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Full Length Research Paper

Glucose-lowering effect of xoconostle (*Opuntia joconostle* A. Web., Cactaceae) in diabetic rats

Rúbia Cassiana Paiz[1], Bertha Irene Juárez-Flores[2]*, Juan Rogelio Aguirre Rivera[2] Norma Cecilia Cárdenas Ortega[3], Juan Antonio Reyes Agüero[2], Erika García Chávez[2] and Gregorio Álvarez Fuentes[2]

[1]Programa Multidisciplinario de Posgrado en Ciencias Ambientales, Universidad Autónoma de San Luis Potosí, Mexico.
[2]Instituto de Investigación de Zonas Desérticas, UASLP, Altair 200 Colonia del Llano CP. 78377, San Luis Potosí, S.L.P., México.
[3]Facultad de Ciencias Químicas, UASLP, Mexico.

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The anti-diabetic effect traditionally attributed to the mesocarpium and cladode of *Opuntia joconostle* was assessed experimentally in male wistar rats with streptozotocin-induced diabetes (40 mg/kg bodyweight). Groups of six diabetic and six healthy rats were dosed with either water or aqueous extracts of mesocarpium, cladode or a 50:50 mixture of both. The dose, defined through a screening experiment, was 100 mg/kg bodyweight of the freeze-dried aqueous extract, administered orally by esophageal cannula for 12 weeks. Variables assessed at weekly intervals were: blood levels of cholesterol, high-density lipoproteins (HDL), glucose and triglycerides. Total cholesterol and HDL levels were statistically similar among diabetic and healthy animals. A reduction ($p < 0.001$) in glucose concentration was observed in both healthy and diabetic rats dosed with the three *O. joconostle* supplements; this effect was most evident with the mesocarpium (72%). Triglycerides decreased ($p < 0.001$) only in healthy rats. These findings reveal that *O. joconostle* possesses a glucose- and lipid-lowering effect in both healthy and diabetes-induced rats; this suggests that the frequent consumption of *O. joconostle* by humans in the diet may contribute to prevent and control the complications associated with type-2 diabetes mellitus.

Key words: *Opuntia joconostle*, hipoglucemic, xoconostle, hipolipidemic.

INTRODUCTION

Diabetes mellitus (DM) is a disease that affects glucose homeostasis causing visual, heart and renal impairment, as well as circulatory and digestive complications, which may lead to permanent health alterations and even death (Starr and Mcmillan, 2007). Given the pathological diversity of this disease, DM has been regarded as one of the major public-health issues worldwide. In the year 2000, some 171 million cases of diabetes were recorded worldwide, and estimates suggest that this figure will rise to 366 million by 2030 (Wild et al., 2004). In Mexico, DM is the second leading cause of death and the most important chronic-degenerative disease (Zárate and Ramírez, 2007). According to the Mexican Official Standard (Anonymous, 1994), several DM types have been characterized, the most common ones being type-1 (DM1) and type 2 DM (DM2); of these, DM2 is the most frequent type (90%), commonly associated with obesity (Hernández-Ávila and Olaíz-Fernández, 2002).

The therapeutic strategies to properly control this disease in its early stages include modifications in diet, exercising and administration of glucose-lowering agents. However, this scenario changes once the disease has reached the degenerative stage, when treatment becomes expensive and usually beyond reach for most persons. For this reason, the use of traditional medicine

*Correspondent author. E-mail: berthajf@uaslp.mx. Tel: +52 (444) 8422475 ext. 110. Fax: +52 (444) 8422359 ext. 106.

has risen, especially in developing countries and among the population with the lowest income and with no access to public healthcare services (Andrade-Cetto and Heinrich, 2005). The World Health Organization acknowledges the use of natural products as cheap and effective treatments for DM (Castillo, 2002). However, misuse of this therapeutic option may lead to serious alterations and, therefore, the experimental assessment of the risks and benefits associated with these therapies is relevant.

In Mexico, the use of *Opuntia* species, belonging to the Cactaceae, is an alternative treatment commonly use for diabetes; this plant can be taken before breakfast by preparing a shake with joconostle mesocarpium, cladode or both (Ibáñez-Camacho and Merckes-Lozoya, 1979; Bravo-Holis, 1978). The species most commonly used for this purpose include the wild *O. joconostle*, *O. leucotricha* and *O. streptacantha*, and the cultivated *O. ficus-indica* Mill and *O. matudae* Scheinvar, the latter being grown commercially in the State of Mexico. The traditional use of *Opuntia* to treat DM has stimulated a number of investigations (Pimienta-Barrios et al., 1994; Bwititi et al., 2000; Alarcón-Aguilar et al., 2003) aimed at determining the qualities attributed to this genus. *O. joconostle* A. Web. typically grows in semiarid areas across central and northern Mexico, where it prospers equally well in wild "nopaleras" (*Opuntia* spp. dominated plant communities); backyard orchards and commercial plantations (Bravo-Holis, 1978; Bautista, 1982; Sánchez and Figueroa, 1994; Scheinvar, 1999). This is a shrub measuring up to 2.0 m high, with a well-defined stem. The obovate, ovate or rhomboid cladodes measure up to 28 cm long by 21 cm wide; the epidermis is glabrous (occasionally waxy), light green (slightly yellowish) with purple spots under areoles in winter; fruits range from globose to subglobose and cylindrical, 3.5 cm long and up to 5.5 cm in diameter, with a sunken yellowish-green to red floral scar, easily recognized by a thick peel with a pleasant consistency and acid flavor (Bravo-Holis, 1978; Sánchez and Figueroa, 1994; Reyes et al., 2009).

Although this species is highly appreciated and commonly used in traditional medicine as an anti-diabetic agent, it has been rarely included in preclinical and clinical trials to investigate this effect. Therefore, the aim of the present investigation was to confirm the glucose-lowering effect traditionally attributed to the mesocarpium and cladode of *O. joconostle*. To this end, a freeze-dried aqueous extract of these organs, either separate or combined, was administered to male wistar rats with experimentally streptozoticin-induced diabetes.

MATERIALS AND METHODS

This study used fruits and cladodes of *O. joconostle* from the experimental plantation of the Instituto de Investigación de Zonas Desérticas (Institute of Arid Zone Research) at the Universidad Autónoma de San Luis Potosí (San Luis Potosi Autonomous University) (22°43' N; 100° 57'W; 1860 m.a.s.l.). These materials were harvested from the same plant, at the same stage of maturity and simultaneously. Fruits were collected when these were ripe; cladodes, at approximately 9 months old. Fruits were cut in half; the epidermis (epicarpium) and seeds along with the scarce pulp associated with them (endocarpium) were removed. The fleshy mesocarpium was cut into thin slices and dried in a forced-air oven (Shel La, Model FX14, USA) at 35 ± 2°C to constant weight. Areoles were removed from cladodes; afterwards, cladodes were sliced and dried similarly to mesocarpium. Dried materials were pulverized in a conventional blender.

One hundred grams of each powdered material were extracted using the water-reflux method (1:10 w/v) for two hours; aqueous extracts were filtered through a Whatman No. 1 filter paper and then freeze-dried at -50°C (Lobconco Corporation, Model 117, England). The yield after lyophilization was 42.4 g/100 g mesocarpium powder, and 30.4 g/100 g cladode powder.

Animals and diabetes induction

Forty eight adult male Wistar rats weighing 250 to 300 g were used in the experiment. These were obtained from the Animal Facility Laboratory at the College of Medicine, Universidad Autónoma de San Luis Potosí. Animals were individually housed in polypropylene cages kept in a room under controlled temperature and humidity, with an inverted 12 / 12 h light-darkness cycle. Animals were kept in this room under the experimental housing and feeding conditions for one week prior to the trial. Animals had ad libitum access to water and were fed 20 g commercial rodent food (Rodent Laboratory Chow 5001, Agriands Purina, México). Animals were handled in compliance with the ethics recommendations of the Mexican Official Standard: Technical Specifications for the Breeding, Care and Use of Laboratory Animals (NOM-062-ZOOO-1999) (Anonymous, 1999).

DM was induced experimentally in rats using streptozotocin (STZ) (Sigma SO130, St. Louis, MO, USA) dissolved in 0.01 M sodium citrate buffer (pH 4.5). To this end, a single dose of 40 mg/kg bodyweight was administered intraperitoneally to rats fasted for 12 h. Three days post-administration, blood samples were drawn from the caudal vein and the animal's glycemic status was determined with a portable glucose meter (Ascencia Elite, Bayer, Francia). Rats with blood glucose levels above 250 mg/dL after a 12 h fast were deemed diabetic. These rats received slow-acting insulin (Eli Lilly HI-310 NPH, México) (one to three units) subcutaneously at 12 h intervals daily over the experimental period (12 weeks), to keep glucose levels between 250 and 350 mg/dL and hence mimic the metabolic condition of a DM2 patient with no therapeutic control.

To determine the optimum dose for the mesocarpium, cladode or mesocarpium/cladode mixture supplement, in terms of the biological response of diabetic and healthy animals, a screening assay was conducted with 24 rats similar to those already described: 12 with STZ-induced diabetes and 12 healthy rats. Three healthy and three diabetic rats received the same supplement and dose, that is, extract of either mesocarpium, cladode or 50:50 mesocarpium/cladode mixture, dosed at 100.0, 200.0 or 300.0 mg lyophilized extract using water as a vehicle, per kg of body weight, and the blood glucose concentration was measured at 30 min intervals for three hours.

Experimental design, treatments, variables assessed, and statistical analysis

The experiment was conducted according to a fully randomized experimental design, with a 2 x 4 factorial arrangement of treatments. Factors and levels were: (a) animal condition (diabetic and healthy), and (b) supplement type (mesocarpium, cladode,

Table 1. Mean squares and F test for concentrations (mg/mL) of compounds in blood of diabetic and healthy rats supplemented with water (W), mesocarpium (M), cladode (C) or mix of mesocarpium and cladode (M/C) of *O. joconostle*.

	D. F.	Glucose	Triglycerides	Cholesterol	HDL
Suplement	3	25447.54***	242.22***	52.39	70.74*
Animal condition	1	89874.24***	6657.21***	817.27*	11.87
Animal condition x suplement	3	19250.79***	84.88*	67.54	34.03
Error	36	861.97	26.78	63.64	26.87
V.C. (%)		22.65	6.63	9.9	20.53

***Significant level p<0.0001. *Significant level p< 0.05. D. F. = Degrees of freedom. V. C. = Variation coefficient.

mesocarpium/cladode mixture, and water) with six replicates, one rat each. The experimental period lasted 12 weeks, during which supplements were administered via oral cannula, once daily, at the beginning of the darkness period. Each week, about two hours post-dosing, a blood sample was drawn from the caudal vein. These samples were tested for the effects of treatments in terms of glucose, total cholesterol, high-density lipoprotein (HDL) and triglyceride concentration. These variables were determined using commercial enzymatic kits (Sera Pack Plus, Bayer, Argentina) in a spectrophotometer (Bayer, RA-50 Chemistry Analyzer, Ireland) with wavelengths from 500 to 600 nm. Furthermore, the body weight of each rat was recorded each week. The change in body weight was calculated weekly using the equation: bodyweight gain (%) = ((final weight - initial weight)/initial weight) • 100.

The data analysis was conducted through the PROC GLM procedure in SAS (SAS, versión 8.0; SAS Institute, Cary, North Carolina), and using a multiple comparison of means (Steel and Torrie, 1999). Results are reported as means ± standard error of the 12 assessments.

RESULTS AND DISCUSSION

The preliminary experiment revealed that healthy animals supplemented with 100 mg of the lyophilized mesocarpium extract/kg bodyweight had statistically similar glucose levels as water-supplemented animals; rats supplemented with 200 and 300 mg of this extract/kg displayed statistically higher glucose levels ($p < 0.05$) relative to water-supplemented animals. Diabetic rats supplemented with 100 mg of the lyophilized mesocarpium extract/kg bodyweight showed a lower glucose level ($p < 0.01$) compared with diabetic animals supplemented only with water and with twice and three times the amount of fruit ($p < 0.05$). Based on these findings, 100 mg of the lyophilized mesocarpium extract/kg bodyweight was chosen as the optimum experimental dose, for leading to the smallest rise in glucose concentration in diabetic rats while causing no alterations in healthy rats.

The effect of the various supplements on glucose concentration differed statistically (Table 1) and was associated with the animals' health status (Figure 1). Thus, both healthy and diabetic rats supplemented with mesocarpium showed a lower glucose concentration ($p < 0.001$) compared with water-supplemented rats. At the same time, mesocarpium supplementation administered to diabetic rats led to the greatest reduction (70%, $p < 0.0001$) in glucose levels, up to concentrations statistically similar to those in healthy rats. In contrast, diabetic animals supplemented with cladode displayed the smallest reduction in glucose concentration, and showed the characteristic symptoms of DM during handling and care, such as irritability, polyuria, polydipsia and polyphagia. Besides, diabetic rats supplemented with the mesocarpium-cladode mixture displayed glucose concentrations between those associated with either mesocarpium or cladode alone, hence confirming that the mesocarpium is the main cause of the reduction in glucose concentration.

Mesocarpium administration resulted in an immediate decrease in blood glucose level, which became accentuated during the last weeks of the experiment. This finding contrasts with observations in healthy persons by Pimienta-Barrios et al. (1994), where glucose concentration rose 20 and 40 min after consuming *O. joconostle* fruits; these authors attributed this rise to the mucilage present in the fruit. However, the fact that the mesocarpium caused a reduction in glucose concentration in both diabetic and healthy rats approximately three hours post-dosing indicates that the glucose-regulating homeostasis mechanisms functioned normally in all animals (Mathews et al., 2002). Furthermore, since mesocarpium administration was associated with glucose concentrations returning to the normal range in diabetic rats, such reduction is likely caused by a chemical present only in this plant organ.

The lowering of glucose levels caused by *O. joconostle* has also been observed with other *Opuntia* species, including *O. ficus-indica* (Frati-Munari et al., 1989), *O. fuliginosa* Griffiths (Trejo-González et al., 1996), *O. lindheimeri* Eglem. (Laurenz et al., 2003), *O. megacantha* Salm-Dyck (Bwititi et al., 2000; Bwititi et al., 2001), *O. robusta* Wendl. (Wolfran et al., 2002) and *O. streptacantha* Lem. (Ibáñez-Camacho and Román-Ramos, 1979; Ibáñez-Camacho and Meckes-Lozoya, 1983; Meckes-Lozoya and Ibáñez-Camacho, 1989; Frati-Munari et al., 1988; 1989a; 1989b; 1989c; Román-Ramos et al., 1991; 1995); hence, the various *Opuntia* species likely share similar metabolites that are responsible for the glucose-lowering effect associated with them.

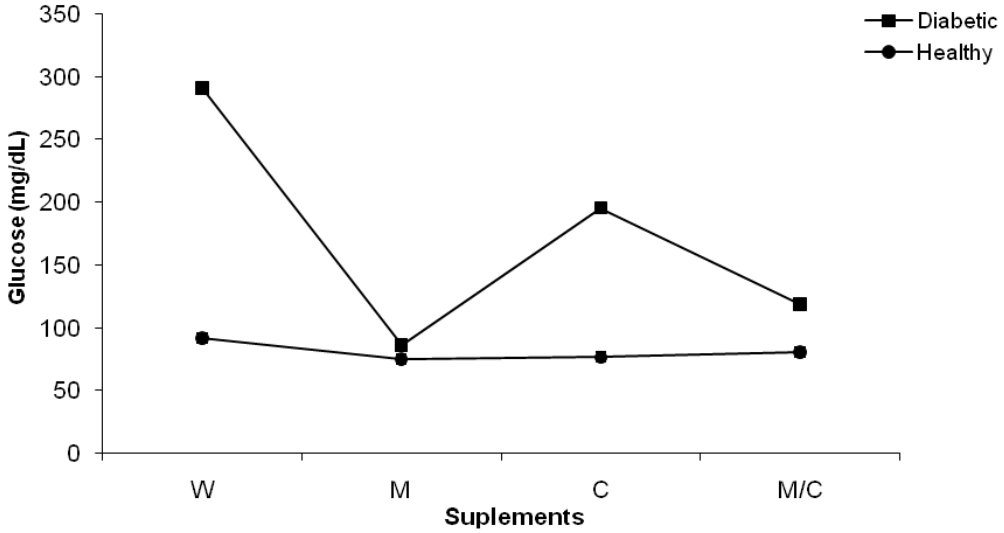

Figure 1. Effect of water (W), mesocarpium (M), cladode (C) or mix of mesocarpium and cladode (M/C) of *O. joconostle* supplementation on glucose concentration in diabetic and healthy rats. Each point represents the mean ± SEM of six rats.

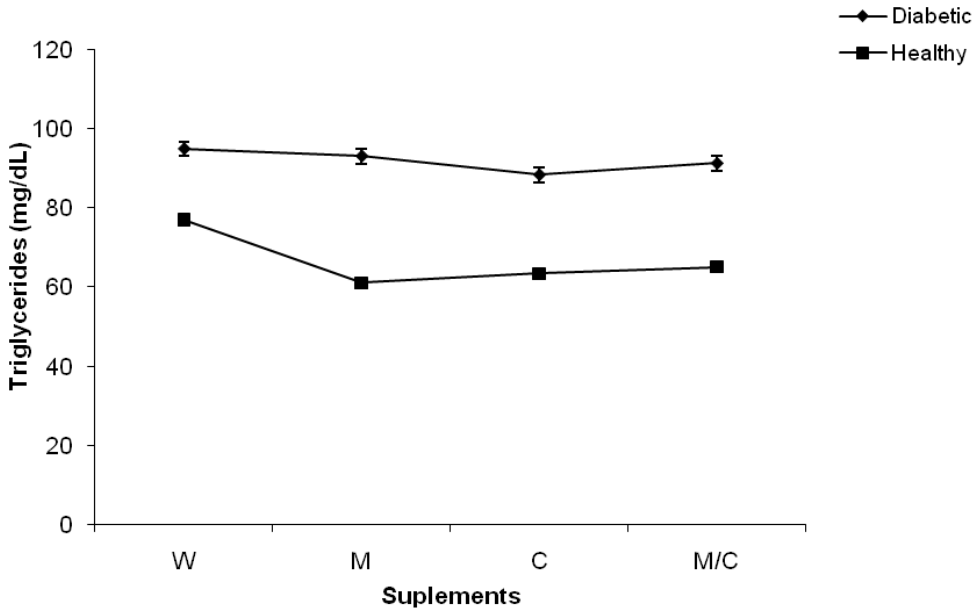

Figure 2. Effect of water (W), mesocarpium (M), cladode (C) or mix of mesocarpium and cladode (M/C) of *O. joconostle* supplementation on tryglicerides concentration in diabetic and healthy rats. Each point represents the mean ± SEM of six rats.

In addition to the glucose-metabolism impairment, DM also disrupts lipid metabolism in the long term (Suash-au et al., 2007). As regards triglycerides, the effect of supplementation on rat health status was also highly significant (Table 1); that is, supplements modified blood triglyceride levels, as a function of the animal's health condition. Triglyceride concentration dropped significantly ($p < 0.001$) in xoconostle-supplemented healthy rats; however, the higher triglyceride concentration observed in diabetic rats did not drop significantly (Figure 2). However, these findings contrast with those reported by Pimienta-Barrios et al. (1994), who affirm that triglycerides showed no reduction in healthy patients supplemented with xoconostle fruit. The decrease in triglyceride

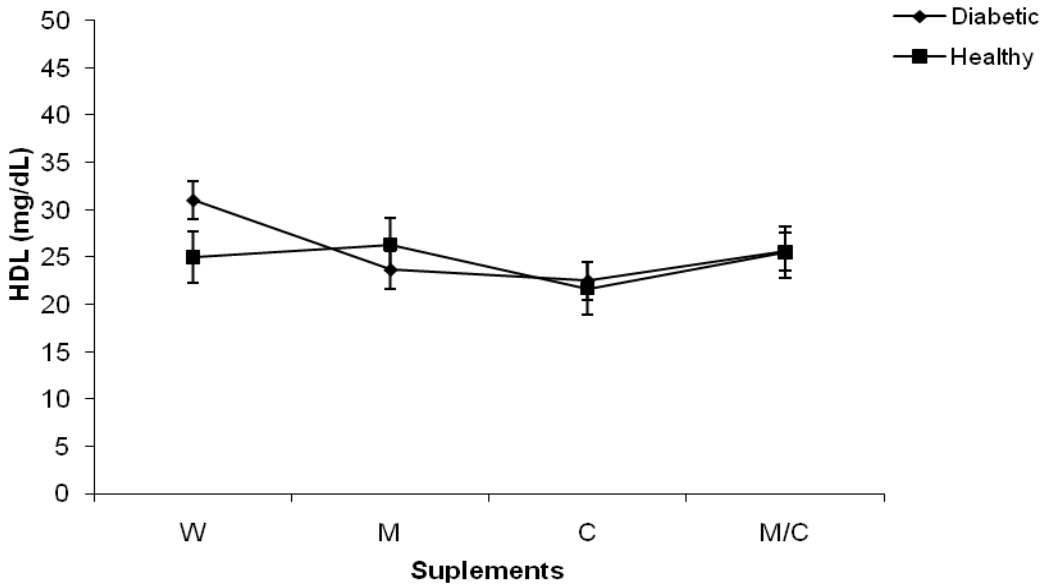

Figure 3. Effect of water (W), mesocarpium (M), cladode (C) or mix of mesocarpium and cladode (M/C) of *O. joconostle* supplementation on cholesterol concentration in diabetic and healthy rats. Each point represents the mean ± SEM of six rats.

concentration was also observed by Frati-Munary et al. (1992) in healthy subjects who were given capsules containing flour from *O. ficus-indica* fruits, as well as by Wolfran et al. (2002) when hyperlipidemic subjects were supplemented with fresh pulp of *O. robusta* fruits.

Untreated diabetes results in a rise in the concentration of triglycerides, quilomicrons and free fatty acids; in turn, this frequently leads to lipemic plasma. The rise in triglyceride concentration is largely due to buildup when triglyceride translocation to fat deposits is reduced (Ganog, 2003). The reduction in triglyceride concentration in healthy rats may be due to that xoconostle mesocarpium extracts contain some type of polysaccharide or mucilage (soluble fiber) that favors lipid metabolism (Ou et al., 2001; Weickert et al., 2005; Chen et al, 2009). Thus, the *O. joconostle* mesocarpium might be useful as an adjuvant treatment in persons not suffering DM but showing high triglyceride levels.

Only the differences in cholesterol concentration between diabetic and healthy animals were statistically significant (Table 1 and Figure 3). Specifically, cholesterol concentration was higher in diabetic rats supplemented with either cladode or the mesocarpium-cladode mixture ($p < 0.05$ and $p < 0.01$, respectively) compared to healthy rats. In contrast, cholesterol concentration was statistically similar in both diabetic and healthy rats supplemented with water and mesocarpium. This finding evidences again the beneficial effect of mesocarpium in regulating the blood lipid complex in DM animals.

The results obtained with the mesocarpium supplement contrast with reports by Pimienta-Barrios et al. (1994), who describe a reduction in cholesterol levels in healthy patients supplemented with xoconostle fruit, with findings by Frati-Munari et al. (1992), who administered capsules containing dried *O. ficus-indica* fruit to healthy subjects, and with findings published by Wolfran et al. (2002) when fresh pulp of *O. robusta* fruit was administered.

Cholesterol is absorbed in the intestine and binds to some quilomicrons formed in the mucosa, which carry it to the liver; cholesterol is also synthesized in this organ and other tissues (Ganong, 2003). It is likely that the mesocarpium soluble fiber interferes with lipid absorption in the intestine (Muñoz et al., 1979; Jenkins et al., 1993; Anderson et al., 2000; van Bennekum et al., 2005), but it is also possible that pectin from the mesocarpium reduces cholesterol biosynthesis, hence regulating blood levels (Fernández et al., 1994). In general, cholesterol levels in plasma increase in diabetic patients, and this is regarded as one of the factors associated with the accelerated development of arteriosclerotic vascular disease, an important long-term complication of DM (Ganong, 2003).

In the present investigation, supplementation led to significant differences ($p < 0.05$) in HDL concentrations (Table 1 and Figure 4). Thus, the differences found only in water-supplemented healthy and diabetic rats evidence the regulatory effect exerted by mesocarpium supplements on HDL concentration. Plasmatic HDL comprises complex compounds including proteins and lipids synthesized in the liver and small intestine, organs that participate in lipid transport and metabolism. HDL contain small cholesterol levels, since the former recapture remnant levels of the latter present in the

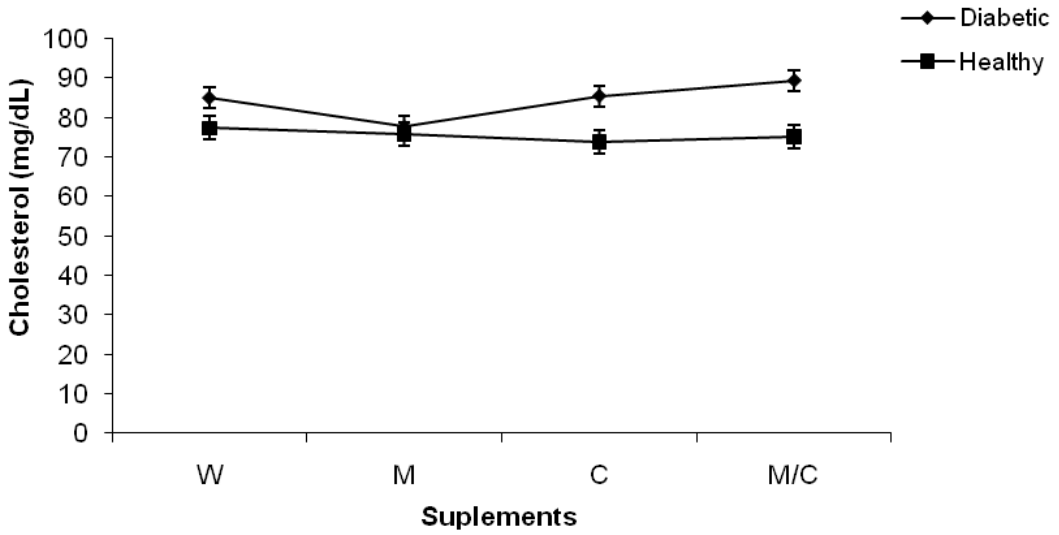

Figure 4. Effect of water (W), mesocarpium (M), cladode (C) or mix of mesocarpium and cladode (M/C) of *O. joconostle* supplementation on HDL concentration in diabetic and healthy rats. Each point represents the mean ± SEM of six rats.

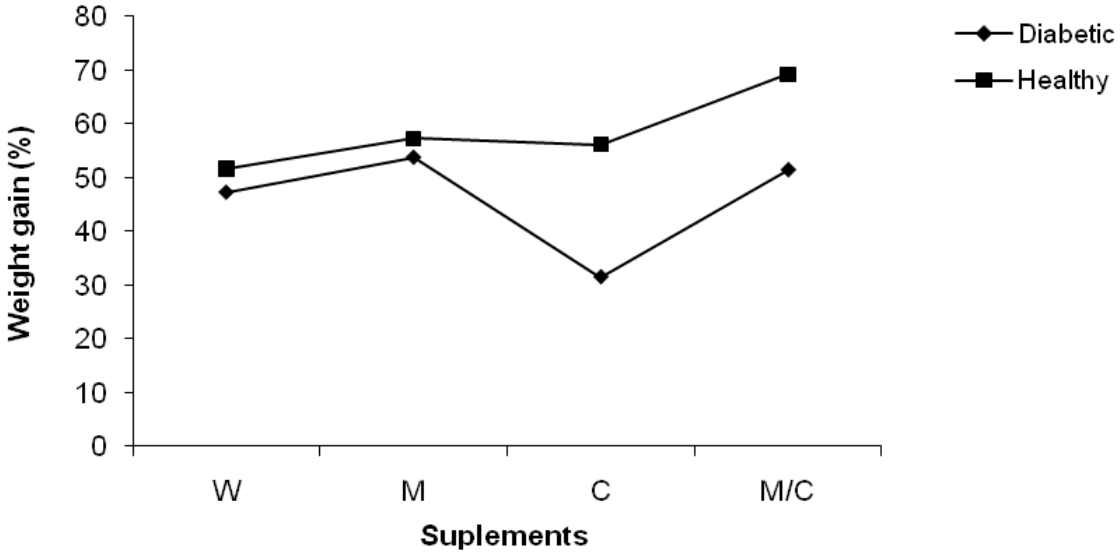

Figure 5. Weight gain ([final weight – initial weight]*100/initial weight) of diabetic and healthy rats supplemented with water (W), mesocarpium (M), cladode (C) or mix of mesocarpium and cladode (M/C) of *O. joconostle.* Each point represents the mean ± SEM of six rats.

organism and transport it to the liver, where these are metabolized into bile salts (Kiss et al., 2006).

At baseline, all experimental specimens displayed a similar weight (250 to 300 g). At the end, water-supplemented diabetic and healthy rats displayed a statistically similar 50% gain in body weight. The smallest gain in body weight (31.50%) corresponded to cladode-supplemented diabetic rats. Additionally, diabetic rats supplemented with either mesocarpium or the mixture displayed a relative gain in body weight that was statistically similar to that observed in water-supplemented rats, which in turn was similar to the one recorded in healthy rats; the exception was rats supplemented with the mesocarpium-cladode mixture, which displayed the greatest relative gain in body weight (69.3%; $p < 0.01$) (Figure 5).

The smaller relative gain in body weight in diabetic rats supplemented with cladode, even along with insulin administration, matches the overall trend that appears in diabetic patients over time, who tend to lose weight when

the treatment administered is not totally adequate. This agrees with the higher glucose concentrations in rats that received this treatment. The fact that supplementation with both fruit and the fruit-cladode mixture in diabetic rats had resulted in a weight gain similar to healthy rats further evidences their glucose-lowering effect.

The precise mechanism underlying the glucose-specific effect of the xoconostle mesocarpium remains unknown, but it has been hypothesized that glucose-lowering agents: (1) increase insulin release by stimulating pancreatic β cells; (2) increase the resistance to hormones involved in rising blood glucose levels (Marles and Farnsworth,1995; Volpato et al., 2002); (3) increase the number and sensitivity of insulin receptors (Li et al., 2003); (4) reduce the loss of glycogen by stimulating glucose intake in tissues and organs (Said et al., 2002); (5) increase the elimination of free radicals, thus favoring resistance to lipid peroxidation (Budinsky et al., 2001); and (6) correct the metabolic impairment related to lipids and proteins, and stimulate microcirculation of blood in the organism (Huo et al., 2003).

Our findings, together with the consumption of the *O. joconostle* fruit in some sectors of the Mexican population and their traditional use to treat DM2, warrant the conduct of clinical trials in humans to determine the detailed mechanism that leads to the glucose-lowering effect and potential as an adjuvant for treating DM2. In parallel, the identification of the specific chemicals that account for the glucose-lowering action of the *O. joconostle* fruit is an aspect that deserves further investigation.

Conclusions

The oral administration of mesocarpium, cladode or a mixture of these two components of *O. joconostle* resulted in a lowering of plasma glucose and triglycerid levels in rats; the mesocarpium led to the greatest reduction of glycemia and lipidemia. Since DM2 is a degenerative chronic disorder that requires long-term therapy, our findings suggest that the continuous adjuvant treatment with *O. joconostle* mesocarpium and cladode supplements may contribute to prevent and control the complications of DM2 in humans. However, further pharmacological and chemical research is required to characterize the active chemical(s) participating in this effect and understand the mechanism of action.

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