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Comparison of hypoglycemic activity of two varieties of *Averrhoa carambola* L. in streptozotocin-induced diabetic rats as a model of type 2 diabetes mellitus

Comparación de actividad hipoglucemiante de dos variedades de *Averrhoa carambola* L. en ratas diabéticas inducidas por estreptozotocina como modelo de diabetes mellitus tipo 2

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Abstract

The fruits of *Averrhoa carambola* have different uses as food; it is also used empirically as an adjunct in the treatment of various diseases including diabetes, an important disease, mainly in developing countries, such as Mexico. The main objective of this study was to compare the hypoglycemic activity of two varieties of *A. carambola*. Winstar rats, induced to type 2 diabetes with 60 mg of streptozotocin / kg of body weight (BW), were used as the experimental model. Four experimental groups with a total of 40 rats each were formed, using the Arkin and Golden Star varieties. A dose of 200 mg of the lyophilized fruit per kg of BW, dissolved in a final volume of 500 µL, was orally administered for 40 days, using an esophageal catheter. Blood glucose levels were determined with a glucometer in samples taken from the tail vein every five days during the experiment, while the final blood glucose was obtained in samples by retroorbital bleeding using the enzymatic method based on glucose oxidase activity. Blood glucose levels were lower in the treatments than in the controls. Both varieties showed an effective hypoglycemic effect, although a significant difference in their effectiveness was observed between them.

Antioxidant activity, Carambola, Hypoglycemic effect

Resumen

Los frutos de *Averrhoa carambola* tienen diferentes usos como alimento. Aunque también se utilizan empíricamente como coadyuvantes en el tratamiento de diversas enfermedades, como la diabetes, una enfermedad importante, principalmente en países en vías de desarrollo, como México. El objetivo principal de este estudio fue comparar la actividad hipoglucemiante en dos variedades de *A. carambola* utilizando como modelo experimental ratas Winstar, inducidas a diabetes tipo 2 por estreptozotocina utilizando una dosis de 60 mg / kg de peso corporal (PC). Se conformaron cuatro grupos experimentales con un total de 40 ratas, empleando las variedades Arkin y Golden Star. Se suministró oralmente, 200 mg del fruto liofilizado por kg de PC disueltos en un volumen final de 500 µL, durante 40 días, utilizando un catéter esofágico. Los niveles de glucosa en sangre se determinaron con un glucómetro en muestras tomadas de la vena caudal cada cinco días, durante el experimento, mientras que la glucosa final se obtuvo en muestras por sangrado retroorbitario mediante el método enzimático basado en glucosa oxidasa. Los niveles de glucosa en sangre fueron más bajos en los tratamientos que en los controles. Ambas variedades mostraron un efecto hipoglucemiante, aunque se observó una diferencia significativa entre ellas.

Actividad antioxidante, Carambola, Efecto hipoglucemiante

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Introduction

Averrhoa carambola L., is a woody, perennial tropical plant belonging to the Oxalidaceae family. Although known to be native of Southeast Asia, the origins of this plant species are not well defined, as manifested by diverging reports that place its center of origin and domestication in Indochina (Orduz and Rangel, 2002), Malaysia and Indonesia (Watson et al., 1988) or, more precisely, in the islands formerly known as the Moluccas (Nakasone and Paull, 1999). It was introduced into Mexico at the beginning of the 18th century, and it is now distributed in its tropical and subtropical regions, where the tree is cultivated mostly for its edible fruits. Cultivation is concentrated in the states of Colima, Chiapas, Guerrero, Michoacán, Morelos, Nayarit, Sinaloa, Jalisco, Tabasco and Veracruz (Cruz and Garza, 2006). The star-shaped carambola fruits are fleshy and have an oblong to ellipsoidal shape, with five enlarged vertices. They are green before reaching maturation, turning yellow inside when ripe, which occurs four to five months after the onset of flowering (Crane, 1994).

The tree is also cultivated for diverse purposes, principally due to several properties that have been attributed to antioxidant, hypoglycemic and anti-inflammatory properties (Lim, 2012; Pantaleón-Velasco et al., 2014). For example, it is used in Western, Mexico as an empiric auxiliary for the treatment of several illnesses associated to type II diabetes mellitus (T2DM), one of the most important world-wide public health issue, due to its persistent increase in the last years, most importantly in developing countries, such as Mexico (Salcedo et al., 2008; Shamah-Levy et al., 2020). T2DM consists of a battery of dysfunctions characterized by a hyperglycemic condition resulting, in part, from the combination of insulin resistance and inadequate insulin secretion, due to faulty β pancreatic cells (INSP, 2006). When this happens, a cellular balance is broken that leads to oxidative damage caused by the excess production of free radicals able to act deleteriously on the proteins, carbohydrates, lipids and nucleic acids of the cell. As a result, cellular, structural and functional alterations originate that lead to cellular deterioration and cell death and, eventually, to the appearance of different chronic diseases (Cuerda et al., 2011).

In the case of T2DM, increased free radicals disrupt the action of insulin at the peripheral level and contribute to pancreatic beta cell dysfunction, in addition to promoting the development of chronic complications (Evans, et al., 20003; Forbes et al., 2008; Giugliano, et al, 1996; Robertson et al., 2004).

In addition, there is a general metabolic syndrome, for which the patient must be monitored clinically. The latter due to the fact that glucose accumulation is generally accompanied by an increase in triglycerides, total cholesterol and free fatty acids (Ogbonnia et al., 2008; Saravanan and Ponmurugan, 2012). Furthermore, numerous oxidative reactions at the mitochondrial level trigger cell apoptosis (Chowdhury et al., 2008; Turk and Stoka, 2007). Another associated problem is that a secondary effect of many drugs used for T2DM treatment, designed to target insulin resistance (Manka et al., 2021), is the emergence of non-alcoholic fatty liver disease, although liver fat, or steatosis, and even more advanced stages of liver fibrosis can occur in the absence of diabetes (Ranjbar et al., 2019). Therefore, recent interest has arisen to generate alternative treatments for diabetes that do not produce damaging secondary effects. Based on the above, a study was performed to compare the hypoglycemic activity of two varieties of *A. carambola*, which was tested in streptozotocin-induced type II diabetic rats. Here, the most important results obtained are presented and succinctly discussed.

Materials and methods

Description of the study site, sample collection and preparation of plant material.

A recent study compared the nutritional composition of fresh and freeze-dried carambola fruits of the Golden Star (GS) and Arkin (Ar) varieties and determined the conservation of these components in different tissues of both varieties (Temores-Ramírez, 2021). Based on this data, we proceeded to perform experiments designed to test the hypoglucemic effect of these fruits after aesophagic catheter delivery to diabetically induced rats.

Averrhoa carambola fruits were of both the Arkin (Ar) and Golden Star (GS) varieties were randomly collected in a commercial plantation located in the municipality of Cihuatlán, in the south-west of the state of Jalisco, México (19° 22' 30" N, 104° 42' 30" W, at 13 m above sea level). For transportation, the fruits were kept at approximately -20°C with solid CO_2, and were subsequently stored at the same temperature until needed for analysis. Fruits were then ground in an electrical blender and the resulting pulp was subsequently lyophilized.

Extraction and determination of ascorbic acid levels, antioxidant capacity, total soluble phenols and flavonoids

The lyophilized fruit material was used to determine several factors that could be associated with a possible hypoglycemic effect such as ascorbic acid levels (AA) and antioxidant capacity (AOC). AA was determined using a manual electronic refractometer, (Atago Pocket Acidity Meter; Atago Tokyo, Japan). AOC in MeOH fruit extracts was determined by the 2, 2´-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-pricrylhydrazyl (DPPH) radical scavenging activity assays according to Brand-Williams et al. (1995) and Re et al., (1999), and subsequently modified by Pulido et al., (2000), and Yahia et al. (2011), respectively. All AOC assays were modified to fit a micro-plate format.

The total soluble phenols (TSP) and flavonoids (TF) contents in fruits were determined as described previously by Maranz et al. (2003) and Sakanaka et al. (2005), respectively.

Evaluation of hypoglycemic capacity of Averrhoa carambola fruits in rats

The hypoglycemic capacity of carambola fruits was examined in 30 male Winstar adult rats having an average weight of 200 g (obtained and kept in the bioterium of the Western Biomedical Research Center, Guadalajara, Jalisco, México). The adult rats were injected with streptozotocin [STZ; 60 mg/ kg of body weight (BW) in 0.1 M citrate-buffered saline, pH 4.5] to induce T2DM.

All animal trials were conducted according to The International Ethical Committee for the Experimental Use of Animals, All the animals received a commercial concentrate for laboratory animals (Rodent Laboratory Chow, Nestlé Purina, St. Louis, MO, USA) with a 10% fat composition. Three experimental groups were formed: diabetic or positive control, and two additional groups treated with the Ar and GS fruit varieties, respectively. In addition, a group of 10 individuals comprised the healthy or negative control. The animals were distributed by placing two rats per cage in each treatment group. They were kept at room temperature (approximately 23ºC ± 2) with a 12:12 light / dark photoperiod in the above-mentioned bioterium. Lyophilized fruit pulp was fed orally (200 mg of ripened fruit pulp per kg of BW dissolved in a final volume of 500 µL) to the experimental rats for 40 days using an aesophagic catheter. Blood glucose levels were determined with a glucometer in samples taken from the caudal vein every five days, for the duration of the treatment with the carambola extract, whereas the final blood glucose (FBG), triglycerides and cholesterol determination were performed in samples obtained by retro-orbital bleeding. Glucose was determined using a glucose oxidase-based enzymatic method (Trinder, 1969). Blood serum cholesterol was quantified based on the enzymatic hydrolysis of cholesterol esters, oxidation of cholesterol by cholesterol oxidase, and colorimetric measurement of liberated perioxide with 4-aminoantipyrine, phenol, and peroxidase (Lie et al., 1976). Triglycerides in serum were measured enzymatically using a series of coupled reactions designed to hydrolyze triglycerides to glycerol, which is subsequently oxidized with glycerol oxidase to produce H_2O_2, which, is measured at 500 nm (Bucolo and David, 1973; Fossati and Prencipe, 1982). Three experiments were carried out, in which similar results were obtained.

Results and Discussion

Ascorbic acid levels, antioxidant capacity, total soluble phenols and flavonoids in lyophilized carambola (A. carambola) fruits, varieties Golden Star (GS) and Arkin (Ar)

AA is an organic acid with excellent anti-oxidant properties, which plays an important role in the disease prevention activities of the immune system (Toledo, 2008).

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No difference in AA content was observed in GS and Ar fruits (Table 1). The AA levels in ripe Ar fruits, although high enough to provide a distinctive acid taste and be considered a good source of vitamin C (Dürüst et al., 1997), were lower than those detected in other AA-rich fruits, such as sour orange (16.25 to 51.0%), mandarin (12.32%), and grapefruit (28.17%) (Muñoz de Chávez et al., 1996).

The ABTS and DPPH methods yielded similar AOC levels in the fruit extracts of both carambola fruit varieties, although slightly higher AOC values were obtained using the DPPH method. However, AOC values determined by both methods were higher in the Ar variety (7.5 [Ar] *vs.* 2.3 [GS] µM Eq Trolox/g dry weight on average) (Table 1). The values recorded in this study were similar to those reported by Troya-Santos et al. (2017) in black maca (*Lepidium meyenii*) by the DPPH method. The relatively high AOC levels detected in ripe Ar fruits could have represented a factor contributing to the hypoglycemic effect observed. This, by ameliorating the deleterious oxidative effects on metabolism produced as a consequence of the diabetic condition. A significantly higher AOC, also triggered in response to ripening (Temores-Ramírez, personal observations) may have also contributed to the hypoglycemic effect observed by providing increased protection against oxidative cell processes.

Antioxidants are considered as adjuvants in the treatment of chronic degenerative diseases. Regarding T2DM, various studies have reported that they can decrease lipid peroxidation and the oxidation of LDL-cholesterol particles, in addition to their contribution to improve endothelial function and endothelium-dependent vasodilation (Cuerda et al., 2001). Some other reports have described the benefit of oxygen radical absorption capacity and equivalent Trolox antioxidant capacity in human serum after the consumption of high-fat diets. Also, a significantly positive correlation believed to occur via a decreased lipid peroxidation, was observed between anthocyanin content in human serum, the metabolic syndrome and the postprandial antioxidant status, (Basu et al., 2009; Folli et al., 2011; González-Jiménez et al., 2015; Mazza et al., 2002).

However, the positive effect of antioxidants in the treatment of T2DM and the complications derived from this disease remains a controversial issue considering the lack of significant effects on the metabolic control of diabetic patients reported by some workers (Cuerda et al., 2001).

On the other hand, no significant differences in TSP were observed between the varieties, although a slightly higher value was determined in Ar fruits, whereas an almost 2-fold higher TF levels were detected in GS fruits (Table 1). Similar TF values have been detected in nopal and wereque roots (Ramírez-Ortíz et al., 2016), black tea, red pepper, apple and the lowest value-range in red wine (González-Sánchez et al., 2011).

*Evaluation of the hypoglycemic capacity of A. **c**arambola fruits in rats*

The parameters used to evaluate the hypoglycemic effect of *A. **c**arambola* fruit extracts in diabetic rats were FBG, blood serum cholesterol and triglyceride levels. As shown in Table 2, these parameters remained high in the diabetic control group maintained with the experimental diet only, without *A. **c**arambola* fruit extract supplementation. In contrast, FBG levels, 348.75 and 430 mg/ dL, were lower in the experimental groups treated with Ar and GS fruit extracts during 40 days, respectively (Table 2). Compared to the diabetic control group, FBG levels were 2 and 1.5 times lower in the Ar- GS-treated groups, respectively. Thus, both fruit varieties tested showed an effective hypoglycemic effect. Similar reduction of FBG levels were reported in diabetic rats treated with an aqueous-ethanol extract of *A. **c**arambola* roots (Xu et al., 2014).

The high fructose content detected in *A. carambola* fruits could partially explain why these fruits reduced the blood glucose level in diabetic rats (Temores-Ramírez et al., 2021). The latter considering that fructose does not increase blood glucose levels, even though it is metabolized mainly in the liver but, unlike glucose, it does not require insulin for its metabolism. Thus, carambola fruits could be considered as an adjunct food for the treatment of T2DM patients, since their high fructose levels could be tolerated better than glucose-rich fruits.

However, other studies have suggested that hypoglycemic effect of some aqueous or alcoholic plant extracts may result from the inhibition of alpha amylase and alpha glucosidase activities (Ramírez-Ortíz et al., 2016). This is a possibility that remains to be defined by further experimentation in carambola fruits.

Similar to FBG, the cholesterol content detected in the diabetic control group was higher. However, there were no significant differences between the negative control and the GS-treated group, whereas the Ar-treated group showed a slight but significant reduction in cholesterol levels with respect to these two groups, which were 1.5-times lower than diabetic rats (Table 2).

Compared to the positive control, the triglyceride levels were also lower in the GS- and Ar-treated groups. The reduction observed was *ca.* 72% in the GS-treated group (Table 2). In this regard, the lyophilized fruit extracts of both varieties, but mostly GS, contributed to a significant reduction in the blood triglycerides concentration, since they were lower than the reference values of 150 mg/dL and much lower than those detected in the positive control group, that registered 247 mg/dL. Values similar to these were previously reported by Sanhueza et al. (2014). Compared to GS, no significant differences were recorded between Ar and the negative control.

Blood glucose levels (BGL) and FBG were significantly higher in the positive control group (Table 2; Graphic 1) compared to the two carambola-treated experimental groups. However, the hypoglycemic effect was more effective and pronounced in rats fed with Ar fruits, which showed a consistent reduction of BGL which remained stable during the duration of the experiment (Graphic 1). Conversely, the hypoglycemic effect in rats fed with GS fruits was slower, being detected 40 days after the experiment was started.

Compared to diabetic rats, both fruit varieties tested had an effective hypoglycemic effect, although the effect was significantly species-specific (Graphic 1). The effect produced, however, was still significantly higher than the negative control group of healthy rats, in which the BGL remained below 100 mg/ dL for almost the entire experiment.

The hypoglycemic effect, determined as BGL, was consistent with the lowered FBG levels detected. A similar decrease of glycemia over time was observed in diabetically induced rats treated with black maca extracts (Troya-Santos et al., 2011).

Annexes

Parameters	Variety	
	GS	Ar
Ascorbic acid (%)	5.80 ± 0.95a	5.23 ± 0.11a
Antioxidant capacity (μM Eq Trolox/g dry weight)[1]	2.25 ± 0.19b	6.12 ± 0.10a
Antioxidant capacity (μM Eq Trolox/g dry weight)[2]	2.32 ± 0.16b	8.85 ± 0.49a
Total soluble phenols (mg GAE/g dry weight)	4.82 ± 0.41a	5.87 ± 0.40a
Total soluble flavonoids (mg EQ/100g dry weight)	15.23 ± 1.89a	8.68 ± 0.13 b

Table 1. Ascorbic acid levels, antioxidant capacity, total soluble phenols and flavonoids in lyophilized carambola (*Averrhoa carambola* L.) fruits, varieties Golden Star (GS) and Arkin (Ar). [1]Measured by the ABTS method. [2]Measured by the DPPH method. The data are means ± SE (n =10). Different letters within each column indicate statistically significant differences between the two varieties at $P < 0.05$, determined by an ANOVA followed by a Tukey-Kramer test.

	Parameters		
Treatment	Blood glucose (mg/dL)	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)
Golden Star	430.66±172.40ab	63.17±5.58b	69.21±12.99c
Arkin	348.60±83.19b	55.04±3.65c	94.87±6.85b
Control +	674±23a	80.19±0.86a	247.92±12.14a
Control -	155±1.15c	61.96±0.92b	91.08±15.33b

Table 2. Evaluation of hypoglycemic effect of the supply of *Averrhoa carambola* fruit varieties Golden Star and Arkin in rats, data were compared to those determined in diabetic controls or positive control (Control +) and healthy control or negative control (Control -). Different letters within each column indicate statistically significant differences between treatments at $P < 0.05$, determined by an ANOVA followed by a Tukey-Kramer test.

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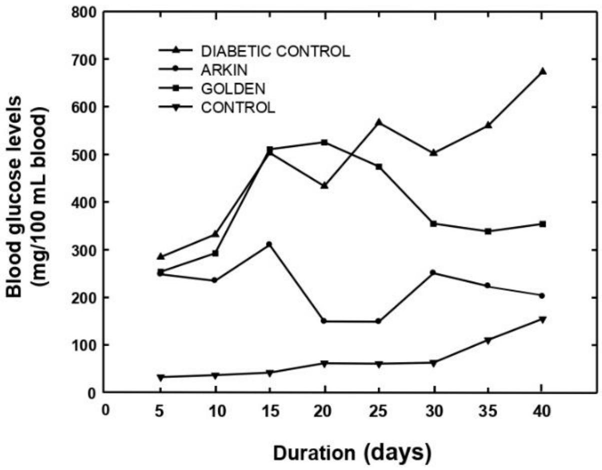

Graphic 1. Blood glucose levels (BGL) (mg/100 mL of blood) in male adult Winstar rats whose diet was complemented with pulp of two varieties of *Averrhoa carambola* fruits. BGL were determined in T2DM-induced rats fed with a standard diet alone [(diabetic controls or positive control (triangles)], complemented with fruit of two varieties: Golden Star (squares) and Arkin (circles). BGL were compared to those determined in healthy control or negative control (inverted triangles). Each point represents the mean value of n = 10 measurements.

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Conclusions

A strong hypoglycemic effect was observed in streptozotocin-induced diabetic rats treated with extracts obtained from the *Averrhoa carambola* fruit varieties GS and Ar. A significant reduction of blood cholesterol and triglyceride levels was also observed. The effect was variety-specific, since the Ar variety had a greater hypoglycemic effect and GS was more effective in the reduction of blood triglycerides.

Thus, a diet including ripe carambola fruits could be used as a auxiliary for the treatment of T2DM patients.

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