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Anti-Diabetic Effects of *Hibiscus* spp. Extract in Rat and Mice Models: A Review

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ABSTRACT
Diabetes mellitus, a chronic metabolic disease characterized by sustained hyperglycemia, has become a worldwide concern due to the upward trend of recorded cases each passing year. It is one of the leading causes of death in the world. Medication for the management and treatment of diabetes is neither affordable nor accessible in most parts of the Philippines thus raising the need for cost-effective alternatives. Plant extracts have long been used as a treatment for a variety of diseases. One of the plants to display biological activity is Hibiscus spp. It is used to treat a variety of diseases and has steadily gained recognition for its anti-diabetic properties. Several of its plant parts such as the leaves, flowers, and calyces had been used in laboratory models of type 1 and 2 diabetes mellitus. However, methods of extracting biologically active components of the plant vary and yield different results depending upon the concentration and temperature of the extraction procedure. Furthermore, it has shown hypoglycemic effects comparable to commonly used drugs in the treatment of diabetes such as metformin and glibenclamide. Although these studies suggest the efficacy of Hibiscus spp. extract as an antidiabetic agent, it still warrants further clinical trials to establish its efficacy and limitations.

Keywords: diabetes mellitus, Hibiscus spp., plant extract, herbal medicine, mice, rats

BACKGROUND

Diabetes mellitus (DM) is a chronic metabolic disease characterized by impaired insulin production and variable degrees of peripheral insulin resistance resulting in increased blood glucose. Sustained hyperglycemia, the primary clinical manifestation of diabetes, is indicated in the development of complications in the circulatory system, kidney, eyes, and nerves which could be fatal if left untreated.[1] It is considered one of the most common metabolic diseases diagnosed in companion animals and humans alike. According to the International Diabetes Federation, 537 million adults aged 20-79 years old are living with diabetes, and it is estimated to rise to 643 million by 2030. Additionally, over 3 in 4 adults affected by diabetes are from low- and middle-income countries with the Philippines ranking 5th in the number of diabetics in the Western Pacific in 2019 while data from the Philippines Statistics Authority ranked diabetes as the 5th leading cause of mortality in the country in 2021.[2]

Treatment of diabetes includes weight reduction, diet modification, insulin, and oral hypoglycemics. However, medication and management of diabetes are costly with an estimated cost of $92 billion in healthcare and productivity loss. A cross-sectional study conducted on the availability and affordability of 15 commonly prescribed antidiabetic drugs in the Philippines such as acarbose, linagliptin, sitagliptin, insulin, metformin, dapagliflozin, and empagliflozin showed that antidiabetics had an 18.3% availability nationwide which is below the 80% ideal availability set by the World Health Organization. Additionally, originator brand standard treatments for diabetes cost more than one day's salary for the lowest-paid government workers. Filipinos are considered to have substandard access to antidiabetic medicine due to low availability and affordability thus raising the need for cost-effective alternatives.[3,4]

Herbal medicine such as *Momordica charantia*, *Gymnema sylvestre, Hoodia gordonii*, and *Opuntia spp*. has long been used as a non-prescription treatment for diabetes, but there are only a limited number of herbal medicines that have been well characterized with extensive clinical trials as compared to Western drugs.[5,6] One of the plants to display hypoglycemic properties is *Hibiscus* spp., commonly known as "Gumamela" in the Philippines. It is a popular ornamental plant known for its colorful hues of red, orange, yellow, white, and pink. Its flowers can be consumed fresh or cooked while its leaves can be brewed to produce tea. Moreover, it has been cited in various studies for its medicinal properties and has also been consumed as an herbal tea for a variety of ailments such as dysentery, bronchitis, high blood pressure, and constipation.[7] This review aimed to

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update the knowledge about the therapeutic effects of *Hibiscus* spp. extract in diabetes and its comorbidities based on rats and mice study. It has been careful analysis of the scientific literature in several works for its anti-diabetic properties which provide an opportunity for the development of complementary herbal treatment for the management of Diabetes mellitus.

METHODS

This literature review is from different academic research papers. After collecting the articles, analyze each one by breaking it down and identifying the important information and then synthesize and identify the conclusions that can be drawn.

DISCUSSION

Sources of Glucose

Carbohydrate metabolism

Carbohydrates are energy-rich organic biochemical compounds that can be categorized into four main types according to their structure, namely: monosaccharides, disaccharides, oligosaccharides, and polysaccharides.[8] Large aggregates of carbohydrates are not absorbed in the body thus it is metabolized by a series of biochemical processes to reduce them to monosaccharides that can be utilized by the body. The process of metabolism starts in the oral cavity wherein mechanically degraded food meets saliva containing the enzyme, salivary a-amylase, to form a bolus. a(1 → 4)-glycosidic linkages are hydrolyzed by this enzyme to yield maltose, a disaccharide, but this only accounts for approximately 30% of hydrolyzed polysaccharides.[9] Absorption of monosaccharides results in a postprandial increase in blood glucose levels.[10] Glycogenolysis is the process whereby glycogen, the primary carbohydrate stored in the skeletal muscles and liver, is broken down to glucose at periods wherein blood glucose falls below the normal reference range. It starts when the enzyme glycogen phosphorylase is activated by glucagon.[11] Gluconeogenesis is a pathway wherein glucose is synthesized from non-carbohydrate metabolites. The process begins when pyruvate is converted to oxaloacetate by pyruvate carboxylase followed by the conversion of oxaloacetate to malate-by-malate dehydrogenase.[12,13]

To maintain normal function of the body, circulating glucose or plasma glucose must be kept at a certain level. It is regulated by a network of hormones and neuropeptides released largely by the brain, liver, intestine, muscles, adipose tissues, and most notably the pancreas. The pancreas is considered an endocrine and exocrine gland located in the abdominal cavity. Its endocrine function is for enzyme production to aid with digestion.[14] The amount of circulating glucose is primarily regulated by the opposing actions of insulin and glucagon. Insulin secretion is stimulated in response to hyperglycemia to lower blood glucose.[15] After insulin release, cells of insulin-sensitive peripheral tissues located abundantly in skeletal muscles increase the uptake of glucose. The feedback mechanism between insulin and glucagon constantly adjusts according to the metabolic demands of the body until normoglycemia is achieved.[16]

Diabetes Mellitus

Type 1 Diabetes Mellitus

Type 1 DM is a progressive metabolic disease largely attributed to selective autoimmune destruction of pancreatic β-cell although a small number of cases are not caused by autoimmune destruction and are idiopathic.[17] Pathogenesis of type 1 DM may be influenced by environmental factors including reduction in gut microbiota, diet, obesity, toxins, and viruses that may either destroy β-cells directly or indirectly by triggering an immune response and several genetic factors.[18] The disease progresses sub-clinically over months or years until β-cell impairment significantly affects insulin concentration resulting in inadequate control of plasma glucose.[19] In addition to the destruction of pancreatic β-cells, there is also increased secretion of glucagon by pancreatic a-cells which exacerbates hyperglycemia and metabolic defects. This is followed by the development of diabetic ketoacidosis wherein the body compensates for the loss of intracellular glucose by breaking down fats resulting in the release of gluconeogenic substrates, mobilization of free fatty acids, and excess production of ketones in the body. Furthermore, decreased insulin triggers the production of counterregulatory hormones that suppress glucose metabolism in peripheral tissues. Deficiencies in insulin and excess glucose contribute to impairments in lipid, glucose, and protein metabolism by various organs resulting in a multisystemic disturbance.[20]

Type 2 Diabetes Mellitus

Type 2 diabetes is characterized by defective insulin secretion and insulin resistance, or an impaired response of insulin-sensitive tissues to the hormone.[21] Hepatic insulin resistance results in the inability to regulate hepatic glucose production while peripheral insulin resistance hinders glucose uptake by peripheral tissues. This leads to the accumulation of glucose in the bloodstream coupled with high levels of insulin; however, as the disease progresses insulin production may decrease due to damage in pancreatic β-cells brought about by overcompensation to insulin resistance.[22] Pathogenesis of type 2 DM is complex and not completely understood. Prolonged hyperglycemia would trigger the same compensatory mechanisms employed in type 1 DM to make up for decreased glucose uptake. Clinical signs often manifest when insulin secretion can no longer sustain insulin resistance. The development of this disease is often linked to obesity, family history, a sedentary lifestyle, and old age.[23]

***Hibiscus* spp.**

Hibiscus is considered the genus with the most diverse vegetative, floral, and canopy expressions in its family, Malvaceae.[24] It is an evergreen shrub that can grow up to 8 ft tall in the wild with a light-gray bark that is easy to peel and smooth.[25] One fruit may contain up to 20 brown kidney-shaped seeds. The capsule splits open when the fruit is mature and dry.[26] Hibiscus is native to tropical Asia, but it can be traced back to ancient Egypt and across China through plant anatomy, iconography, published literature, and archaeological records. It naturally grows in warm temperate tropical and subtropical regions in the world, but it is now commonly planted as a flowering shrub throughout the world, especially in China, India, Pakistan, South Indian Islands, and the Philippines.[27]

Hibiscus spp is now widely cultivated for its flowers, fruits, and calyces that may be used as an ornament, medicine, and food source. Plant parts may be prepared fresh or processed to consume as a food product with almost all parts of the plant considered edible. Its flowers have been widely incorporated in some beverages while its seeds are roasted to be eaten alone or with other meals. Its leaves and shoots can be eaten raw or cooked and prepared as a condiment or ingredient in salads. Traditionally, it has been used to treat colds, loss of appetite, and respiratory disorders. It has also been extensively utilized for its diuretic, laxative, and expectorant properties in traditional medicine. Furthermore, it was noted that *Hibiscus* spp has emmenagogue effects that can stimulate menstruation and cause abortion.[28] Proponents of traditional Chinese medicine believe that it can be used to treat a variety of diseases including diabetes.[29] Some of its medicinal properties can now be backed up by modern studies. Among its species, *H. sabdariffa, H. tiliaceus, H. rosa-sinensis*, and *H. taiwanensis* have shown antidiabetic properties in studies using in-vivo models.

Chemical Compounds and Mechanism of Action

The plant is made up of approximately 15-30% plant acids including citric, malic, tartaric acids, allo-hydroxycitric acid, lactone, and Hibiscus acid which is specific to the plant. It also contains alkaloids, L-ascorbic acid, anthocyanin, Beta Carotene, Beta-sitosterol, citric acid, polysaccharides arabians, arabinogalactans, quercetin, gossypetin, and small quantities of galactose, arabinose, glucose, xylose, mannose, and rhamnose.[30] The main constituents of *Hibiscus* spp in relevance to its pharmacological activity are organic acids, anthocyanins, and flavonoids. Studies show that calyces of *Hibiscus* spp are rich in polyphenol and flavonoids, substances that are known for their antioxidant properties. Among the phenols found in calyx extract of the plants were anthocyanins such as sambubioside, cyanidin-3- sambubioside, and delphinidin-3-glucoside while flavonoids consist of hisbiscetin and gossypetin with their respective biosides.[31,32] Leaves of *Hibiscus* spp have been found to contain β-sitosteryl-β-d-galactoside while flower extracts yielded luteolin and quercetin. Its polyphenol content had been indicated to reduce blood glucose and increased plasma insulin levels in diabetic rats.[33] These compounds are considered natural enzyme inhibitors of intestinal a-glucosidase and pancreatic a-amylase resulting in reduced postprandial glucose production.[34]

The 3, 4, 6, 8-tetrahydroxy flavonol-5 - methyl ether 7-O-neohesperidoside, a flavanol biocide, showed significant hypoglycemic activity comparable to glibenclamide, but its exact mechanism of action is still unknown.[26,35] Furthermore, quercetin, hibiscetin, gossypetin, and protocatechuic acid are potent phosphoenolpyruvate carboxykinase (PEPCK) enzyme inhibitors compared to metformin, a common drug used for the management of type 2 diabetes.[36] PEPCK enzyme is responsible for decarboxylation and phosphorylation of oxaloacetate to phosphoenolpyruvate. It is considered a rate-limiting step in gluconeogenesis since it bypasses the thermodynamically unfavorable conversion of pyruvate to phosphoenolpyruvate. In a study conducted on streptozotocin-diabetic mice models, silencing of PEPCK liver enzyme in hyperglycemic mice resulted in a 40% reduction of fasting blood glucose 2 days after initial treatment which suggests that expression of PEPCK regulates the rate of glucose production through gluconeogenesis.[37]

Extraction Method

Bioactive compounds are extracted from plant material through different extraction techniques depending upon the desired compounds to be isolated. The successful methods in the extraction of bioactive

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compounds are Soxhlet, heat reflux, hydro distillation, and maceration.[38,39] Solvent extraction is often the preferred method; however, there may be differences in extract yield, for bioactive compounds are highly dependent upon the nature of the extracting solvent. The solvent, plant part, and extraction method are the basic parameters that influence the extract quality.[40] Methanol and ethanol have been proven as effective solvents for phenolic compounds due to their polarity which can extract both hydrophilic and lipophilic plant parts. Bioactive compounds can be identified and characterized by various plant parts such as leaves, flowers, stems, roots, barks, calyx, and fruits.[38,41] Successful extraction begins with careful selection and preparation of plant samples and a thorough review of the appropriate literature for indications of which protocols are suitable for a particular class of compounds or plant species.

In a study conducted on *Hibiscus calyces*, the influence of three concentrations of 50% aq, 75% aq, and 100% methanol and ethanol solvent on extraction yield was noted. It was observed that a higher concentration of both methanol and ethanol had significantly less extraction yield; however, the total phenolic and flavonoid content of the isolate increased proportionally to the solvent concentration.[42] Furthermore, A study suggests that the temperature at which biochemical compounds are extracted yields varying results. *Hibiscus* calyces extracted with water at 23°C, 50°C, 75°C, and 90°C revealed that extract yield was directly proportional to temperature, but total phenolic and flavonoid content decreased as the temperature increased.[43] The various techniques for extraction of bioactive compounds are shown in Table 1.

Table 1. Extraction methods of *Hibiscus* spp

Plant Species	Plant Part	Extraction methods	References
H. taiwanensis	leaves, fruit, and stem	60% aqueous acetone solution at room temperature for 3 days with occasional shaking and stirring	44
H. rosa-sinensis	aerial parts	80% aqueous ethanol yielded 10% crude extract	45
H. platanifolius	Bark	90% ethanol on a reflux water bath for 3 hours then concentrated using a rotary flash evaporator until a semi-solid consistency	46
H. taiwanensis	Stem	60% aqueous acetone with a 2 mL/g ratio of solvent volume to dry weight	47
H. rosa-sinensis	Leaves	80% methanol at room temperature for 7 days with shaking and stirring which yielded a 9.42% w/w of the crude extract	48
H. rosa-sinensis	dried ground leaves	methanol in a soxhlet apparatus then the aqueous layer was made alkaline using 5% NaOH to obtain the basic fractions while neutral fractions were obtained by neutralizing the aqueous layer with H_2SO_4	49
H. surattensis	Leaves	extracted for 24 hours using 96% ethanol by maceration method and further concentrated using a rotary evaporator	50
H. sabdariffa	Leaves	Use cold water with powdered leaves for 24 hours then evaporated using water bath evaporation. And use boiled water for 30 minutes. The sample was then left to soak for 24 hours	51
H. cannabinus	pulverized leaves	submerging the sample in 1.5 mL methanol for 8 days	52
H. rosa-sinensis	Flower	defatted using petroleum ether in a soxhlet apparatus at 60-80°C then extracted using chloroform, ethyl acetate, and then 95% ethanol.	53
H. tiliaceus	Flower	defatting using petroleum ether at 60-80°C which is then followed by further extraction using methanol	54
H. rosa-sinensis	Flower	using ethanol at 60-80°C for 48 hours	55
H. sabdariffa Linn	Petal	boiled with water at a concentration of 2g/200 mL and was further concentrated using an evaporator until its volume reached 10 mL	56
H. sabdariffa Linn	Flower	ethanol which had a yield of 45%. It was further concentrated using a rotary evaporator at 40° C	57

Plant Species	Plant Part	Extraction methods	References
H. sabdariffa	Calyx	utilized 1 L of distilled water to extract powdered calyxes for 48 hours	58
H. sabdariffa	Calyx	boiled in 50 mL methanol at 60°C for 30 minutes. The extracts were filtered, and the same procedure was repeated twice. It was further partitioned with ethyl acetate	60
H. sabdariffa Linn	Calyx	ethanol by stratified percolation.	61

Experiments on anti-diabetic properties of Hibiscus spp.

Experiments on Type 1 Diabetes Mellitus

The commonly used model for type 1 DM is the non-obese diabetic (NOD) mice. NOD mice develop insulitis at 3-4 weeks of age. Its pancreatic islets are infiltrated by CD4 and CD8 lymphocytes through a process that has immunological and pathophysiological similarities to human type 1 DM.[18] The results of several studies are summarized in Table 2. Type 1 DM caused the person's body reduces very little or no insulin.[62] Type 1 DM, there is autoimmune destruction of the β-cells of the Langerhans islets in the pancreas. Consequently, it reduces or even inhibits insulin secretion by these cells. The summary results showed that the administration of Hibiscus extracts significantly lowered the level of plasma glucose, decreased triglycerides, and improved insulin sensitivity. This effect may be through the stimulation of β-cells of islets of Langerhans secretion of insulin or enhanced transport of blood glucose to the peripheral tissues.[64]

Table 2 Summary of studies conducted on hypoglycemic properties of *Hibiscus* in mice and rat models of type 1 DM

Animal model	Plant Species	Plant Part	Type Extract	Parameters examined				Reference
				Plasma glucose	Plasma insulin	Body weight	triglycerides	
Non-obese diabetic mice	*H. rosa-sinensis*	leaf	Basic ethanol	Decreased	Increased	Increased	Decreased	49
			Neutral ethanol	Decreased	Increased	Increased	Decreased	
Streptozotocin-induced diabetic mice	*H. sabdariffa*	calyx	Ethyl acetate	Decreased		Decreased		60
Streptozotocin-induced diabetic rats	*H. taiwanensis*	Stem Fruit leaf	Aqueous acetone	Decreased				44
Streptozotocin-induced diabetic rats	*H. taiwanensis*	Stem	Aqueous acetone	Decreased				47
Streptozotocin-induced diabetic mice	*H. sabdariffa* Linn	calyx	Ethanol	Decreased				61
Streptozotocin-induced diabetic rats	*H. cannabinus*	Leaf	Methanol	Decreased		Decreased	Decreased	52
Alloxan-induced diabetic rats	*H. sabdariffa* Linn	Flower	Alcohol	Decreased	Increased	Decreased		53
			Ethanol	Decreased		Decreased	Decreased	57
Alloxan-induced diabetic rats	*H. rosasinensis*	Flower	Ethanol	Decreased				55
Alloxan-induced diabetic rats	*H. esculentus*	Fruit	methanol	Decreased			No significant change	65
Alloxan-induced diabetic rats	*H. platanifolius*	Stem	ethanol	Decreased		Increased at 500 mg/kg dosage	No significant change	46
	H. sabdariffa	Calyx	Aqueous	Decreased				49

Alloxan-induced diabetic rats		Leaf	Aqueous	Decreased	Increased	Decreased		51

Experiments on Type 2 Diabetes Mellitus

Type 2 DM decreased insulin sensitivity of tissue especially skeletal muscles or liver and caused high-risk factors of hypertension, obesity, dyslipidemia, and insulin resistance.[62] A study conducted by [45] on ethanolic extracts of aerial parts of *H. rosa-sinensis* (HRSAE) administered orally to streptozotocin-induced diabetic mice showed decreased blood glucose to near control level in groups treated with 500 mg/kg HRSAE. Furthermore, urea, uric acid, creatinine, plasma protein, and alanine transaminase (ALT) were lower in treated mice compared to diabetic groups. These are common markers used to determine liver and kidney function in cases of diabetes mellitus, for liver and kidney function is often compromised due to the body's compensatory mechanism to sustained hyperglycemia.[63] This is further supported by a study conducted by[48] that histopathological examination of diabetic rats treated with the extract appeared mostly normal with minimal signs of degeneration while kidney samples had decreased pathological alterations compared to that of the diabetic control group. Similar results were seen in a study of ethanolic leaf extract of *H. surattensis* with those given 300 mg/kg extract having blood glucose comparable to mice treated with 13 mg/kg acarbose, an antidiabetic agent used in the management of hyperglycemia by delaying glucose absorption.[66] A study conducted by[67] found that treatment of pregnant streptozotocin-induced diabetic Wistar albino rats with oral *H. rosa sinensis* flower aqueous extract did not modify blood glucose in treated groups. This is attributed to the severity of the disease suggesting that treatment with Hibiscus extract may only be beneficial in moderate cases of hyperglycemia. The results of several studies confirming the benefits of *Hibiscus* extracts are summarized in Table 3. The administration of *Hibiscus* extracts significantly lowered the level of plasma glucose. Some studies indicate that the administration of *Hibiscus* effectively reduces the level of malondialdehyde as a marker of oxidative stress.[68] Oxidative stress has a two-way mode of action in diabetes that reduces the response of the body's tissues and weakens insulin secretion to its actions, consequently leading to the formation of Type 2 DM. It has been noticed that the metabolic pathways that contribute to the increased formation of oxidative stress in diabetics are the pathways of sugar and fat metabolism.[62] On Type 2 DM mice and rat modelss, it can be concluded that the β-cell dysfunction may be reversible.

Table 3. Summary of studies conducted on hypoglycemic properties of *Hibiscus* in mice and rat models of type 2 DM

Animal model	**Plant Species**	**Plant Part**	**Type Extract**	**Parameters examined**				**Reference**
				Plasma glucose	**Plasma insulin**	**Body weight**	**triglycerides**	
Streptozotocin-induced diabetic mice	*H. rosa-sinensis*	Aerial parts	Ethanol	Decreased				45
			Methanol	Decreased				48
Streptozotocin-induced diabetic rats	*H. sabdariffa* Linn	Flower	Aqueous	Decreased		No significant change		56
Streptozotocin-induced diabetic mice	*H. tiliaceous*	Flower	Methanol	Decreased		Increased		54
Glucose-loaded Swiss Webster mice	*H. surratensis*	Leaves	Ethanol	Decreased				50

Recommended Dosage

Available toxicological data on *Hibiscus* spp. is limited, but infusions and aqueous extracts are generally considered safe as it has a long-standing history in food and medicine. Studies conducted on extracts of *H. sabdariffa* Linn. showed that it is non-toxic with a high margin of safety. In animal models, it could be given at 150-180 mg/kg/BW per orem without signs of adverse side effects in 3 weeks with LD50 between 2000-5000 mg/kg/day.[69] Another study in animal models stated that consumption of *Hibiscus* tea had no side effects on the liver and kidneys given that it does not exceed 5000 mg/kg/day.[70] However, an increase in liver enzymes and kidney parameters was observed in laboratory mice given dried *H. sabdariffa* Linn. calyxes alcoholic and water extract at doses of 300 mg/kg/bw over a BW3-month period. This suggests that at high dosages, *Hibiscus* is hepatotoxic. Additionally, an increase in uric acid was also noted in rodents at high dosages which may be attributed to anthocyanins that are responsible for the pigment in flowers of *Hibiscus*.[57,59]

CONCLUSIONS

Studies on *Hibiscus* spp. plant extracts show that the isolation of biologically active compounds is affected by the solvent type, concentration, and temperature during extraction. The extract yield is directly proportional to the concentration and temperature of the solvent; however, the biologically active compounds such as phenols and flavonoids decrease as concentration and temperature increase. Furthermore, the plant's extracts have shown considerable anti-diabetic properties by reducing blood glucose and other toxic metabolic waste, such as uric acid, urea, creatinine, and alanine transaminase which are products of the body's compensatory mechanisms to hyperglycemia. The hypoglycemic property of *Hibiscus* spp. may be attributed to naturally occurring compounds, glycosides, that inhibit enzymes that are vital for carbohydrate metabolism and gluconeogenesis. Pancreatic a-amylase and intestinal a-glucosidase are inhibited during carbohydrate metabolism resulting in decreased absorption of glucose from the intestines. Additionally, glucose production from gluconeogenesis is reduced due to the inhibition of the PEPCK enzyme. Overall, it has shown great potential as a complementary treatment for management of diabetes; however, clinical studies lack rigorous research as to its biochemical compounds that may contribute to management of the disease. Additionally, animals used in studies are often limited to chemical induction models of diabetes with most studies using alloxan or streptozotocin induced diabetic mice. There is also limited research as to its toxicological properties and margin of safety. Further research is warranted to establish efficacy and limitations of *Hibiscus* spp. plant extract as an antidiabetic agent.

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