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Comparison of the Effects of Neem Extracts (*Azadirachta indica*) and the May Pitaya Flower (*Stenocereus* spp.) on Some Blood Parameters of Diabetic Rats Induced with Streptozotocin

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Abstract

Objective: The objective of this study is to evaluate the effects of Neem extract (*Azadirachta indica*) and pitaya flower extract (*Stenocereus* spp.) in rats with diabetes. **Materials and Methods:** 72 male Wistar rats weighing 150 ± 170 g were used, distributed into four groups (n = 18). 54 rats were induced with type 2 diabetes with intraperitoneal streptozotocin, experimental groups treated with neem, pitaya and streptozotocin were formed, and the remaining intact animals formed the control group. Subsequently, on days 0, 15 and 30, blood samples were obtained and levels of glucose, insulin, total protein, urea, urea nitrogen (BUN), creatinine, cholesterol and triglycerides were quantified. **Results:** In the pitaya and neem groups, there were significant differences in urea and blood urea nitrogen (BUN). In the neem and streptozotocin groups, cholesterol, triglycerides, creatinine, and protein levels remained at normal levels; only the streptozotocin group showed any changes in serum cholesterol. **Conclusions:** The hypoglycemic, detoxifying, and metabolic-regulating effects of both extracts were demonstrated, with health benefits by regulating body homeostasis. Animals in the untreated streptozotocin group showed signs of the disease such as weight loss, polyuria, polydipsia, and hyperphagia.

Keywords

Diabetes, Neem, *Azadirachta indica*, Pitaya (*Stenocereus* spp.), Streptozotocin

1. Introduction

The International Diabetes Federation mentions that in 2019 there were 463 million people with this disease, and that by 2030, 578 million patients may be reached worldwide [1] [2], while the Pan American Health Organization highlights that of these in Latin America there are 34.8 million (IDF 2019) and in Mexico there are more than 17.6 million patients, mainly people over 18 years of age [3].

From the epidemiological point of view, diabetes is the main cause of the effect on some of the blood parameters (cholesterol, triglycerides, urea, creatinine, glucose, insulin and total proteins) in both humans and animals, this makes traditional treatments more difficult to obtain, in addition to the serious side effects they cause, it unconsciously forces us to resort to different alternative substances or medicinal plants with hypoglycemic effects [4].

1.1. Neem as a Medicinal Plant

There are several studies that show that neem is a plant that has various applications in agronomy and veterinary medicine and human health [5], therapeutic properties are attributed to it in diseases such as arthritis, typhoid fever, respiratory problems, cancer, syphilis [6] antimicrobial, antiparasitic [5], and other chronic degenerative diseases such as diabetes [7] due to the more than 140 active ingredients distributed throughout all parts of the plant [8] among which are the neem metabolites (*nimbidiol*, *gedunin*, *and azadiradione*) have a hypoglycemic effect [9] [10].

The hypoglycemic effect of neem has been compared with the effects caused by spirulina on blood glucose levels and its relationship with body weight in diabetic mice induced with alloxan for periods of 7, 14, 21, 28 and 35 days. In this study, the results show that the administration of neem extract at a dose of 20 mg significantly reduced blood glucose levels in mice both alone and in combination with spirulina at a dose of 10 mg/kg. Although the mechanism of action of the extracts is not known, it is suggested that it may be due to the stimulation of insulin production or the ability to regenerate cells [6] [11].

Another study conducted in 2011, analyzed the hypoglycemic effect of *Azadirachta indica* (Neem) in sinergia with *Phyllanthus niruri* on blood glucose levels in male Wistar rats in which both extracts and a combination of the two were used separately, in this study glucose was measured before and after treatment and the results show that both the neem extract and the *Phyllanthus niruri* and in synergy they showed a hypoglycemic effect, but with a better hypoglycemic effect the ani-

mals treated with the neem leaf extract [12] [13].

1.2. Pitaya Used as a Fruit and as Alternative Medicine

In Mexico there are different varieties of pitaya according to the region where they are grown, the fruit used in this study comes from a cactus called (*Stenocereus* spp.) or pitaya de mayo which due to its morphological characteristics is endemic to the entire country, with the state of Jalisco being the largest producer, using the fruit as food, the stems as fodder, and the flower asornaments and as a medicine for the control of various diseases due to its high content of betalains, phenolic compounds, vitamins, minerals and fiber [14] [15].

The pitahaya and the pitaya are fruits that have the same component called betanin or betalain that gives them that characteristic color and chemically they are water-soluble nitrogen compounds that are synthesized from the amino acid tyrosine and are divided into betacyanins and betaxanthins when combining betalamic acid or with other amino compounds and present different contractions of these compounds in the pulp, peel and flower [16] [17].

The pitaya comes from the genus (*Stenocereus* spp.) while the pitahaya or dragon fruit is of the genus (*Hylocereus monacanthus*) in a study, betalains were encapsulated and administered at doses of 10, 20 and 40 mg/kg, for 28 days to diabetic rats using the streptozotocin induction model, and the results were excellent since it reduced blood hyperglycemia but also had a protective effect on the liver, kidney and pancreas since they showed less tissue damage [18] [19].

2. Materials and Methods

In this work we focused on verifying if neem and pitaya flower truly had the beneficial effects on human health that the community of our region claim to have and have been using them for many years to control hyperglycemia, cholesterol and triglycerides mainly and then with solid bases carry out another experimental project we will compare these effects against the most common medications used to control hyperglycemia such as metformin and glibenclamide, where we will include histological analysis of the pancreas and some other parameters.

A total of 72 male Wistar rats weighing 150 to 170 grams were housed in a bioterium under 12-hour light cycles and fed Purina® Nutricubes rodent food and water ad libitum. Animal management was in accordance with NOM-062-ZOO-1999 and the guide for the care and use of laboratory animals (Public Law 99-158-NIH.1985). All animals were housed in cages with three animals each during treatment; food and water consumption was recorded daily.

In order to evaluate the effects of organic extracts on several blood parameters in rats, such as glucose, insulin, cholesterol, triglycerides, creatinine, urea and total proteins that cause several diseases in humans, taking into account the time of effect of streptozotocin, the study was scheduled for 30 days divided into three stages per day (0, 15, 30 days post diabetic induction) and sacrifice 6 animals from each group in each of these and obtain blood samples.

A blood sample was taken from the 72 rats to determine the basal blood levels, then the intact control group was formed with n = 18 animals and the remaining 54 rats were they formed the experimental groups of neem pitaya and streptozotocin and then, through a single dose of 65 mg/kg of weight of streptozotocin diluted in a citrate buffer solution with pH 4.5 intraperitoneally, they induced diabetes mellitus, verifying it by taking another blood sample 24 hours post induction, the next day, that is, two days after the induction, the project was started, marking day 0 in the graphs [20].

Subsequently, the diabetic rats were divided into three experimental groups (n = 18), one neem group that received a dosage of 250 mg/kg of weight of the extract orally daily [21], another group that was administered the pitaya flower extract at a daily oral dose of 4 mg/kg of weight of the extract [18] and the last group was formed with the remaining diabetic animals but that did not receive any treatment in order to determine and evaluate the effects of the disease and to be able to compare them with the animals that received the treatments of both extracts.

2.1. Preparation of Aqueous Extract of Neem

Neem tree leaves were collected, washed, dried under shade conditions for 7 days, then one kg of leaves were weighed, crushed to obtain a fine powder, 250 grams of this powder were weighed on an analytical balance, moistened with 70% ethanol, then, by evaporation, the neem extract was obtained, 250 mg fractions were weighed and diluted in 1 mL of 0.9% saline solution [21].

2.2. Preparation of the Aqueous Extract of Pitaya Flower

Se heated upone liter of water in a beaker on a Cimarec 3 (Thermolyne) brand thermal plate until boiling point, at the same time 200 grams of pitaya flower were weighed and placed in the beaker, it was removed from the plate until it cooled, the pitaya flower was removed leaving a pink liquid which was taken to lyophilization where for every 250 mL of solution one gram of powder was obtained, 400 mg of lyophilized pitaya were weighed and diluted in 100 mL of distilled water to obtain 4 mg/mL.

2.3. Determination of Blood Chemistry

At the end of each stage, six animals from each group were sacrificed with an intraperitoneal overdose of 65 mg/kg sodium pentobarbital. Blood samples were collected intracardially and stored in serum separator tubes. The blood samples were then centrifuged at 10,000 rpm for 5 minutes, immediately separating the serum.

Once the serum was separated, the serum samples were processed by spectrophotometry to determine glucose, cholesterol, triglycerides, total proteins, urea, urea nitrogen (BUN) and creatinine following the instructions of the SPINREACT® laboratory.

3. ELISA Analysis

An ELISA assay was used to quantify serum insulin concentrations in the different groups. The kit used was from the Abcam laboratory (ab100578-Insulin Human ELISA kit) and was processed according to the manufacturer's instructions. Samples were analyzed in duplicate, and the average concentration was calculated. The sensitivity limit was set at <4 μIU/mL. Color was detected immediately after adding the "STOP" solution, and absorbances were read using a microplate reader (POWEAM model WhyM201) at 450 nm.

4. Statistical Analysis

Data analysis was performed using Sigmastat software version 3.1. Data are presented as means ± SD. Differences were examined using one-way analysis of variance (ANOVA) because the effect of treatments was analyzed during the experiment, followed by Tukey's post hoc test. Statistical significance was accepted with a $p < 0.05$. NREACT®.

5. Results

The determination of some blood parameters are a reflection of the physiological balance of the animals, which may depend on the presence or absence of chronic degenerative diseases as can be seen in the results obtained in animals with diabetes mellitus, Figure 1 shows the glucose concentrations where it is observed that on day 0 the different groups present very similar values between them, while on days 15 and 30 of treatment an increase in glucose levels is shown in the Neem, Pitaya and Streptozotocin groups compared to the control group ($p < 0.001$).

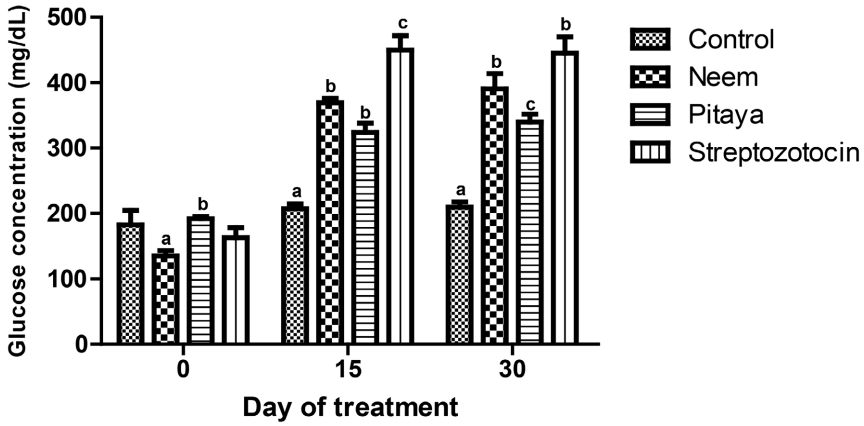

Figure 1. Glucose concentration (mg/dL) by group. Different literals show a significant difference ($p < 0.001$).

Figure 2 shows the insulin concentration and in the same way the levels are similar to day 0 in all groups, while for days 15 and 30 of treatment an increase is observed in the Neem and Pitaya groups compared to the control group, in addition the streptozotocin group showed very high insulin levels ($p < 0.001$).

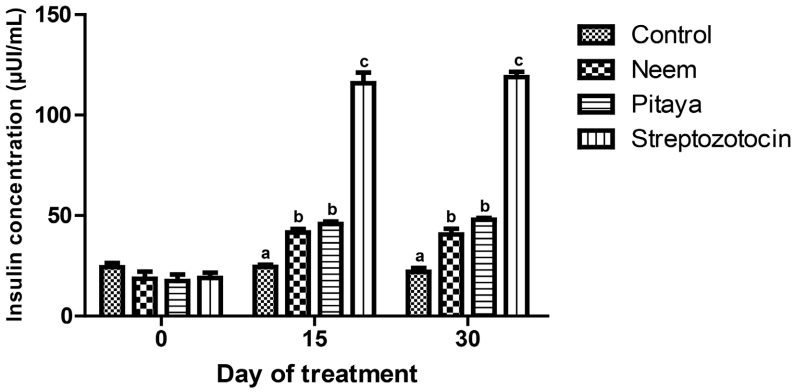

Figure 2. Insulin concentration in µIU/mL. Different literals show a significant difference ($p < 0.001$).

Figure 3 and **Figure 4** show the urea levels and blood urea nitrogen levels correspondingly. In both figures at day 0 the Pitaya and Streptozotocin groups present low urea levels compared to the Control and Neem groups, while on days 15 and 30 the Neem group maintains high urea levels compared to the other groups ($p < 0.001$).

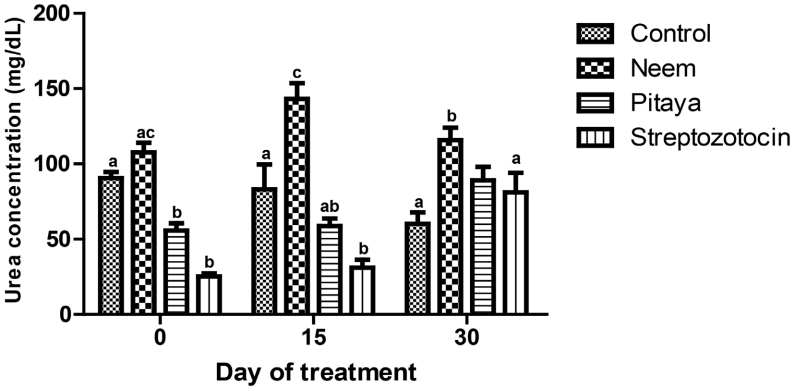

Figure 3. Urea concentration (mg/dL). Different literals show a significant difference ($p < 0.001$).

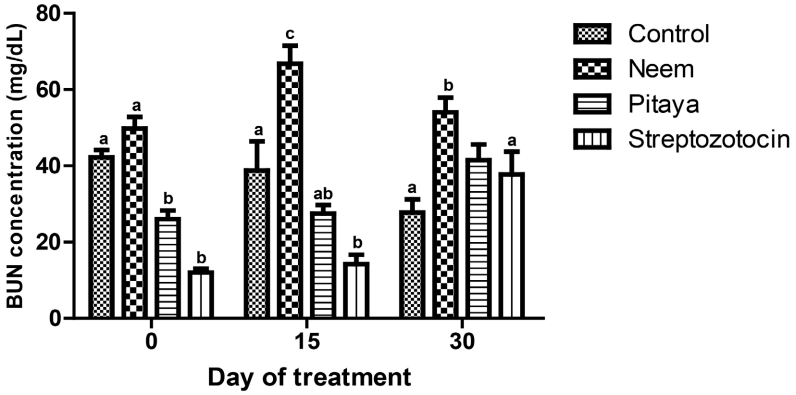

Figure 4. BUN concentration (mg/dL). Different literals show a significant difference ($p < 0.001$).

Figure 5 shows that the Streptozotocin group has high levels on day 30 of treatment compared to the other groups ($p < 0.001$).

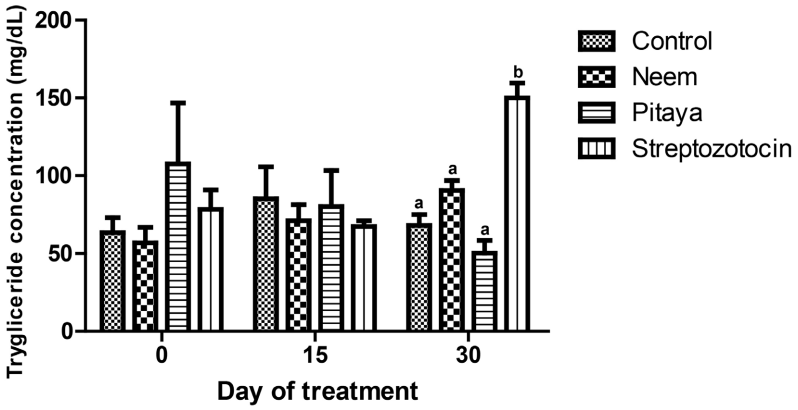

Figure 5. Triglyceride concentration (mg/dL). Different literals show a significant difference ($p < 0.01$).

Figures 6-8 show cholesterol, total protein, and creatinine concentrations, respectively, and show no differences in blood levels at different stages of treatment.

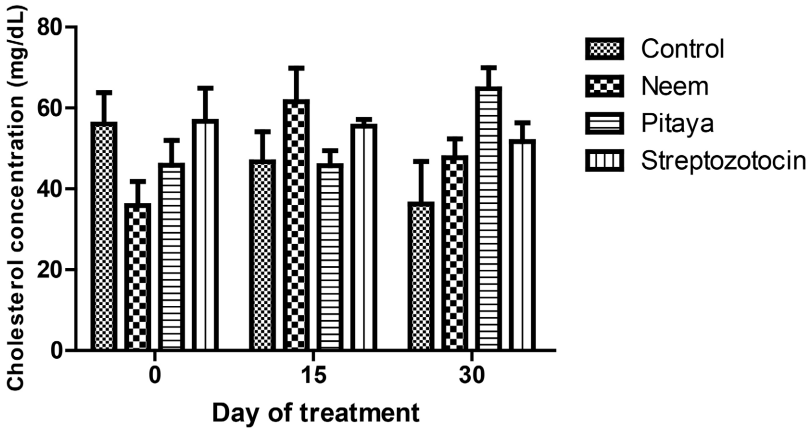

Figure 6. Cholesterol concentration (mg/dL). There was no significant difference ($p < 0.05$).

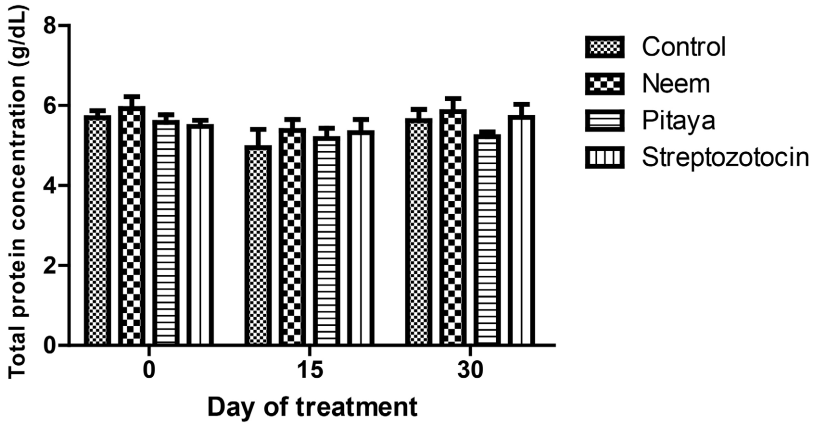

Figure 7. Total protein concentration (g/dL). There is no significant difference ($p < 0.05$).

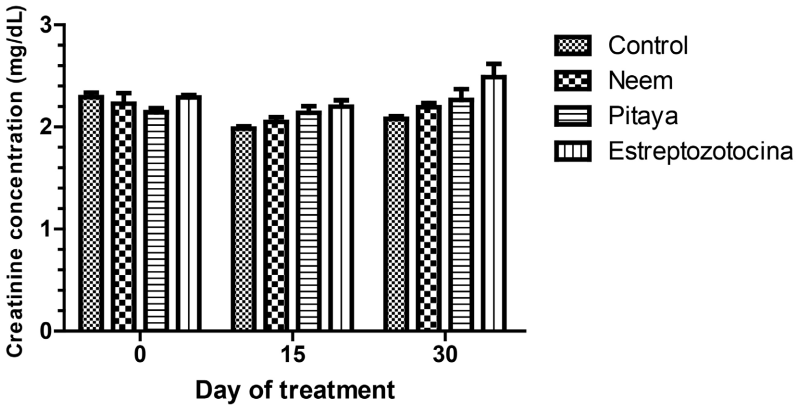

Figure 8. Creatinine concentration (mg/dL). Different literals show a significant difference ($p < 0.001$).

6. Discussion

The parameters of some components of the blood determine the health status and the function of some organs and systems in animals [22], it is known that there are chronic degenerative diseases such as diabetes that gradually deteriorate the health status of the body in general and taking into account that despite having intentionally caused diabetes mellitus to experimental animals the results show that while some parameters suffered alterations in their concentrations during the experiment such as glucose, insulin, urea, urea nitrogen and creatinine, others despite presenting changes in their blood concentrations of total proteins, cholesterol and triglycerides did not show symptoms of any disease but on the contrary the extracts of neem and pitaya helped in the control of them as had already been reported in other studies [5].

The extracts of pitaya and neem flowers definitely showed effects on glucose and insulin concentrations, these parameters go hand in hand because blood glucose levels depend on the effects of insulin, on day 0 they show no changes in glucose and insulin concentrations in the four groups due to the effect of streptozotocin that destroys the insulin receptor glut-2, which causes low concentrations of proinsulin, insulin precursor [23], while insulin also increased on days 15 and 30 respectively to try to decrease blood glucose concentrations [24].

In the concentration of total proteins in blood, there are no alterations in liver function due to the effect of diabetes in experimental animals with reference to the control group and it is reported that both extracts have a liver detoxifying function [4], although it is important to mention that the values obtained are below those reported by [24] [25].

Urea, creatinine and urea nitrogen are parameters that determine kidney function, the values found in this study are within normal values urea 0.4 - 100.39, creatinine 0.25 - 0.79 and urea nitrogen 0.2 - 44.99 for both the control group and those treated for day 0 of the experiment showing statistical differences between days 15 and 30 in the treated groups with a marked decrease in their concentrations without affecting kidney function despite the diabetes induction process to

which they were subjected [25] [26].

The concentration of cholesterol and triglycerides in the blood remained within normal values compared to those reported in previous studies in 2010, where they mention that the components of neem and pitaya help the metabolism by breaking down fat and decongesting the liver [4] [5] [13].

7. Conclusions

The results showed that the metabolites present in the pitaya flower (betanin or betalain) and neem (nimbidiol, gedunin and azadiradione) have hypoglycemic effects since they helped regulate blood glucose and insulin levels in the treated groups.

The effect seen in **Figure 2**, where insulin is elevated by day 30 in the streptozotocin group, is mainly due to insulin resistance as a reaction to the drug, which ends up damaging the pancreas due to its hyperactivity and due to the lack of the protective effects of the neem and pitaya flower extracts.

Also, as the results demonstrate, the extracts of pitaya flower and neem help to decongest and detoxify the liver, since cholesterol and triglyceride levels remained at adequate levels in the treated experimental groups when compared with the control group.

On the other hand, the kidney function of the treated groups was never affected because, according to the data obtained, the concentrations of urea creatinine and urea nitrogen remained within the appropriate parameters for their proper functioning.

The results demonstrate that the doses of both pitaya flower and neem do not represent a risk of toxicity for animals exposed to these metabolites.

Animals in the untreated diabetic streptozotocin group developed hyperphagia, polydipsia, polyuria, and weight loss.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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