Revista Brasileira de Farmacognosia
Brazilian Journal of Pharmacognosy
20(2): 222-227, Abr./Mai. 2010
Received 30 May 2008; Accepted 8 November 2008

Artigo

Hypoglycemic and hypolipidemic effect of leaves from *Syzygium cumini* (L.) Skeels, Myrtaceae. in diabetic rats

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RESUMO: "Efeito hipoglicêmico e hipolipidêmico das folhas de *Syzygium cumini* Lam. em ratos diabeticos". Na região de Criciúma-SC, as folhas de *Syzygium cumini* (L.) Skeels, Myrtaceae, conhecida popularmente como jambolão, são utilizadas para diminuir níveis de glicose plasmática em pessoas diabéticas. Dentro deste contexto o presente trabalho teve o interesse de avaliar o efeito hipoglicêmico e hipolipidêmico do extrato bruto hidroalcoólico (EBH) das folhas de *S. cumini* (125, 250 e 500 mg/kg). Para tal os animais foram divididos em três grupos para o efeito hipoglicêmico: ratos normais, ratos normais submetidos a curva de glicose (hiperglicêmicos) e ratos diabéticos induzidos com aloxana. O efeito hipolipidêmico foi avaliado em animais diabéticos induzidos por aloxana. O efeito hipoglicêmico foi comparado com glibenclamida. O tratamento agudo com EBH de *S. cumini* causou uma diminuição estatisticamente significativa na glicose sanguínea em animais normais que foram submetidos à cura de glicose (250 mg/kg), e sobre os níveis de glicose (125 e 250 mg/kg), triglicerídeo (125 e 500 mg/kg) e colesterol (125 mg/kg) em animais diabéticos. Nenhuma das doses testadas apresentou efeito em animais normais. Dentro deste contexto pode-se sugerir que o EBH das folhas de *S. cumini* pode ser uma alternativa terapêutica no tratamento alternativo ou complementar na diabete, uma vez que apresentou atividade hipoglicêmica e hipolipidêmica em animais diabéticos.

Unitermos: *Syzygium cumini*, Myrtaceae, diabete, hipoglicêmico, hipolipidêmico, plantas medicinais.

ABSTRACT: Ethanolic crude extract (ECE) of leaves from *Syzygium cumini* (L.) Skeels, Myrtaceae was screened for its hypoglycemic and hypolipidemic activity (125, 250 and 500 mg/kg v.o.). Rats were divided into three groups for the evaluation of the hypoglycemic effect: normal rats, rats with alloxan-induced diabetes and hyperglycemic normal rats. Hypolipidemia was evaluated in rats with alloxan-induced diabetes. The antihyperglycemic activity was compared to treatment with glibenclamide, an oral hypoglycemic agent. The acute treatment with *S. cumini* ECE caused a significant decrease in the blood glucose in hyperglycemic normal rats (250 mg/kg), and in glucose (125 and 250 mg/kg), triglyceride (125 and 500 mg/kg) and cholesterol (125 mg/kg) levels of diabetic rats, but no effect was observed in the normal treated rats. *Syzygium cumini* leaves are a good candidate for alternative and/or complementary medicine in the management of diabetes mellitus, since they showed hypoglycemic activity in addition to a hypolipidemic action in diabetic animals.

Keywords: *Syzygium cumini*, Myrtaceae, diabetes, hypoglycemic, hypolipidemic, medicinal plants.

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ISSN 0102-695X

INTRODUÇÃO

Diabetes is a disorder of carbohydrate, fat and protein metabolism. It is attributed to the diminished production of insulin or mounting resistance to its action. Chronic hyperglycemia during diabetes causes glycation of body proteins, which in turn leads to secondary complications affecting the eyes, kidneys, nervous system and arteries (Sharma & Misra, 1993).

Diabetic lipemia ('milky plasma') is a well-recognized manifestation of uncontrolled diabetes mellitus. Because insulin has important regulatory effects on lipid metabolism, diabetes mellitus is associated with significant abnormalities in lipoprotein metabolism. Almost all of the commonly-occurring lipoprotein abnormalities have been observed in diabetes (Taskinen, 1990). The dyslipidemia seen in poorly-controlled type 1 diabetes mellitus is mainly due to the accumulation of cholesterol and triglycerides in the plasma (Chase & Glasgow, 1976). However, normalization of glycemic control is followed by the improvement or normalization of the dyslipidemia (Weidman et al., 1982). Although the increased risk of cardiovascular diseases in diabetes is multifactorial, dyslipidemia is certainly a major factor. Thus, patients with diabetes are at increased risk for all the manifestations of atherosclerosis, including coronary artery disease, cerebrovascular events, and peripheral vascular diseases (Mohamed et al., 1999; Cavalli et al., 2007; Torrico et al., 2007; Figueiredo & Modesto-Filho, 2008; Janebro et al., 2008).

Syzygium cumini (L.) Skeels, Myrtaceae, is a tree with dark purple fruits, originating from Indomalasia, China and the Antilles and cultivated in various countries including Brazil. The bark of the tree, the fruit, the seeds and the leaves of this plant are frequently used in the treatment of diabetes mellitus and administered in the form of different preparations such as the aqueous extract or decoction, the ethanolic extract or the raw plant juice, while the fruits are even consumed fresh (Lorenzi & Matos, 2002; Agra et al., 2008; Leitão et al., 2009). In the South of Brazil, for instance, the leaves are supposed to possess hypoglycemic activity.

Studies using the fruit have shown a reduction in plasma glucose levels in streptozotocin-induced mice, in the glucose tolerance test, and in fructose-fed rats (Grover et al., 2001; Vikrant et al., 2001; Sharma et al., 2006). Meanwhile, studies with the seeds have shown that they reduce the plasma glucose levels in alloxan diabetic rats and rabbits; and a hypolipidemic effect has also been shown for this part of the plant (Sharma et al., 2003; Ravi et al., 2005). Investigations involving the bark have demonstrated that it causes a significant decrease in blood glucose levels in the glucose tolerance test (Villase˜nor & Lamadrid, 2006).

On the other hand, investigations employing the leaf decoction against rat streptozotocin diabetes and in patients with type 2 diabetes mellitus did not show any antidiabetic activity (Teixeira et al., 2000; Pepato et al., 2001). Another study carried out with the crude extract and butanolic fraction of the leaf, in a model of diabetes, also failed to demonstrate a significant hypoglycemic effect (Oliveira et al., 2005).

Here we report a study of the ethanolic crude extract of the leaves of *S. cumini* in different acute models in rats. The acute hypoglycemic activity of different concentrations of the extract was assessed in normal rats, as well as in normal animals submitted to the glucose tolerance test. In addition, we tested the different concentrations of the extract in alloxan diabetic rats. While examining the hypoglycemic activity, we found that the ethanolic extract of the leaves not only possesses hypoglycemic activity, but also confers an improved lipid profile.

MATERIAL AND METHODS

Plant material and preparation of the ethanolic crude extract (ECE)

The leaves of *Syzygium cumini* (L.) Skeels, Myrtaceae, were collected in Criciúma (Santa Catarina, Brazil). They were taxonomically authenticated by Prof[a]. Dra Vanilde Citadini-Zanete, and a voucher specimen of the plant (CRI7375) was deposited in the forestry herbarium Herbário Pe. Dr Raulino Reitz of the UNESC (Criciúma, Brazil). For the preparation of the ECE, leaves of *S. cumini* (15 g) were macerated in ethanol (650 mL) at room temperature for ten days. The final ethanolic extract was concentrated (17.225 mg extract/g raw material) and dissolved in distilled water.

Animals

Male albino Wistar rats (body weight 200-250g) were used in the experiment. These were housed in an air-conditioned room (21 °C) with controlled lighting. The animals were maintained with pelleted food (Supra Lab, Alisul - Braço do Norte - SC), while tap water was available *ad libitum*. The animals were fasted for 12-14 h before experimentation, but were allowed free access to water. All procedures were carried out according to NIH Guide for the Care and Use of Laboratory Animals and institutional policies on the handling of experimental animal.

Study of *S. cumini* ECE in normal rats

Overnight-fasted animals were randomly divided into three groups of six rats:
Group I: received the vehicle only (v.o. control);
Group II: received ECE (125, 250 and 500 mg/kg v.o.);
Group III: received glibenclamide (200 mg/kg, v.o.).
Blood samples were collected from the retro-orbital plexus

before the administration of the extract and they were collected again in the 1, 2 and 3 subsequent hours. Blood glucose levels were then measured.

Oral glucose tolerance test

The oral glucose tolerance test (OGTT) was performed on normal rats. Fasted rats were divided into three groups of six animals:
Group I: glucose 4 g/kg, *v.o.*;
Group II: glucose (4 g/kg, *v.o.*) plus ECE (125, 250 and 500 mg/kg, *v.o.*);
Group III: glucose (4 g/kg, *v.o.*) plus glibenclamide (200 mg/kg).

Blood samples were collected from the retro-orbital plexus before and at 30, 60, 90 and 180 min after the glucose loading, and blood glucose levels were then measured.

Study of *S. cumini* ECE in diabetic rats

Diabetes was induced by a single intraperitoneal injection of 200 mg/kg of alloxan monohydrate (dissolved in water just before use) (Silva et al., 2002, with modifications). Animals in which the development of hyperglycemia was confirmed (around 90%), 72 h after the alloxan injection, with serum glucose levels >300 mg/dl were considered diabetic. These were used for the study and they were randomly allocated into groups of six rats:
Group IV: control and received the vehicle only (*v.o.*);
Group V: *S. cumini* ECE (125, 250 and 500 mg/kg, *v.o.*);
Group VI: glibenclamide (200 mg/kg v.o.).

Blood samples were collected from the retro-orbital plexus before the administration of *S. cumini* ECE and in 1, 2 and 3 h after the treatment, for subsequent analysis of glucose, triglycerides, and total cholesterol.

Biochemical estimations

Fasting blood glucose, serum cholesterol and triglyceride (TG) levels were measured using standard methods (Trinder, 1969; Allain et al., 1974; Bucolo & David, 1973, respectively).

Statistical analysis

The data were expressed as mean±SEM. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to determine the significance of differences between the groups. Differences were considered to be significant when $p \leq 0.05$.

RESULTS

Effect of *S. cumini* ECE on normal rats

The effects of the treatment with *S. cumini* extract and glibenclamide on the serum glucose concentration in normal fasted rats are shown in Table 1. None of the tested doses of *S. cumini* presented any significant lowering of blood glucose when compared to the "zero time" of each respective dose. Only glibenclamide exhibited a reduction in the glucose concentration of 30% ($p<0.01$), after 1 h.

Effect of *S. cumini* ECE on blood glucose, triglyceride and cholesterol levels in alloxan-induced diabetic rats

The administration of alloxan (200 mg/kg) significantly decreased (13%, $p<0.05$) the body weight of the rats while significantly increased the blood glucose (115%, $p<0.001$), cholesterol (34%, $p<0.001$) and triglyceride (52%, $p<0.001$) concentrations when compared to those of the normal animals (data not shown).

The acute treatment with different concentrations of *S. cumini* ECE in alloxan-induced diabetic rats produced a reduction in the blood glucose levels (Table 2). The concentrations of 125 and 250 mg/kg reduced glucose levels at all the time points analyzed. At the dose of 125 mg/kg, the extract brought about a significant reduction in the blood glucose levels at 1 h (29%; $p<0.001$), 2 h (44%; $p<0.001$) and 3 h (33%; $p<0.001$). Meanwhile, at the dose of 250 mg/kg, the extract caused a significant reduction in the blood glucose levels at 1 h (37%; $p<0.001$), 2 h (59%; $p<0.001$) and 3 h (44%; $p<0.001$). At the same time points glibenclamide-treated animals exhibited a significant reduction in serum glucose levels at 1 h (34%; $p<0.001$), 2 h (40%; $p<0.001$) and 3 h (22%; $p<0.01$).

The ethanolic crude extract of *S. cumini* produced a reduction in the blood triglyceride levels at 125 and 500 mg/kg (Table 2) in alloxan-induced diabetic rats. At the dose of 125 mg/kg, the extract brought about a significant reduction in the blood triglyceride levels at 2 h (53%; $p<0.001$) and 3 h (62%; $p<0.001$). Meanwhile, at the dose of 500 mg/kg, the extract caused a significant reduction in the triglyceride glucose levels at 1 h (58%; $p<0.001$), 2 h (59%; $p<0.001$) and 3 h (68%; $p<0.001$). At the same time points glibenclamide-treated animals did not exhibit a significant reduction in serum triglyceride levels.

The acute treatment with different concentrations of *S. cumini* ECE in alloxan-induced diabetic rats produced a reduction in the blood cholesterol levels for the 125 mg/kg dose (Table 2) at all the time points analyzed (1h: 64%, $p<0.001$; 2 h: 39%, $p<0.05$; and 3 h: 59%, $p<0.001$). At the same time points glibenclamide-treated animals did not exhibit a significant reduction in serum cholesterol levels.

Effect of *S. cumini* ECE on the oral glucose tolerance test

Within 30 min of starting the glucose tolerance test, blood glucose concentration almost doubled from its initial control level. This hyperglycemia was maintained

for 60 min, when it began to decrease (Table 3).

Only the concentration of 250 mg/kg of *S. cumini* ECE was able to significantly prevent (44%, $p<0.001$) the increase in blood glucose levels at the 90 min time point after glucose administration. Glibenclamide did not exhibit a significant reduction in serum glucose levels.

Table 1. Acute effect of *S. cumini* ECE in normoglycemic rats[a].

Time (h) Blood glucose level (mg/ dl)	Group I (control)	Group II S.cumini- treated			Group III Glibenclamide
		125 mg/kg	250 mg/kg	500 mg/kg	200 mg/kg
0	160.12±3.69	85.11±4.74	132.44±8.04	106.28±7.13	122.75±3.54
1	115.28±3.15 ***	143.53±16.60	110.54±8.41	75.48±4.60	86.40±4.60**
2	159.87±3.84	145.78±6.60	169.43±12.66	128.45±12.98	98.57±9.88
3	189.12±5.56 ***	144.57±8.89	151.68±9.74	191.58±12.23***	126.73±7.64

[a] Values are expressed as mean±SEM; n = 6 in duplicates for each group; (**); (***) Significantly different from the corresponding zero time value, $p<0.01$ and $p<0.001$, respectively.

Table 2. Acute effect of oral administration of *S. cumini* ECE in alloxan-diabetic rats[a].

	Blood glucose level (mg/ dl)				
Time (h)	Group IV (control)	Group II *S.cumini*- treated			Group VI Glibenclamide
		125 mg/kg	250 mg/kg	500 mg/kg	200 mg/kg
0	345.23 ± 3.93	481.90±30.70	330.73±2.75	424.92±24.8	345.82±16.13
1	349.82 ± 1.76	342.56±13.28***	208.42±16.78***	405.83±31.14	228.90±11.34***
2	362.07 ± 6.54	268.50±6.36***	135.77±7.17***	462.82±16.74	205.53±16.76***
3	344.85 ± 15.75	323.31±19.55***	185.42±5.60***	566.12±20.16**	270.64±8.88**
	Blood triglyceride level (mg/ dl)				
Time (h)	Group IV (control)	Group II *S.cumini*- treated			Group VI Glibenclamide
		125 mg/kg	250 mg/kg	500 mg/kg	200 mg/kg
0	243.58±11.13	383.24±30.85	250.00±33.06	449.97±12.82	305.83±30.03
1	249.27±32.45	332.86±22.15	368.00±25.00*	189.03±7.34***	363.75±17.26
2	145.80±31.80	179.97±20.97***	525.00±5.13***	182.43±16.48***	399.66±17.42*
3	127.82±21.26*	146.11±24.40***	291.86±30.00	142.07±15.00***	358.81±7.91
	Blood cholesterol level (mg/ dl)				
Time (h)	Group IV (control)	Group II *S.cumini*- treated			Group VI Glibenclamide
		125 mg/kg	250 mg/kg	500 mg/kg	200 mg/kg
0	86.84±5.07	119.23±14.62	167.92±34.94	98.98±7.01	76.36±5.89
1	56.77±2.46**	42.71±13.17***	154.00±15.00	105.86±15.35	73.21±2.32
2	83.94±7.96	72.18±4.02*	154.31±25.00	93.05±5.33	73.48±3.96
3	53.30±2.75**	48.72±4.34***	107.62±4.38	102.02±15.33	95.90±5.44*

[a] Values are expressed as mean±SEM; n = 6 in duplicates for each group; (*); (**); (****) Significantly different from the corresponding zero time value, $p\leq0.05$, $p\leq0.01$ and $p\leq0.0001$, respectively.

DISCUSSION AND CONCLUSIONS

The number of people with diabetes mellitus worldwide is increasing rapidly. Presently, there are more than 150 million people with diagnosed disease and 314 million with impaired glucose tolerance, a prediabetic state (International Diabetes and Federation, 2005).

Dyslipidemia, in both type 1 and type 2 diabetes, plays a significant role in the manifestation and development of premature atherosclerosis leading to cardiovascular (CV) disease, and together, they are the major cause of CV morbidity and mortality in diabetic patients (American

Table 3. Effect of *S. cumini* ECE on oral glucose tolerancea.

	Blood glucose level (mg/ dl)				
Time (min)	Group I (control)	Group II glucose (4 g/kg) plus S. cumini			Group III glucose (4 g/kg) plus Glibenclamide
	glucose (4 g/kg)	125 mg/kg	250 mg/kg	500 mg/kg	200 mg/kg
0	72.02±6.76	116.77±8.94	131.048±6.94	145.11±3.10	117.84±4.16
30	152.62±3.97***	260.00±11.22***	144.24±8.54	216.11± 5.46*	173.00±8.55**
60	165.57±5.94***	248.00±7.68***	104.77±10.71	217.14±18.07*	132.05±6.94
90	176.50±13.00***	240.89±11.31***	73.37±5.05***	181.08±18.00	140.23±11.50
180	113.87±7.41*	198.35±9.46***	184.78±4.53***	200.05±8.51	125.47±8.76

[a] Values are expressed as mean ± SEM; n = 6 in duplicates for each group; (*); (**); (***) Significantly different from the corresponding zero time value, $p \leq 0.05$; $p \leq 0.01$ and $p \leq 0.001$, respectively.

Diabetes Association, 2005).

In this study, the hypoglycemic activity of the ethanolic crude extract of *S. cumini* leaves (used in traditional medicine in southern Brazil) was evaluated in normal, alloxan-induced diabetic animals and hyperglycemic normal rats. The hypolipidemic effect was evaluated in alloxan-induced diabetic animals.

The acute treatment with ECE of *S. cumini* caused a significant decrease in the blood glucose in hyperglycemic normal rats, and in glucose, triglyceride and cholesterol levels of diabetic rats, but no effect was observed in the normal treated rats.

The concentration of 250 mg/kg was the only one to block ($p<0.001$) the increase in blood glucose levels at 90 min after glucose administration (44%) in the oral glucose tolerance test.

In the alloxan-induced diabetic rats, the best results for the reduction in blood glucose concentrations with ECE of *S. cumini* were obtained at the lowest concentrations, 125 (2h, 44%) and 250 (2 h, 59%) mg/kg, and this effect was greater than that of the oral hypoglycemic agent, glibenclamide. It has been reported that high concentrations of *S. cumini* extract may autoinhibit its hypoglycemic action (Prince et al., 1998). These results are different from those obtained by Oliveira et al. (2005), who described the crude extract and the butanolic fraction of the leaves as ineffective in reducing glycemic levels in diabetic mice.

For the triglyceride levels the best results were presented by the concentrations of 125 mg/kg (62%) and 500 mg/kg (68%), both at the 3 h time point after administration of the extract. The extract's effect on diabetic hypertriglyceridemia may occur through its control of hyperglycemia. This is in agreement with the finding that the level of glycemic control is the major determinant of total and very low density lipoprotein (VLDL) triglyceride concentrations (Laakso, 1995). For cholesterol levels only the concentration of 125 mg/kg (1h, 64%) returned a result.

The mechanism(s) of hypolipidemic and hypoglycemic actions of the ECE from *S. cumini* are not known, but may involve insulin, since in addition to causing hypoglycemia, insulin lowers lipid levels (Ahmed et al., 2001) and normalizes plasma lipids (Pepato et al., 2005). Studies with the seeds of *S. cumini* have already demonstrated hypocholesterolemic and hypotriglyceridemic effects (Sharma et al., 2003; Ravi et al., 2005).

Glibenclamide is an allopathic drug used to control glucose levels in diabetics and belongs to the class of sulphonylureas. These medicines act by stimulating residual β-cells of the pancreas to increase the production and release of insulin (British National Formulary, 1995). In our study glibenclamide reduced the glucose concentration in diabetic animals, as well as in normal animals.

In summary, the *S. cumini* extract exhibited hypoglycemic activity in addition to its hypolipidemic action in diabetic animals. That brings clinical implications, since if used as a hypoglycemic agent, it may also reverse the dyslipidemia associated with diabetes, and may prevent the CV complications which are very prevalent in diabetic patients. Our results suggest that *S. cumini* has the potential to be a candidate for investigation as an anti-diabetic agent in humans.

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