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Research Article

Effects of Averrhoa Carambola Fruit Aqueous Extract on Some Aspects of Glucose Metabolism

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Abstract

An aqueous extract of Averrhoa carambola fruit decreases the activity of glucose-6-phosphatase, mainly in intact microsomes and to a lesser extent in disrupted microsomes, suggesting a higher inhibition of the T1 transporter in comparison with the effects on the enzyme catalytic subunit. The fruit extract also decreases glucose intestinal absorption. These actions reduce the glucose supply to the blood and in consequence have an anti-hyperglycaemic effect. The A. carambola fruit extract increased diaphragm muscle glycogenogenesis probably due to a higher translocation of the GLUT4 to the plasma membrane. These results suggest that in the fruit of the plant there are compounds insulin mimetic, that exert a hypoglycemic effect.

The freeze dried fruit aqueous extract was fractionated by vacuum liquid chromatography; by the use of TLC and different revealing agents, the compounds present in the fruit extract and its fractions were tentatively identified as polyphenols and oxygenated compounds not terpenoids. The fraction soluble in acetone-methanol was the most effective inhibitor of glucose-6-phosphatase. The results suggest that the A. carambola fruit contains compounds that might be useful in the treatment of diabetic patients and encourage continuation of the fractionation of the extract in order to purify the active compounds.

Keywords: Averrhoa carambola; diabetes; glucose-6-phosphatase; glycogenogenesis; glucose Intestinal absorption

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Introduction

Glycaemia is a homeostatic parameter very well controlled thanks to equilibrium between the mechanisms that supplies and remove glucose from the blood. The intestinal absorption of glucose is a mechanism that supply glucose to the blood and occurs in two steps, the first one taking place at the apical membrane of the intestinal epithelium thanks to the participation of the sodium-glucose transporter 1 (SGLT 1) carrying glucose and Na+ to the enterocyte from the intestinal lumen, and the second occurring at the basolateral membrane of the same epithelium and is catalyzed by the glucose transporter 2 (GLUT 2) that transports glucose from the enterocyte to the blood [1].

During a short fast period, the hepatic glycogen is degraded (glycogenolysis) increasing the supply of glucose to the blood. If the fast period is prolonged the glucose synthesis from no carbohydrate metabolite takes place (gluconeogenesis) mainly in liver and kidney, increasing also the glucose supply to the blood. The last step of these two mechanisms, glycogenolysis and gluconeogenesis, is catalyzed by the glucose-6-phosphatase (G-6-Pase, EC: 3.1.3.9) which hydrolyzes glucose-6-phosphate, giving phosphate and glucose that passes to the blood, and in consequence the G-6-Pase plays an important role in the maintenance of the glycaemia [2]. The G-6-Pase is located in the endoplasmic reticulum which is the main component of the microsomal fraction, the enzyme is constituted by a transporter for glucose-6-phosphate called T1, which is very specific for its substrate and a catalytic subunit that is less specific, and in consequence is able to hydrolyze few phosphoric esters [3]. In the intact microsomes, both components are required for the hydrolysis of the glucose-6-phosphate; on the other hand when the microsomes are disrupted by different methods, such as the use of histones [4], only the catalytic subunit participates in the reaction.

The glucose transporters, GLUTs [5] carry out the facilitated transport of carbohydrate in and out of the cells. GLUT 4 is of particular interest, it is present in skeletal muscle, cardiac muscle and adipose tissue. In such cells, during the rest period it is located in intracellular vesicles. Upon stimulation by insulin the vesicles containing GLUT 4 are translocated to the plasma membrane resulting in increased of the glucose entry to the cell from the blood, and lowering of glycaemia. Since time immemorial, humans have used plants in the empiric treatment of different illness in particular diabetes mellitus, one of such plant is Averrhoa carambola L. which belongs to the exalidaceae family, and whose fruits are thick indehiscent berries of 5-8 cm with a green-yellow color and a sweet-acid flavor. It has been claimed that the fruit has medicinal properties in particular hypoglycemic activity [6]. In the present work we study the effects that an aqueous extract of A. carambola fruit has on: G-6-Pase activity of intact and disrupted microsomes, the glucose intestinal absorption and the diaphragmatic glycogenogenesis. In addition we fractionate a freeze dried aqueous extract of the fruit, partially characterize the compounds present in it and study the effects that the fractions have on the G-6-Pase.

Materials and Methods

Animals

Male Sprague-Dawley rats with a body weight of 180-220 g were used in all experiments, the animals were from the endogamy colony of the Institute of Experimental Medicine, Faculty of Medicine, Central University of Venezuela.

Plant and extract preparation

The plant, Averrhoa carambola, was identified by Dr. Stephen Tillet from the herbarium Ovalles, Faculty of Pharmacy, Venezuela Central University. The fruits were harvested in May 2017, after cleaning with distilled water being cut into small pieces, homogenized in distilled water (5 ml/ g) using a blender and filtered, this extract being used for the G-6-Pase assay, the glucose intestinal absorption and the diaphragmatic glyconeogenesis. Aliquots of the extract were dried in order to quantify the solid material present.

Microsomal fraction preparation

Liver microsomes were prepared from 24 hours fasted rats as described in [7] and were used as the source of G-6-Pase. The amount of proteins present in the microsomal fraction was quantified using a modification of the Lowry method [8].

Microsomal G-6-Pase activity

The G-6-Pase activity was measured in a final volume of 100 µL, using intact and disrupted (by the use of histones) microsomes following the method described in [9] at a concentration of glucose-6-phosphate of 5 mM, in the absence or presence of the aqueous extract of the plant fruit or the fractions obtained from it.

Glucose intestinal absorption

The glucose intestinal absorption was studied using 48 hours fasted rats as described in [10] in the absence or presence of the fruit extract. The amount of glucose present in the liquid initially placed in the intestinal segments and after 30 min of absorption was measured by the glucose oxidase-peroxidase method [11] and the glucose absorbed was estimated by difference.

Diaphragm glycogenogenesis

The diaphragm glycogenogenesis was studied using 48 hours fasted rats [12]. The diaphragms, after eliminating the central tendinous portion, were divided into 4 segments of similar weight, all segments were incubated in 4 mL Krebs-HEPES [13] supplemented with 5 mM glucose in an oxygen atmosphere for 90 min at 37º C in an orbital bath rotating at 60 cycles/min. The first segment was incubated without addition, being the control; the second one was incubated in the presence of insulin (1 mU/mL Eli Lilly & Co Mexico); the third and fourth were incubated in the presence of different amounts of the fruit aqueous extract (see Table 3). After the incubation, the diaphragm segments were weighed, the glycogen present purified [14] and quantified using anthrona [15].

Partial fractionation of a carambola fruit aqueous extract

A portion of the plant fruit aqueous extract was freeze dried, absorbed on silica, and afterwards a vacuum liquid chromatography was performed using the following solvents: dichloromethane (Ac-1) 20 mL 6 times, acetone (Ac-2) 20 mL 6 times and methanol (Ac-3) 20 mL 6 times. In the methanol fraction was observed an insoluble part (Ac-5) which was treated with acetone to obtain a soluble portion (Ac-4) and an insoluble one which was combined with that previously obtained (Ac-5). The fraction soluble in dichloromethane (Ac-1) almost contain no solid material and was not further analyzed. The methanol fraction (Ac-3) showed no activity on the G-6-Pase assay and also was not analyzed. In consequence only three fractions were studied: acetone soluble (Ac-2), acetone-methanol soluble (Ac-4) and the insoluble in acetone-methanol (Ac-5), from each of these fractions solutions of 5 mg/mL were prepared in dimethyl sulfoxide (DMSO) at 20%.

TLC of the vacuum liquid chromatography fractions obtained from the A. carambola fruit aqueous extract

Aliquots of the A. carambola fruit aqueous extract and of the fractions: Ac-2; Ac-4 and Ac-5 were seeded on silica gel thin layer plates and developed with one of the following solvent mixes: ethyl acetate: acetic acid: formic acid: water (100: 11: 11: 27; v:v:v:v) for high polarity compounds; ethyl acetate: methanol: water (100: 13.5: 10; v:v:v) for intermediate polarity compounds or hexane: ethyl acetate: formic acid (75: 25: 1; v:v:v) for low polarity compounds. The following revealing reagents were used: anisaldehyde in sulphuric acid for essential oils, terpenes, polyphenols and saponins; Draggendorf for alkaloids and NP/PEG (1 % methanolic diphenylboric acid-ß-ethylamino ester and 5% ethanolic polyethyleneglycol) for flavonoids and phenylpropenoids and its derivatives. TLC plates, after revealing were observed under visible light, 254 nm and 365 nm.

Statistical analysis

The data were analyzed using the statistical program GraphPad Prism 6 version 6.07. The t-Student test was used to establish if the differences were of statistical significance and the ANOVA of two ways to compare the effects of de vacuum liquid chromatography fraction on G-6-Pase.

Results

As can be seen from (Table 1) showing the effects of the aqueous extract of A. carambola fruit on the activity of the hepatic microsomal G-6-Pase, a higher inhibition was observed of the enzyme activity in intact microsomes in comparison to that seen in disrupted microsomes, however the effect on the latter was not negligible; in consequence the enzyme latency was increased from 11.3 % in controls to 49.3% in the microsomes treated with the fruit extract.

	Intact Microsomes		Disrupted Microsomes	
	Activity	% of Inhibition	Activity	% of Inhibition
Control	2,44 ± 0,33		2,75 ± 0,27	
Fruit Aqueous Extract	0,76 ± 0,14*	68,9	1,50 ± 0,16*	45,5

Table 1: Effects of Averrhoa carambola fruit aqueous extract on the hepatic microsomal G-6-Pasa.

As shown in (Table 2), the glucose intestinal absorption was moderately decreased by the presence of the A. carambola fruit aqueous extract, however the change was statistically significant.

	Glucose Absorbed	% of Inhibition
Controls	0,78 ± 0,04	
Fruit Aqueous Extract	0,70 ± 0,04*	10,3

Table 2: Effects of the Averrhoa carambola fruit aqueous extract on the glucose intestinal absorption.

The effects of the A. carambola fruit aqueous extract on the diaphragm glycogenogenesis are shown in (Table 3). The diaphragm segments incubated in the presence of insulin (1 mU/mL) contain almost double the amount of glycogen compared with the controls, value that is nearly identical to that seen in the diaphragm segments incubated in the presence of 0.2 mg of the A. carambola fruit aqueous extract. When the amount of the fruit extract was duplicated in the incubation medium the quantity of glycogen present in the diaphragm segments was 2.9 times that found in controls. From the migration characteristics on TLC plates and the color observed with the revealing reagents used, in the A. carambola fruit aqueous extract and in the fractions obtained from it by vacuum liquid chromatography, it is possible to suggest that the main compounds present were polyphenols and oxygenated compounds non terpenoid; there were no flavonoids nor alkaloids. The polyphenols were of the phenylpropenoids acid type and more abundant in the Ac-4 fraction (soluble in acetone-methanol).

Controls	1313,78 ± 645,16	
Insulin	2733,14 ± 797,65*	108,0
0.2 mg of Aqueous Extract	2744,87 ± 545,45*	108,9
0.4 mg of Aqueous Extract	3771,26 ± 1800,59*	187,1

Table 3: Effects of Averrhoa carambola fruit aqueous extract on diaphragm glycogenogenesis.

The presence of DMSO, at a final concentration of 8 % in the assay, does not modify the G-6-Pase activity neither in controls nor in A. carambola fruit aqueous extract treated microsomes (Tables 1 and 4).

	Intact Miicrosomes		Disrupted Microsomes	
	Activity	% of Inhibition	Activitiy	% de Inhibition
Controls	2,33 ± 0,19; n=3		2,80 ± 0,14; n=4	
Aqueous Extract	0,74 ± 0,04*; n=7	68,2	1,54 ± 0,0*5; n=8	45,0
Ac-2	1,04 ± 0,05*; n=6	55,2	1,49 ± 0,11*; n=10	46,9
Ac-4	0,82 ± 0,09*; n=7	65,0	2,01 ± 0,12*; n=7	28,3
Ac-5	1,70 ± 0,13*; n=5	27,1	2,51 ± 0,17; n=12	10,2

Table 4: Effects of the fractions obtained by vacuum liquid chromatography from the Averrhoa carambola fruit aqueous extract on the G-6-Pase.

In (Table 4) are shown the effects of the fractions Ac-2 (soluble in acetone), Ac-4 (soluble in acetone-methanol) and Ac-5 (insoluble in acetone-methanol) obtained by vacuum liquid chromatography of the freeze dried material obtained from the fruit plant aqueous extract on the G-6-Pase of intact and disrupted microsomes. All the three fractions strongly inhibit the G-6-Pase activity mainly in intact microsomes as does the fruit aqueous extract; the most active fraction was Ac-4, Ac-5 being the least active. It is interesting to point out that the vacuum liquid chromatography concentrates the active compound(s) present in the fruit aqueous extract, due to the fact that 1.6 mg of the later are required to get a 68.5 % G-6-Pase inhibition and only 0.2 mg of Ac-4 fraction to obtain a 65.0 % enzyme inhibition.

Discussion

In (Tables 1 and 4) are shown the values of the G-6-Pase activity of the hepatic intact and disrupted (by the use of histone) microsomes, which are similar to those reported earlier [16]; it is interesting to point out that the enzyme activity increases as the microsomes are disrupted, an aspect that is characteristic of the enzymes bound to membranes and is called latency. The A. carambola fruit aqueous extract and the fractions obtained from it by vacuum liquid chromatography showed a higher inhibition of intact microsomal G-6-Pase in comparison to that observed in disrupted microsomes (Tables 1 and 4). These results strongly suggest that in the fruit extract and its fractions, there is (are) compound(s) that mainly inhibit the glucose-6-phosphete transporter (T1) and exert a lower effect upon the catalytic subunit of the G-6-Pase [16]. It has been reported, that several different compounds are able to inhibit T1, between them we can mention: chlorogenic acid, phlorizin, 3-mercaptopicolinic acid [17] and flavonoids such as quercetin galloyl rhamnoside and kaempferol galloyl rhamnoside [18]. An extensive list of T1 inhibitors has been reported. The amount of glucose absorbed by the control intestinal segments (Table 2) was similar to that reported. The inhibition, of this process, by A. carambola fruit aqueous extract was small but statistically significant and it is possible due to the effects of the polyphenols present in the fruit plant extract. [19] have reported that the green tea and other infusions, rich in polyphenols, are able to inhibit the glucose intestinal absorption, they contain chlorogenic and caffeic acids, both being polyphenols [20]. It is also interesting to mention that kaempferol rhamnoside, purified from Bauhinia megalandra leaves, [21] similarly inhibits glucose intestinal absorption.

As shown in (Table 3) the diaphragm segments were able to perform glycogenogenesis, and the values observed were almost doubled by the presence of insulin (1mU/mL) in the incubation medium in a similar way as reported by others, suggesting that the experimental conditions were adequate to study this metabolic pathway.

The diaphragm glycogenogenesis was increased in a dose dependent manner by the presence of the A. carambola fruit aqueous extract in the incubation medium, with the lower concentration of the extract (0.2 mg) the value obtained was similar to that observed in the presence of insulin (Table 3). The glycogenogenesis increase may be due to a rise in the activity of the enzymes that participate in this metabolic pathway such as glycogen sintase and UDP-glucose pyrophosphorylase, however the entry of glucose to the muscle cells is a prior requirement for the glycogen synthesis. The glucose entry to the muscle cells is mediated by the GLUT 4, and the presence of this transporter in the plasma membrane due to the insulin action [22]. From the above consideration, it is possible to suggest that in the fruit extract there is (are) compound(s) that increase the diaphragm glycogenogenesis by raising glucose entry to cells in a similar way to insulin. Due to the fact, that the polyphenols are the most abundant compounds present in the fruit plant extract, it might be possible that such compounds were responsible for the insulin mimetic effect of the extract. It has been suggested that the polyphenol chlorogenic acid [23] increases the translocation of GLUT 4 to the plasma membrane from intracellular vesicle.

The fraction soluble in acetone-methanol (Ac-4) contains the highest amount of polyphenols and shows the maximum percentage of hepatic intact microsomal G-6-Pase inhibition (Table 4), these results strongly suggesting that those compounds are responsible for the biological effects. The A. carambola fruit aqueous extract and the fraction obtained from it, especially Ac-4, inhibit the hepatic microsomal G-6-Pase (Tables 1 and 4), enzyme that catalyzes the final step of glycogenolysis and gluconeogenesis pathways and in consequence reduce the hepatic supply of glucose to the blood, showing an anti-hyperglycemic effect. The glucose intestinal absorption reduction exerted by A. carambola fruit aqueous extract (Table 2) also decreases the glucose supply to the blood increasing the anti-hyperglycemic effect. On the other hand, the increase of the muscle glycogenogenesis produced by the presence of the A. carambola fruit aqueous extract (Table 3), might be due to a rise in glucose entry to that tissue, having a hypoglycemic effect.

The three aspects mentioned above strongly suggest that in the A. carambola fruit aqueous extract there is (are) compound(s) that could be useful in the treatment of the hyperglycaemia of diabetic patients. The results present here encourage the continuation of the phytochemical analysis of the A. carambola fruit aqueous extract in order to purify the active compound(s) responsible for the biological action.

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