Colegio de Postgraduados

Effects of juice of ten variants of prickly pear (*Opuntia* spp.) on the energy metabolism of Wistar rats with induced diabetes

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ABSTRACT
The effects of juice of 10 variants of prickly pear fruit on blood sugar level and related metabolic parameters were evaluated on glycostatic (GS) and hyperglycemic (HG) Wistar rats. The selection of variants was based on their abundance and the economic potential of their fruit in the state of San Luis Potosi, their humanization degree, and fruit colors. The experimental design used was completely randomized with an 11×2 factorial arrangement, where factor A was the juice of the pear variant (10 variants and water for control), and factor B was the health condition of the rats (GS and HG). In most of the treatments there was an increase in weight, except for GS animals which received juice from Tapón rojo variant. HG rats which received water showed higher plasma levels of glucose ($p<0.05$) than those which received juice from the variant Sangre de toro, as well as all GS rats. Although both wild and cultivated prickly pears are seasonal fruits, they have a wide variety of colors and contain different compounds that, after regular consumption, benefit glucose and lipid metabolism. Prickly pear juices significantly modified the concentration of glucose in the blood of Wistar HG and GS rats.

Keywords: *Opuntia* spp., glucosa, diabetes, Wistar rats.

INTRODUCTION

The epidemic of diabetes mellitus (DM) is recognized as a global threat by the World Health Organization (WHO). It is estimated that worldwide 180 million people suffer from diabetes, and that this figure will be more than double by 2030 (Shaw *et al.*, 2010; WHO, 2018; IDF, 2023). In 2005, 1.1 million deaths were recorded due to diabetes, of which around 80% occurred in low-to-medium income nations, the majority of which are less prepared to face this epidemic (NOM-015, 2010). In Mexico, DM takes first place in

the number of deaths per year; mortality rates in both men and women show an increasing tendency, with more than 70,000 deaths and 400,000 new cases every year (WHO, 2014; NOM-015, 2010; INEGI 2019; SSA, 2019).

DM type 2 (DM2) corresponds to what used to be known as DM non-insulin-requiring diabetes or adult DM, but currently it is occurring in young people too. Its importance lies in the multiple disorders it produces because of the relationship between insulin secretion and the sensitivity of the receptors to this hormone's action in the complicated glucose homeostasis (ElSayed *et al.*, 2023). This metabolic disease modifies the cellular transmission signals, partially blocks the action of the surface receptors and the expression of specific genes, it diminishes adenine dinucleotide phosphate (NADPH) and the levels of glutathione, which increases oxidative stress (Calabrese *et al.*, 2012). Other important effects related with DM are: auto-oxidation of glucose and cholesterol associated with low density lipoprotein (cLDL), the increase of myeloperoxidase activated by protein kinase C, and the increase in free radicals (Mansoor *et al.*, 2022).

In view of the complexity of this condition, the Mexican Secretariat of Health, in its Effective Medical Practice Bulletin, proposes a plan to treat DM2, in which it suggests identifying the etiology, delimiting risk factors, establishing criteria for its diagnosis, and carrying out clinical evaluations to establish pharmacological treatment and develop an coadjuvant nutrition plan that includes foods rich in antioxidants, low in sugar and with considerable concentrations of soluble fiber (Mao *et al.*, 2021). The consumption of soluble fiber improves glucose control, reduces hyperinsulinemia, as well as plasmatic concentrations of lipids in individuals with DM2 (Li *et al.*, 2020). Soluble dietary fiber has the capacity of absorbing water and forming gels, producing a laxative effect, reducing carbohydrate absorption, and generating a satiety sensation (Silveira, 2003; Chawla and Patil, 2010).

The fruit of the prickly pear (*Opuntia* spp.) in addition to containing a considerable amount of soluble fiber (mucilage and pectin), has compounds of biological, technological and commercial interest such as simple sugars, antioxidants like betalains, phenolic compounds, flavonoids as well as important amounts of vitamin C (Zenteno *et al.*, 2015). All of these compounds are appreciated as very favorable in terms of a healthy diet and also as ingredients for the design of new functional foodstuffs (Sáenz *et al.*, 2007). Several investigations have credited the hypoglycemic effect of the *Opuntia* spp. cladode in animals with streptozotocin induced diabetes, or in patients with DM2 (Andrade and Wiedenfeld, 2011; Madrigal *et al.*, 2022; García *et al.*, 2024). In addition to the cladodes, the diversity of the nopal fruits can be used to take advantage of and encourage the consumption of both commercial varieties and other less known varieties but with biological and commercial potential (Reyes *et al.*, 2009, 2011). Furthermore, the prickly pear fruit has lately drawn attention because the fructose it contains can be an alternative way to provide energy to cells incapable of receiving glucose, thus avoiding the activation of other metabolic actions which cause complications, especially in diabetic patients (Kaur *et al.*, 2012; Gouws *et al.*, 2019; Sabtain *et al.*, 2021).

Thus, the objective of this study was the evaluation of the effect of consuming juice from 10 different variants of prickly pear fruit on body weight and blood glucose levels on

Wistar rats with normal levels of glucose or with streptozotocin induced hyperglycemia, as part of the evaluation of prickly pear juice as a functional foodstuff. Due to on our previous results on the nutritional content of a wide diversity of wild and cultivated prickly pears, we hypothesize that after regular consumption, metabolic health benefits will be obtained in an optimal and diabetic state.

MATERIALS AND METHODS

Selection of variants and juice extraction

According to Reyes *et al.*, (2009), the selection of all these variants was based on three criteria: (a) abundance and economic potential of the fruit in the state of San Luis Potosi, (b) degree of humanization (cultivated and wild), and (c) diversity of colors of the prickly pear fruit.

The prickly pear fruit of the 10 different variants were picked at full ripeness; six of these are cultivated: Rojo Pelón (*Opuntia ficus-indica*), Blanca (*O. albicarpa*), Amarilla Monteza, Pico Chulo, Torreoja and Sangre de Toro (*O. megacantha*), and four are wild: Cardona (*O. streptacantha*), Charola (*O. streptacantha* ssp. *aguirrana*), Tapona and Tapón Rojo (*O. robusta*). The fruit were picked or harvested in the municipality of Villa de Arriaga, located in the high plain of the state of San Luis Potosi, Mexico (21° 55″00‴N; 101° 22″59‴O). Peel and glochids (slender, hair-like thorns) were removed from the fruit; the juice of the flesh was extracted with a stainless-steel blender (International LI-12-106, Mexico); the seeds were separated with a conventional 8 mesh filter. The filtered juice was stored in sterile containers at −20 °C until it was used.

Animal model

Male Wistar rats (263±38.6 g) provided by the Bioscience Center of the Faculty of Agronomy, UASLP, were used as the experimental units. Each animal was kept in individual polypropylene cages in a conditioned room in the Instituto de Investigación de Zonas Desérticas, with continuous ventilation, controlled temperature and relative humidity conditions and with a circadian cycle inverted to 12 h light/12 h dark. The study was conducted following the animal care guidelines specified in accordance with the corresponding institutional and local ethical regulations and recommendations for care and maintenance and with an approved institutional bioethical protocol (NOM-051, 1995; NOM 062, 1999).

The animals were subjected to a seven day adaptation period with standard rodent feed (Lab Diet® Rodent Chow 5001, USA) and *ad libitum* water. Subsequently, they were randomly distributed into two different health conditions: normal levels of glucose (GS) and hyperglycemic streptozotocin-induced (HG). The experimental period was 12 weeks, during which body weight change of the animals were recorded.

Preliminary trial to estimate the dosage of the prickly pear juice

In order to establish the dosage of prickly pear juice for each variant that would be administered to the experimental units, a preliminary trial was conducted with normal rats. According to our previous studies (Zenteno *et al.*, 2015; 2018) and based on the amount of total sugars in the juice of each prickly pear variant, the variants with the most and the least sugar concentration were selected (Tapón Rojo with 15.13% and Tapón with 10.91%). The two juices of these prickly pears, and two beverages of reference (commercial brand cranberry juice and water) were evaluated, in doses equivalent to 150, 300 and 450 mL intended for a healthy person of 65 kg of body weight, but adjusted to the weight of the each rat, were administered through esophageal cannula in order to generate glucose tolerance curves. For this purpose, blood glucose levels were measured with glucometer (Accu-Check® Performa, USA) at 0, 30, 60 and 120 min after the administration of the corresponding beverages (n=3 per group).

Based on the glucose tolerance curves, the dose of 300 mL was selected, since after 60 min, the blood glucose of the rats that received prickly pear juice was similar to that of rats that were administered only water or commercial brand juice; in this way metabolic alterations in the rats were avoided. Once the dosage was selected, the volume of prickly pear juice was calculated for each animal, considering the percentage of total sugars in the juice of each variant, the weight of the animal, and the total sugars in the recommended portion of the commercial brand cranberry juice. In this way, altering the normal blood sugar levels of healthy rats was avoided, since simple sugars immediately impact the levels of blood glucose.

The feed and thawed and homogenized prickly pear juices were administered every day at the beginning of the dark period.

Induction of hyperglycemia

Sixty six rats with normal levels of glucose (GS) were considered as healthy rats. In week one of the experimental period and after an 8 h fasting, 66 experimental units were administered on a single occasion and intraperitoneally 50 mg streptozotocin (Sigma Aldrich® SO130, USA) per kg body weight dissolved in sodium citrate buffer (0.1 M, pH 4.5). Six experimental units of treatment (water) were administered by the same route only with citrate buffer. After one week of streptozotocin induction and with 8 h of fasting, the hyperglycemia status was assessed by caudal vein puncture of the animals and measurement with glucometer (Accu-Check® Performa, USA) and they were considered as experimental units with DM2 when presented fasting glucose levels >200-450 mg/dL. In order to maintain the hyperglycemic state of these rats, similar to the state of a patient with DM2 without therapeutic control (200-300 mg/dL), the rats received an individual dosage of insulin (1-4 U) of insulin (Lantus®, Sanofi, France) every 12 h by subcutaneous administration during all the experimental period.

Biochemical evaluation

At the end of the experimental period for slaughter, the animals were fasted for 8 hr, weighed and given an individualized overdose of sodium pentobarbital (Sedalpharma® Pet's Pharma, Mexico) intraperitoneally according to established ethical protocols (NOM-033, 2014).

Intracardiac whole blood was obtained from all experimental units for serum collection by resting (10 min) and centrifugation at 2500 rpm/10 min (Solbat J-40, Mexico) for biochemical analyses of glucose with commercial enzyme kits (Bayer, Sées, France) and semiautomated chemistry analyzer (Excel™, Stanbio, USA).

Experimental design and statistical analysis

The experiment was conducted according to a completely randomized experimental design with an 11×2 factorial arrangement of treatments (n=6) where each animal was considered as an experimental unit. The factor A was the juice of the cactus pear variant (10 variants and water), and factor B was the health condition of the rats (glycostatic and hyperglycemic). The data obtained from the evaluated variables were tested for normality using the Shapiro-Wilk test ($p>0.43$), which indicated that the information was normal, allowing a variance analysis to be carried out for a design completely randomized, using the PROC GLM of the SAS program version 9.2 (SAS Institute, Inc., Cary, North Carolina, USA), when ANOVA indicated differences between treatments, it was applied a Tukey multiple means test, setting a significance level of $p<0.05$.

RESULTS AND DISCUSSION

The effect of prickly pear juice on the body weight of glycostatic rats (GS) (Figure 1) and hyperglycemic rats (HG) ($F=2.82$, $P=0.0054$) (Figure 2) are shown. In the majority of treatments there was an increase in weight, except in GS animals which received juice of variant Tapón Rojo and HG animals which received juice from variants Rojo Pelón, Charola and Blanca, which actually lost weight; although, there was only significant difference in the final weight between HG rats which received juice from Pico Chulo variant, in GS and HG rats with Sangre de Toro juice, and in HG rats with juices from Charola and Blanca variants. It is important to note that, out of the 10 evaluated variants, the juice from variant Pico Chulo had the highest content of ascorbic acid and total phenolic compounds, and this was the only juice registering the presence of protocatechuic acid (Zenteno *et al.*, 2015). It has been demonstrated that this phenolic acid reduces oxidative stress by inhibiting the

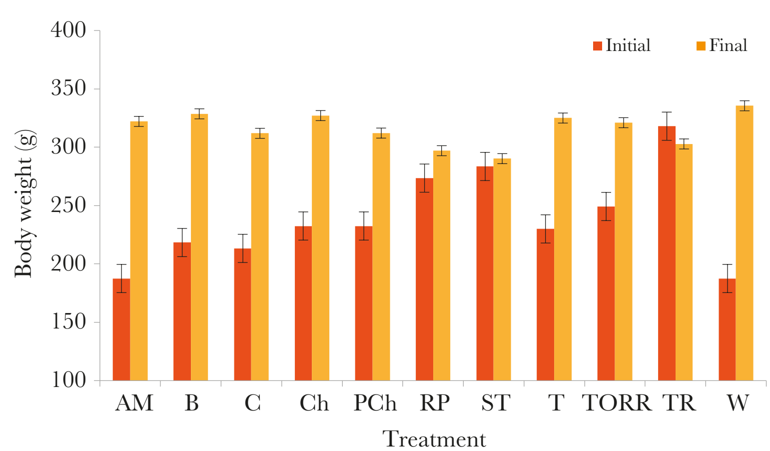

Figure 1. Initial and final weight of glucostatic rats supplemented with juice of 10 variants of prickly pear (*Opuntia* spp.). (Means ± standard error). AM: Amarilla Monteza, B: Blanca, C: Cardona, Ch: Charola, Pch: Pico Chulo, RP: Rojo Pelón, ST: Sangre de Toro, T: Tapona, TO: Torreoja, TR: Tapón Rojo, W: water.

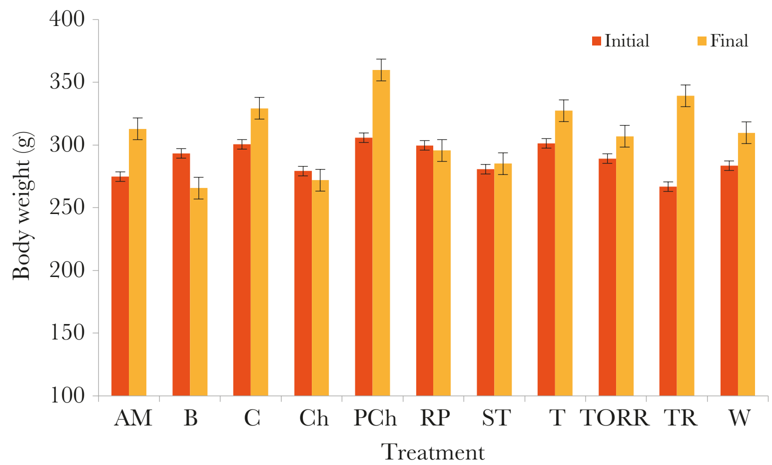

Figure 2. Initial and final weight of hyperglycemic rats supplemented with juice of 10 variants of prickly pear (*Opuntia* spp.). (Means ± standard error). AM: Amarilla Monteza, B: Blanca, C: Cardona, Ch: Charola, Pch: Pico Chulo, RP: Rojo Pelón, ST: Sangre de Toro, T: Tapona, TO: Torreoja, TR: Tapón Rojo, W: water.

enzymatic NADPH oxidase system, a multiproteic complex that generates free radicals, especially superoxide radical (de Faria *et al.*, 2012).

In general, glycostatic rats that received prickly pear juice had a lower body weight, which coincides with Trejo *et al.*, (1996), Fernandes *et al.*, (2009) and Fatma and Hassan (2011), who administered prickly pear juice from *O. fuliginosa* and from *O. ficus-indica* to healthy rats and observed a lesser weight gain than in diabetic rats.

The increase of plasmatic levels of glucose is the best metabolic indicator of DM2 (NOM-015, 2010). HG rats that received water showed higher plasmatic levels of glucose than HG rats that received juice from variant Sangre de Toro and all GS rats (Table 1); nonetheless, in HG rats receiving juices from variants Blanca, Charola, Rojo Pelón, and Tapona ($P \geq 0.05$), plasmatic glucose values can be observed within the normal amplitude for Wistar rats, that is, from 98 to 152 mg/dL (Bolani, 1990).

The concentration of plasmatic glucose in GS rats receiving the juices is within the normal amplitude of reference. It is important to note that HG rats receiving the juice of variant Sangre de Toro showed concentrations of plasmatic glucose similar ($P \geq 0.05$) to those of GS rats receiving juice of the same variant. This may be due to the fact that such variant showed lower quantities of sugar and higher content of total phenol compounds, which reduce the absorption of carbohydrates and regulate the enzymes involved in the metabolism of glucose (Chun *et al.*, 2007; Ovaskainen *et al.*, 2008), and an important amount of soluble fiber, which reduces hyperglycemia, cardiovascular risks, body weight and improves sensibility of insulin receivers (Weickert *et al.*, 2006; Qi *et al.*, 2006). In spite of its moderate content of flavan 3-oles, the Sangre de Toro juices show the highest amount of procyanidine b, which inhibits the biosynthesis of lipids (Vidal *et al.*, 2005), reduces the biosynthesis and secretion of apolipoproteins, and prevents the esterification of cholesterol and the production of lipoproteins (Sugiyama *et al.*, 2007); additionally, the juices of Sangre de Toro contain intermediate quantities of betalains and ascorbic acid, and showed good antioxidant capacity (Zenteno *et al.*, 2015). In general, polyphenols have favorable

Table 1. Effect of prickly pear juice on the concentration of metabolic blood indicators (mg/dL) in hyperglycemic (HG) and glucostatic (GS) Wistar rats at the end of the experimental period.

Variant	Glucose		Cholesterol		Triglycerides	
	GS	HG	GS	HG	GS	HG
Rojo Pelón	140.5±20.1[b]	151.1±67.0[ab]	88.4±7.2[abcd]	112.0±7.2[a]	95.1±8.4[abc]	57.8±10.7[c]
Blanca	114.4±9.6[b]	158.6±90.0[ab]	104.2±8.8[ab]	54.8±7.2[cdef]	156.5±14.8[abc]	178.8±77.3[abc]
Amarilla Monteza	141.4±11.7[b]	211.5±121.9[ab]	81.7±8.8[abcde]	50.4±7.2[def]	83.5±8.5[bc]	191.1±62.0[abc]
Pico Chulo	105.0±10.1[b]	174.9±55.4[ab]	55.9±8.8[cdef]	56.5±7.2[cdef]	60.6±7.6[c]	201.1±99.6[abc]
Torreoja	116.6±10.9[b]	231.5±94.6[ab]	58.2±8.8[cdef]	92.5±7.2[abc]	75.4±26.1[bc]	79.2±29.4[bc]
Sangre de Toro	124.2±3.8[b]	127.0±42.8[b]	68.8±8.8[bcdef]	59.8±7.2[cdef]	81.0±25.7[bc]	66.8±11.0[c]
Cardona	103.5±9.9[b]	168.3±78.3[ab]	43.2±7.9[ef]	68.1±7.2[bcdef]	53.8±23.8[c]	242.8±204.0[a]
Charola	97.1±13.0[b]	155.8±75.1[ab]	75.2±7.2[abcde]	33.5±8.8[f]	67.4±8.7[c]	228.0±110.2[ab]
Tapona	115.3±6.9[b]	145.3±47.6[ab]	63.0±8.8[bcdef]	60.5±7.2[cdef]	97.2±39.1[abc]	74.3±39.9[bc]
Tapón Rojo	121.3±8.0[b]	222.7±67.8[ab]	75.8±8.8[abcde]	90.3±7.2[abcd]	108.4±24.3[abc]	94.7±44.7[abc]
Water	125.6±6.6[b]	292.9±194.7[a]	64.4±7.9[bcdef]	49.8±7.2[def]	110.3±19.5[abc]	186.6±39.2[abc]
F	4.62	13.53	2.88	4.11	12.71	3.64
p-value	≤0.001	≤0.001	0.0042	0.0002	≤0.001	0.0006

Means ± standard error. Means with different literals are statistically different (P≥0.05).

effects on the cardiovascular system of diabetic individuals, which is probably due to their metabolic regulation of lipids and apolipoproteins (Vidal *et al.*, 2005), and their stimulation of insulin secretion (Bahadoran *et al.*, 2013).

CONCLUSIONS

With the consumption of prickly pear juice of various variants, regardless of their color or whether they were wild or cultivated, a maintenance of body weight gain and diminish the concentration of glucose in healthy rats, oscillating in optimal and adequate ranges for healthy rats, in addition to a considerable benefit on the glycemic of rats with induced diabetes. Therefore, more biochemical and genetic studies are needed to understand the specific mechanisms of action by which prickly pear juice exerts its beneficial actions in the body.

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Declaration of competing interest

The authors declare no actual or potential conflict of interest, including financial, personal or relationship with other organizations.

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