indicum* extract may probably possess insulin- like effect or stimulate the  $\beta$  cells of the pancreas to produce insulin which in turn lowers the blood glucose level.

*Sesamum indicum* may also have brought about hypoglycaemic action through stimulation of surviving  $\beta$ -cells of islets of Langerhans to release more insulin. This was clearly evidenced by the increased levels of plasma insulin in diabetic rats treated with *Sesamum indicum*. Since the percentage fall in plasma glucose levels was different in models with varying intensity of hyperglycaemia, it implies that the antihyperglycaemic effect of that plant is dependent on the dosage of diabetogenic agent, which in turn leads to  $\beta$ -cell destruction (Grover *et al.*, 2000). Treatment with *Sesamum indicum* and glibenclamide increase insulin secretion, which, in turn, activates the glucokinase, thereby increasing utilization of glucose and thus, the increased utilization leads to decreased blood sugar level. The standard drug, Glibenclamide has been used for many years to treat diabetes, to stimulate insulin secretion from pancreatic  $\beta$ -cells.

In diabetes, the glycogen content of the skeletal muscles and liver, markedly depleted (Grover *et al.*, 2000) and the reduced level of hepatic glycogen is due to inadequate insulin secretion, which results in the inactivation of glycogen synthetase system (Sumana & Suryawashi, 2001). In a similar way, in the present study decreased levels of glycogen and glycogen synthase were observed in diabetic control rats. It may be due to insufficient secretion of insulin in the diabetic state as stated earlier. It was reported that the treatment with insulin favours the accumulation of glycogen and its content rises to 300% of normal level within 24hr and this inordinate restoration of glycogen may account for up to 60 % of dry liver weight in diabetic animals (Anderson, 1974). This may be due to activation of glycogen synthetase system by the modulatory effects of constituents of ethanol extract of *Sesamum indicum* through induction of insulin secretion.

Insulin is the main regulator of glycogenesis in muscle and liver. The decrease of liver glycogen level observed in this study may be due to lack of insulin in diabetic condition or oxidative stress which may inactivate the glycogen synthetase (Daisy *et al.*, 2010). In the view of glycogen level, there may be three possible ways of antidiabetic action; one possible way may be increased insulin level by preventing the inactivation of the glycogen synthetase and by synthesize the glycogen synthetase (Selvan *et al.*, 2008).

The decrease in glycogen contents in the liver homogenates of STZ diabetic group may be attributed to the depression of glycogenesis pathway in the liver of STZ diabetic group (Ghosh *et al.*, 2004). Glycogen content of normal animals in fasting stage was only slightly higher than the diabetic animals and this may be due to the degradation of glycogen to maintain normal blood glucose levels,

whereas glycogen levels in diabetics were found to be very low despite high blood glucose levels possibly due to lower levels of glycogen synthase activity (Singh, 2001). Accumulation of glycogen in liver of treated animals is somewhat similar to that reported during insulin therapy. The glycogen content is decreased in liver muscles of diabetic rats (Grover *et al.*, 2000). Similar observations, i.e. hypoglycaemic activity and improved levels of hepatic glycogen, were reported by Kedar and Chakrabarti (1982) in diabetic animals with the treatment of *Momordica charantia* for 8 weeks. This prevention of depletion of glycogen in the liver and muscle is possibly due to either stimulation of insulin release or due to insulomimetic activity of some component of extract resulting in direct peripheral glucose uptake. Glucose synthesis in the rat liver and skeletal muscles was impaired during diabetes (Hwang *et al.*, 1997); hence glycogen content of skeletal muscle and liver markedly decreased in diabetes (Welihinda & Karunanayake, 1986).

There is an increased glycosylation of a number of proteins, including hemoglobin (Alberti & Press, 1982). In long term diabetes HbA<sub>1c</sub> makes up 3.4–5.8% of total Hb in normal human red blood cells, but it is increased in patients with overt diabetes mellitus (Paulsen, 1973). The hyperglycemia and the vascular complication of diabetes (Hall *et al.*, 1984) are related to increase in non-enzymatic and auto-oxidative glycosylation. The level of glycosylated hemoglobin was found to increase in diabetic patients up to 16% (29) and the level of HbA<sub>1c</sub> is monitored as a reliable index of glycemic control in diabetes. Several medicinal plants with antidiabetic potential have earlier been reported to have the ability to reduce HbA<sub>1c</sub> levels in diabetic rats (Venkateswaran & Pari, 2002).

In diabetic animals total haemoglobin levels were found to be low when compared to normal rats, as the Hb synthesis might also be depressed. Thus *Sesamum indicum* treated animals showed improved levels of Hb because of its glucose lowering effect. The various proteins including hemoglobin undergo an enzymatic glycation in diabetes. Glycosylated hemoglobin was found to be increased in diabetes mellitus and the amount of increase is directly proportional to that of fasting blood glucose level (Sheela & Augusti, 1992). Lowered levels of total hemoglobin were observed in diabetic rats which might be due to the increased formation of HbA<sub>1c</sub>. Hyperglycemia is the clinical hallmark of poorly controlled diabetes, which is known to cause glycation, and also known as non-enzymatic glycosylation. HbA<sub>1c</sub> was found to increase in patients with diabetes mellitus and the increase was directly proportional to the fasting blood glucose levels (Alberti, 1982). Anila & Vijayalakshmi, (2000) have reported that the flavonoids present in *Sesamum indicum* were effective in raising the hemoglobin levels in rats.

Glycohemoglobin (also known as hemoglobin A<sub>1c</sub>) is the best measurement of long-term glucose control. A high glycohemoglobin number correlates with uncontrolled diabetes. The decreased level of total haemoglobin in diabetic rats is mainly due to the increased formation of HbA<sub>1c</sub>. HbA<sub>1c</sub> was found to increase in patients with diabetes mellitus and the amount of increase is directly proportional to the fasting blood glucose level (Al-yassin & Ibrahim, 1981). During diabetes mellitus, the excess glucose present in the blood reacts with haemoglobin to form HbA<sub>1c</sub> (Koenig *et al.*, 1976). Anemia is much more common disease in type 2 diabetic patients, contributing to the pathogenesis of diabetic complications.

HbA<sub>1c</sub> is used as a marker for estimating the degree of protein glycation in diabetes mellitus. Administration of *Sesamum indicum* to diabetic rats reduced the glycosylation of haemoglobin by virtue of its normoglycaemic activity and thus decreases the levels of glycosylated haemoglobin in diabetic rats. This normalisation of glycosylated haemoglobin indicates decreased glycation of proteins. In our study, the diabetic rats have showed higher levels of glycosylated haemoglobin compared to control rats indicating their poor glycaemic control (Chatterjee and Shinde, 2000). Diabetic rats treated with plant extract showed a significant decrease in the glycosylated Hb levels that might be due to the antihyperglycaemic effect of *Sesamum indicum*.

The typical characteristics of diabetes is the increase of serum glycated protein such as glycated hemoglobin (HbA<sub>1c</sub>), which is a

parameter for glycemic control where glucose or other reducing sugars react with the amino residues of proteins to form Amadori products such as glycated hemoglobin (Michela *et al.*, 2010). Animals treated with ethanol extract of *Sesamum indicum* significantly decreased the glycosylated hemoglobin level which could be due to an improvement in insulin secretion from the remnant pancreatic beta cells in diabetic rats (Kondeti *et al.*, 2010).

## CONCLUSION

Streptozotocin induces diabetes in laboratory animal models for scientific studies and breakthroughs in medicine. In the light of the above background, we have studied the efficacy and potency of *Sesamum indicum* extract in STZ-induced diabetic rats. This will help to determine if they have any therapeutic effects on both Diabetes mellitus and associated complications and thereby improve the quantity of choices and cheaper medical treatment. The experimental evidence obtained in the present animal study indicates that, the ethanolic extract of *Sesamum indicum* possesses hypoglycaemic property.

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