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Hypoglycemic effect of *Allophylus cominia* (L.) Sw leaves aqueous extract in a rat model of type 2 diabetes

[Efecto hipoglicémico del extracto acuoso de hojas de *Allophylus cominia* (L.) Sw en ratas en un modelo de diabetes tipo 2]

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Abstract*: Allophylus cominia* (L) Sw (Sapindaceae), is one of the most popular medicinal plant in Cuba. It is traditionally used in the treatment of diabetes. The aim of this study was to investigate the effect of A cominia leaves aqueous extract in a type 2 diabetes model induced by streptozotocin treatment in neonatal rats. Two experiments was executed: at 6 weeks old rats, before starting the plant evaluation, and at 11 weeks old rats, after the oral administration daily of three doses 0.25, 0.5 and 1.0 g/kg of A cominia aqueous extract during 3 weeks and plasma blood glucose level was evaluated. At 6 weeks old rats, the group of diabetic animals showed significant decrease in blood glucose and body weight values compared to the control group ($p < 0.05$). At 11 weeks old rats, the groups of diabetic animals treated with A cominia aqueous extract significantly decreased blood glucose values compared to the untreated diabetic group ($p < 0.05$). Only the groups treated with 0.5 and 1.0 g/kg of A cominia extract showed a recovery of normal glycaemic values. Hence, it can be concluded that aqueous extract from A cominia leaves has antidiabetic properties and may be effective in the type 2 diabetes treatment.

Keywords: *Allophylus cominia* (L) Sw, antidiabetic property; hypoglycemic activity, type 2 diabetes neonatal rats model.

Resumen: *Allophylus cominia* (L) Sw (Sapindaceae), es una de las plantas medicinales más populares en Cuba habiendo sido empleada tradicionalmente en el tratamiento de la diabetes. es una de las plantas medicinales Cubanas más populares. Esta ha sido empleada tradicionalmente en el tratamiento de la diabetes. El objetivo de este estudio fue investigar el efecto del extracto acuoso de hojas de A cominia en un modelo de diabetes tipo 2 inducida por tratamiento con estreptozotocina en ratas neonatales. Se realizaron dos experimentos: a las 6 semanas de vida de las ratas, antes de comenzar la evaluación de la planta, y a las 11 semanas de vida de las ratas, después de la administración oral diaria de tres dosis de 0.25, 0.5 y 1.0 g/kg del extracto de *A cominia* durante 3 semanas y se evaluó la concentración de glucosa en sangre. A las 6 semanas de vida de las ratas, el grupo de animales diabéticos mostró un decrecimiento significativo en los valores de glucosa en sangre y el peso corporal comparado con el grupo control ($p < 0.05$). A las 11 semanas de vida de las ratas, los grupos de animales diabéticos tratados con el extracto acuoso de A cominia decrecieron significativamente las concentraciones de glucosa en sangre comparado con el grupo diabético no tratado ($p < 0.05$). Solamente los grupos tratados con 0.5 y 1.0 g/kg del extracto de *A cominia* mostraron una recuperación de los valores glicémicos normales. Por tanto, se puede concluir que el extracto acuoso de hojas de *A cominia* tiene propiedades antidiabéticas y puede ser eficaz en el tratamiento de la diabetes tipo 2.

Palabras Clave: *Allophylus cominia* (L) Sw, propiedades antidiabéticas, actividad hipoglicémica, modelo de diabetes tipo 2 de ratas neonatales.

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INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia and altered metabolism of lipids, carbohydrates and proteins, due to defects in insulin secretion and /or insulin action. The two major forms of diabetes are: type 1 (insulin-dependent), characterized by destruction of the pancreatic beta cells, absolute deficiency insulin and requires insulin treatment to live and type 2 (non-insulin-dependent), characterized by insulin resistance in peripheral tissues and deficiency (not absolute) of insulin. Type 2 diabetes is the most common form, which represents more than 90% of all cases (ADA, 2012).

Conventional hypoglycemic agents cause inadequate efficacy and number of serious adverse effects. Thus, there are wide variety of new therapeutic agents, specially from plant extracts source, being examined for the treatment of type 2 diabetes (Shubhapriya *et al*., 2008; Shen *et al*., 2008; Teng *et al*., 2011; Davis *et al*., 2012).

Allophylus cominia (L) *Sw* (Sapindaceae), also known as *Rhus cominia* (L) or *Schmidelia cominia Sw*, which common name is palo de caja, caja or caja común, is one of the most well-known medicinal plant in Cuba. It was initially used as a remedy against gastrointestinal disorders, but was subsequently employed as a remedy for diabetes. It has also been reported in the use of tuberculosis and catarrhal diseases in general. In addition, medicinal properties against toothache and use as a blood purifier in venereal diseases have also been attributed to this plant (Roig, 1988).

The phytochemical studies of the aqueous extract of leaves from *A cominia* revealed the presence of tannins, free amines, phenols, triterpenes and steroids. In addition, in this extract proteins, carbohydrates such as arabinose, xylose, galactose, glucose and fatty acids (lauric, miristic, palmitic, estearic and arachidonic) were identified (Véliz *et al*., 2004; Véliz *et al*., 2005).

Several investigations have reported the hypoglycemic activity of *A cominia* aqueous extracts in normoglycemic rats (Melchor *et al*., 1999; Veliz *et al*., 2004) and type 1 diabetic animals models (Valls *et al*., 2000; Veliz, 2001; Safonts *et al*., 2007). However, there are no studies of this plant on animal models of type 2 diabetes.

The aim of this study was to investigate the effect of *A cominia* leaves aqueous extract on type 2 diabetes model induced by streptozotocin treatment in neonatal rats.

MATERIALS AND METHODS

Plant material

Allophylus cominia (L) *Sw* (Sapindaceae) leaves were collected from forest of Cotilla (San José de Las Lajas, Mayabeque, Cuba) in the month of February (2008). Plants were taxonomically authenticated by Prof. Fernando Franco Flores, in the Laboratory of Botany at the Agriculture University of Havana, Cuba and a voucher specimen of the plant is kept for reference (HFA-1769) in the Herbarium of this institution.

Plant extract

Fresh leaves of *A. cominia* were dried in a stove at 37° C for 96 hours. The dry leaves were milled in fine particles of 5 mm. The plant extract was obtained from powder aqueous extraction at 95° C for 30 min, in a 10% (w/v) relation. The resulting extract was freeze dried. Dry extract was stored in plastic bottles in a desiccator for future experiments.

Animals

Pregnant Sprague-Dawley rats were purchased from stock at CENPALAB (Havana, Cuba). Animals were housed individually and maintained at 21 ± 2° C with a 12 h light/12 h dark cycle. Animals were allowed continuous access to water and fed *ad libitum* on standard pellet diet. All animals studies were carried out in accordance with the International Committee for Animal Care and in accordance with National Regulations for Animal Experimentation (R 15: Care and management of laboratory animals. Ethical Principles).

Experimental Procedure

Non-insulin-dependent diabetic animals model were produced as previously described (Permutt *et al*., 1984). 2-d-old Sprague-Dawley pups were injected intraperitoneally with streptozotocin (90 mg/kg in 0.1 M citrate buffer, pH 4.5). Controls were injected with an equal volume of citrate buffer. Animals were weaned at 24 d. The diabetic animals at 8 weeks old were randomly divided into four groups, 10 rats each. Group A was given 2 ml distilled water, groups B, C and D received respectively 0.25, 0.5 and 1.0 g/kg of *Allophylus cominia* aqueous extract orally during 21 days daily using gavage. At the end of the experiment, the blood was collected from the orbital

plexus by capillary tubes into test tubes containing EDTA (ethylenediaminetetraacetic acid) at the time of sacrifice for plasma glucose level, which was determined by a standard glucose oxidase method.

Oral glucose tolerance test (OGTT)

Two experiments were carried out, one with 6 weeks old rats before starting with the plant evaluation and the other at the end of the assay. In both cases, rats were fasted for 18 hours before the OGTT and an oral administration of glucose (2 g/kg) was performed. The glucose concentration was measured using a glucose oxidase method, in the first experiment, at 30, 50, 90 and 120 min after glucose administration. In the second experiment, at 50 min after glucose administration, selected before as the optimal time for the measurements.

Animals weight

The body weight of the rats was measured at 6 weeks old before starting OGTT in order to assess the significant changes of this indicator between control and diabetic groups.

Statistical analysis

Data are expressed as the mean ± standard error of mean (SEM). Results were analyzed by a ANOVA F-test and after a Duncan's multiple range test. Statistical significance was considered at $p < 0.05$.

RESULTS AND DISCUSSION

Figure 1 shows the results of oral glucose tolerance test in the type 2 diabetic rat model, which were measured plasma glucose concentrations at 30, 50, 90 and 120 min, after oral administration a high dose of glucose (2 g/kg) to 6 weeks old rats with 18 h of fasting. It is observed that glucose levels were significantly increased in the group of diabetic animals compared to control group at 30 and 50 min ($p < 0.05$). At 50 min was reached the highest value of glucose concentration and it was selected as the optimal time for measurements during the evaluation of a product with potential antidiabetic effect. It is shown, from 50 min of oral glucose administration, started to decrease the glucose levels, obtaining no statistically different values between control and diabetic groups at 90 and 120 min ($p < 0.05$).

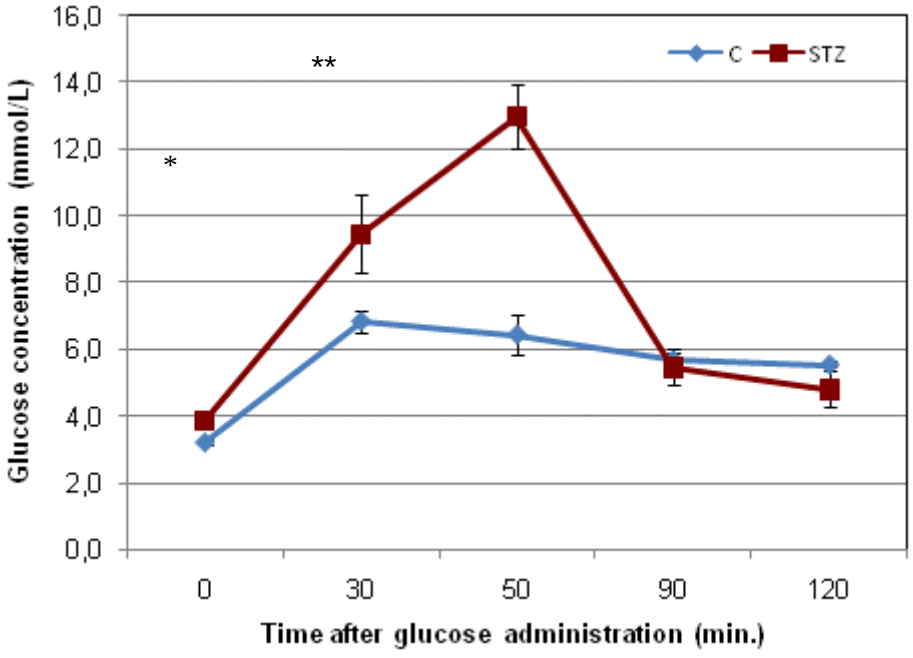

Figure 1
Oral Glucose Tolerance Test in type 2 diabetes model induced by streptozotocin treatment in neonatal rats. Data are expressed as the mean ± ESM of 7 animals per group. (*) and (**) represent significant differences between treatments ($p < 0.05$) and ($p < 0.01$) respectively. C: control group, STZ: diabetic group.

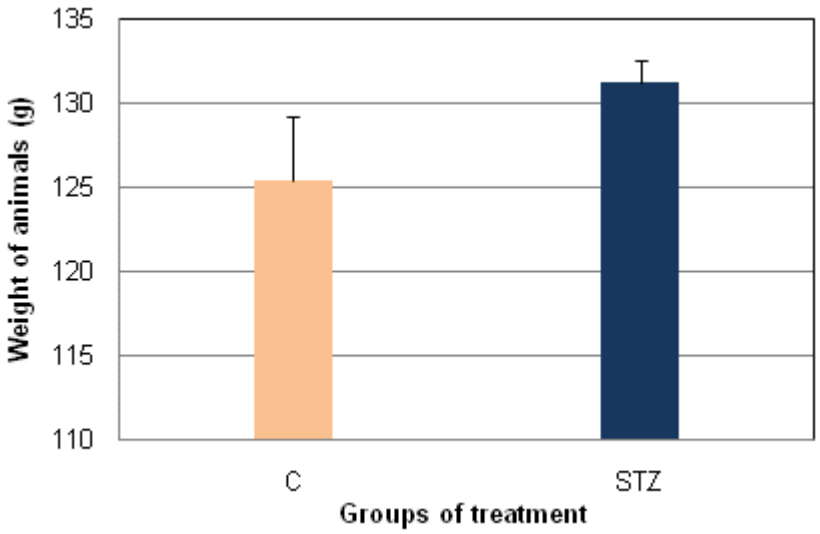

Figure 2
Effect of type 2 diabetes on body weight in rats of 6 weeks of age. Data are expressed as the mean ± ESM of 10 animals per group. Different letters represent significant differences between groups ($p < 0.05$). C: control group, STZ: diabetic group.

The figure 2 shows the average weight of controls and diabetic animals groups at 6 weeks old rats. It is observed that the group of diabetic animals showed an average weight value increased significantly compared to the control group ($p < 0.05$).

The figure 3 shows the effect of reiterated administration daily during 21 days of A cominia aqueous extract (0.25, 0.5 and 1.0 g/kg) on blood glucose concentration at 11 weeks old rats. It is appreciated a significant increase of glycemia values in the diabetic group compared with control group of normal animals. In the group of animals treated with the lower dose of extract (0.25 g/kg), decreased significantly blood glucose values with respect to the group of diabetic animals ($p < 0.05$), but they were still significantly increased compared to control group. There is not significant differences in the glycemia values between groups treated with 0.5 g/kg and 1.0 g/kg of A cominia extract. In both groups, blood glucose values were decreased significantly compared with the group treated with 0.25 g/kg of extract and with group of diabetic animals, but were not statistically different of the control group ($p < 0.05$), indicating recovery of normal glycemic values. These results demonstrate the efficacy of the aqueous extract from A cominia as antidiabetic in an in vivo model of type 2 diabetes mellitus.

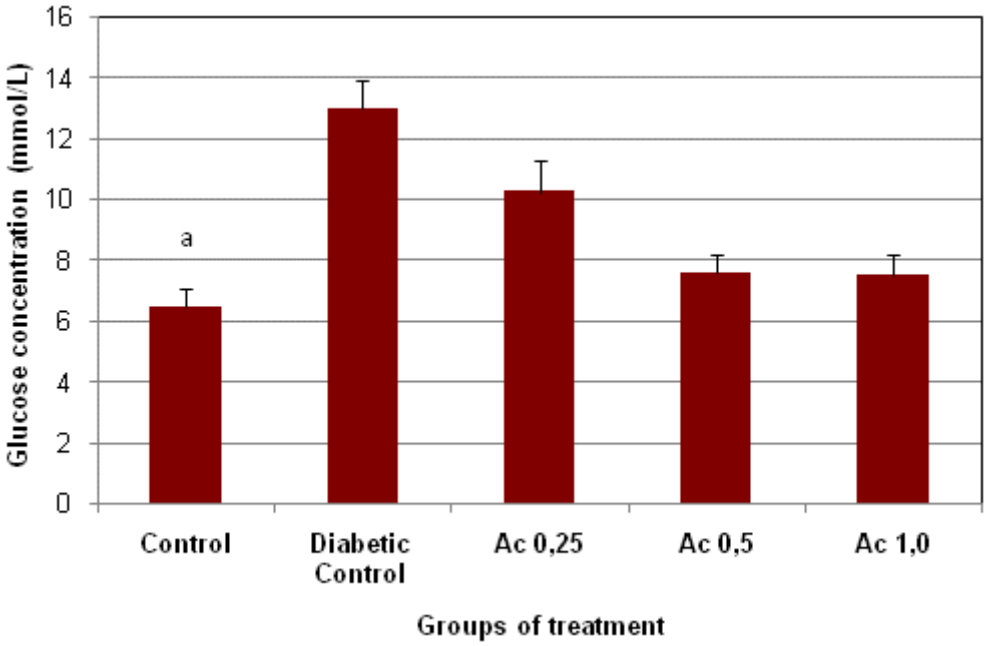

Figure 3
Effect of reiterated administration of aqueous extract from *A cominia* leaves on blood glucose levels in a model of type 2 diabetic rats. Data are expressed as the mean ± ESM of 7 animals per group. Different letters represent differences between groups ($p < 0.05$). Control group: normal animals treated with citrate buffer; Diabetic control: type 2 diabetic animals treated with Streptozotocin at 2-days-old; Ac groups: type 2 diabetic animals treated with different doses of *A cominia* extract (0.25, 0.5 and 1.0 g/kg).

The observed antidiabetic effects with *A cominia* aqueous extract in the present work, correspond to those obtained with other plant extracts tested in diabetic animal models. Other authors has reported that a proteoglycan, named FYGL (Fudan–Yueyang–G. lucidum), screened from the fruiting bodies of *Ganoderma lucidum*, administered orally to type 2 diabetic mice showed a decrease in plasma glucose level compared with the diabetic controls without drug treatment, comparable with diabetic mice treated with metformin, a clinical drug (Teng *et al*., 2011). Other reports have informed that long-term feeding of the aqueous extract from guava leaves on type 2 diabetic rats significantly reduced blood glucose level, increased plasma insulin level in an oral glucose tolerance test, and stimulated activities of some glucose metabolic enzymes, however, the underlying mechanisms have not yet been clearly elucidated (Shen *et al*., 2008). Recently, studies with this extract revealed that the improvement of hyperglycemia is considered to be associated with the suppression of postprandial blood glucose elevation by alpha-glucosidase inhibition, although the exact mechanism remains uncertain (Deguchi and Miyazaki, 2010). Moreover, the oral administration of *Annona squamosa* hexane extract in ob/ob mice for 21 days caused significant reduction in glucose (27.7%; $P < 0.01$ vs. control) comparable to Rosiglitazone treatment (32.3%; $P < 0.01$ vs. control) and it also showed a significant reduction in plasma triglyceride comparable to Rosiglitazone (Davis *et al*., 2012).

Several studies have demonstrated hypoglycemic activity of some phytochemical constituents present in the plant extracts. Thus, saponins obtained from a methanolic extract of *Momordica cimbalaria*, administered in a dose of 175mg/kg for 30 days, to diabetic mice non-insulin dependent, decreased blood glucose and the proposed mechanism is to increase insulin secretion probably by regeneration of pancreatic β cells (Shubhapriya *et al*., 2008). Furthermore, Resveratrol, a red wine polyphenol antioxidant, administered to diabetic rats for 14 days decreased the plasma glucose concentration after 14 days at 25.3 ± 4.2% (Su *et al*., 2006). It was also reported that Piceatannol, a

Resveratrol derivative, decreased hyperglycemia and impaired glucose tolerance in db/db mice, suggesting that this compound has antidiabetic properties so it can be used for the treatment of this disease (Minakawa *et al*., 2012). In other study it was found that genistein, an isoflavone, decreased levels of fasting glucose, in KK-Ay/Ta Jcl mice, an animal model of type 2 diabetes (Ha *et al*., 2012). Preliminary phytochemical studies of *A cominia* aqueous extract have detected the presence of polyphenolic compounds (Véliz *et al*., 2005), which could be involved in the hypoglycaemic effect.

CONCLUSION

In our study, the aqueous extract obtained from *Allophylus cominia* showed antidiabetic properties in a rat model of type 2 diabetes. Due to reducing glucose levels this plant might be used as a traditional herbal remedy for the treatment or prevention of certain metabolic diseases.

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