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Effect of a pitaya-based nutraceutical product (*Selenicereus megalanthus*) over the hypercholesterolemia regulation in *Mus musculus* mice

Abstract

Objective: To evaluate the effect of a nutraceutical product based on yellow pitaya (Selenicereus megalanthus) on serum total cholesterol levels in a murine model of hypercholesterolemia.

Material and methods: Twenty-six male Mus musculus mice (BIOU: NMRI line, 4 weeks old) were divided into four groups (n=5-6): Healthy, Control, Treatment 1 (T1), and Treatment 2 (T2). Hypercholesterolemia was induced in all but the Healthy group using a high-fat diet for 15 days. Subsequently, for 15 days, the T1 and T2 groups received the pitaya-based nutraceutical (2 g/day, ad libitum). During this treatment phase, T1 was switched to a normal diet, while T2 continued on the high-fat diet. Total cholesterol was measured at 0, 15, and 30 days via the retroorbital sinus technique (Colestat, Wiener Lab.). Data were analyzed using Kruskal-Wallis and Bonferroni post-hoc tests (SPSS v.20.0).

Results: The high-fat diet successfully induced hypercholesterolemia. A statistically significant reduction in total cholesterol was observed exclusively in the T2 group, which received the nutraceutical while maintaining the high-fat diet. In this group, cholesterol levels decreased from 293.14 mg/dL at day 15 (post-induction) to 195.28 mg/dL at day 30 (post-treatment, p-value ≤ 0.01 vs. Healthy group). No significant cholesterol reduction was observed in the T1 group, which received the nutraceutical alongside a normal diet.

Conclusion: In this murine model, the S. megalanthus-based nutraceutical demonstrated a significant cholesterol-lowering effect only when administered concomitantly with a high-fat diet. This finding suggests a potential mechanism involving interference with dietary fat absorption, rather than a systemic lipid-lowering effect independent of diet. Further studies are warranted to elucidate the mechanism of action and to evaluate its safety and efficacy in humans.

Keywords: nutraceutical, hypercholesterolemia, yellow pitaya

Volume 13 Issue 1 - 2026

Ariene Chicata,[1] Katiusca Villasana,[2] Angélica Cartay,[3] Issis Arraiz[1]
[1]Department of Nutrition and Feeding, Faculty of Medicine, University of Los Andes, Venezuela
[2]Departament of Pathology, Faculty of Dentistry, University of Los Andes, Venezuela
[3]Lead Medical Laboratory Scientist Adventhealth Winter Garden Fl, USA

Correspondence: Katiusca Villasana, Departament of Pathology, Faculty of Dentistry, University of Los Andes, Merida, Venezuela, Tel +584247438957

Received: February 17, 2026 | **Published:** March 4, 2026

Introduction

A nutraceutical product is a non-food supplement that contains a natural bioactive substance and differs from a medicine in that the latter is not from natural biological origin. So, it differs from an extract too; in that it does not have the capacity for therapeutic action that a nutraceutical has.[1] The interaction of the active compound and its possible mechanisms of action is of the ultimate importance, where elaboration of a product, capable of involving these aspects through the prevalence and suitable conservation of active biological substances together with non-nutritional elements, which can contribute to prevention or delay of any specific pathology. Therefore, the need to formulate new natural products that allow a healthier future for humanity, consequently this study aims to determine the effect of a pitaya-based nutraceutical, prepared at the School of Nutrition and Dietetics, Faculty of Medicine of University of Los Andes (ULA) - Venezuela; over the regulation of hypercholesterolemia.

In reference to hypercholesterolemia, this is a hereditary pathology or it can be induced by means of a hypercaloric diet, hormonal disorders, sedentary lifestyle, among other factors.[2] At the global level, the World Health Organization (WHO) reported that the prevalence of hypercholesterolemia is 39% in people over 25 years of age. European region presents 54% of hypercholesterolemia in both sex, while the regions of Southeast Asia and Africa report 29% and 22%, respectively.[3]

Material and methods

Nutraceutical product

A nutraceutical product based on pitaya (*Selenicereus megalanthus*) was elaborated in the School of Nutrition and Dietetics of the Faculty of Medicine ULA - Venezuela (under the protocol of the special work for the degree of Nutrition and Dietetics). Final form of this product was individual gummies, administered *ad libitum* at a dose of 2 grams/day per animal.

Normal diet

It consisted of feeding the animal with a diet based on rat croquettes (pellets form), *ad libitum*, in a portion of 5 grams/day per animal.[4]

Initial diet or hyperlipidic diet

This diet consisted of supplying the animal with a hypercaloric diet at the expense of saturated fatty acids, *ad libitum*, in a portion of 5 grams/day per animal[4] following protocol settled by Ricafuerte & Lema[5], consisting of a mixture of rat croquettes (processed until

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obtaining a flour texture) with lard, until obtaining a compact mass which was molded in the form of pellets.

The design and protocol of this study were evaluated and approved by the Ethics Committee of the Animal Facility of the University of Los Andes, Venezuela (CEBIOULA) (protocol number 116) in 2018.

Experimental animals

To evaluate the nutraceutical effects over hypercholesterolemia levels, was worked with the mice species *Mus musculus* Line BIOU: NMRI since it is the most used in laboratory experiments.[6] A total of 26 four-week-old male animals (mice) were used. Distributed as follows: 6 male *Mus musculus* animals with an initial weight of 14.67 g (±SD 1.50) used to carry out a pilot test and 20 male *Mus musculus* animals to carry out the experimental part, which had within an initial weight of 17.15 g (±SD 3.21); they were handled by specialized and trained personnel at the Animal Facility of the Universidad of Los Andes, Mérida – Venezuela.

Regarding the sex of the animals, it was decided to work with the male gender only, to keep their biochemical values constant throughout their lives[7] as the matter of fact that testing on females, could influence the results as caused by hormonal levels, in addition to being more vulnerable against stress and to develop defensive behaviors associated with anxiety, and even when extrapolating the dose, males are the most suitable.[8]

Pilot test

In order to generate an animal model to induce hypercholesterolemia, it was proceeded as follows, working with 6 male *Mus musculus* animals with an initial weight of 14.67 g (±SD 1.50). During the course of the experiment, the same environmental conditions were maintained to maintain the consistency of the results. The mice were individually housed in seal safe polycarbonate cages (Tecniplast, Xenoplus, Universidad de Los Andes, BIOULA Biotherium, and Mérida – Venezuela) throughout the study. General procedures for the care and housing of animals are in accordance with the Guide for the Care and Use of Laboratory Animals.[9] While ambient temperature and humidity were maintained in accordance with United States Department of Agriculture (USDA) animal welfare laws with a light period with timer-controlled lighting.[9]

Test

It lasted one month. Twenty male mice (*Mus musculus* Line BIOU:NMRI) were used, 4 weeks old. These animals were distributed as follows:

I. Healthy Group: made up of 5 male *Mus musculus* animals. Animals in this group were not subjected to the induction of the pathology, so their biochemical values served to be compared with the rest of the experimental groups. Throughout the study, his diet was based on rat croquettes (normal diet) and they did not receive the nutraceutical product.

II. Control Group: made up of 5 male *Mus musculus* animals. Fifteen days after the induction of the pathology (with a hyperlipidic diet), this group's diet was changed to rat croquettes. In this group, a change in their cholesterol levels was expected in relation to the modification of the diet.

III. Treatment Group: made up of 10 male *Mus musculus* animals and in turn divided into two subgroups. Two weeks after the induction of the pathology, these groups began to receive the treatment (nutraceutical product), making a dietary modification in one of the subgroups:

a) Treatment 1 (T1): made up of 5 male *Mus musculus* animals. This group received the treatment and their initial diet was changed to ratarin (Rat croquettes).

b) Treatment 2 (T2): made up of 5 male *Mus musculus* animals. This group received the treatment, but maintained the initial diet (hyperlipid diet).

Sampling

Blood samples were taken using the retro orbital venous sinus technique, which consists of introducing a blue micro hematocrit capillary through the retro orbital venous sinus (obtaining a volume of 200 µL);[10] for further processing and analysis of the sample. Sampling were taken three times: at 0 days, at 15 days and at 30 days.

Sample analysis

For the analysis of total cholesterol in plasma, the Wiener Lab. enzymatic colorimetric method was used, measuring each of the samples made (at 0, at 15 and at 30 days) in the study animals by means of a visible light spectrophotometer (Stat fax®). These samples were analyzed at the Biochemical Laboratory, at the Faculty of Medicine of the Universidad de Los Andes, Mérida - Venezuela.

Statistical analysis

Once the information provided by the blood of the experimental animals was collected, a database was created for analysis with the Statistics Package for Social Sciences (SPSS) program from IBM, version 20.0. The Kruskal-Wallis test was used as a processing technique for a confidence level of 99% with a P value of 0.01 ($p \leq 0.01$), observing that there were statistically significant differences between the measurements taken, and differences between the measurements were established by means of the Bonferroni post-hoc test. Similarly, the Microsoft Excel program was used for the construction of tables and charts. During this processing, an edge of error of 1% was maintained.

Results

Table 1 shows the biochemical analyzes of the pilot test, which allowed corroborating that through the hyperlipidic diet it was possible to induce the pathology (elevation of total blood cholesterol), within the estimated time (fifteen days). The healthy group started with values of 169.3 mg/dL (range established as a reference to determine cholesterol; that is, any value above this fifteen days after the induction of the pathology began, would be indicative of hypercholesterolemia in the animal), and ended (at thirty days) with 174 mg/dL.

Table 1 Results of Cholesterol Level From Mice (Mus musculus Line BIOU:NMRI) of the Pilot Test

Induction phase			Treatment	
Group	0 day Chol. (mg/dL)	15 days Chol. (mg/dL)	21 days Chol. (mg/dL)	30 days Chol. (mg/dL)
Healthy	169,3	169,3	203,7	174
Control 1	160,1	167,1	319,5	258
Control 2	168,5	178,5	246,3	195
T 1	169,4	210,5	259,5	146,29
T 2	171,5	219,5	261	196,3
T 3	176,7	231,3	122,2	215,5

Note: Chol: cholesterol; T1: Treatment group 1; T2: Treatment group 2; T3: Treatment group 3.

Citation: Chicata A, Villasana K, Cartay A, et al. Effect of a pitaya-based nutraceutical product (*Selenicereus megalanthus*) over the hypercholesterolemia regulation in *Mus musculus* mice. *J Diabetes Metab Disord Control.* 2026;13(1):22–25. DOI: 10.15406/jdmdc.2026.13.00308

Similarly, in the experimental groups a positive difference was observed. Both control groups did not receive treatment and despite the fact that one of them changed the diet (Control 2), they presented an increase in cholesterol levels at the end of the test. Control 1 group started with values of 167.1 mg/dL and ended with 258 mg/dL; while Control 2 (group whose diet was modified after induction), went from an initial value of 178.5 mg/dL to 195 mg/dL at the end of the pilot test.

On the other hand, the treatment groups presented a different behavior when receiving the nutraceutical product and modifying their diet. Group T1 began with a value of 210.5 mg/dL and ended with a value of 146.29 mg/dL, while T2, who maintained the same criteria, started with a value of 219.5 mg/dL and ended with a value of 196.3 mg/dL; Regarding the T3 group, it initially reported a value of 231.3 mg/dL and ended with a value of 215.5 mg/dL.

However, if the results obtained are compared with other preliminary studies based on cholesterol in mice, it can be noted that these values vary considerably from one line to another, between genders and even inbred or not. In this sense, Ojeda[11], highlights that in a study conducted at the University of Carabobo (UC) that same year, total cholesterol levels were reported in NMRI mice similar to those obtained during the pilot test. It is important to mention that eight-week-old non-inbred female mice of the NMRI breed were used in this study; that is, the same breed, same line and similar ages were used. However, the differential factor is in the gender, which shows that the levels are much higher compared to those of the males.[11] This same phenomenon was reported at the records of the biotherium of the University of Los Andes.

The animals belonging to Group T2 presented a decrease in total cholesterol values at thirty days (195.28 mg/dL) in relation to the values reported at fifteen days (293.14 mg/dL) at the moment of established the pathology during the induction phase and even in relation to the initial phase (292.65 mg/dl), as shown in Table 2.

Table 2 Cholesterol Level Results From Project Mice (Mus musculus Line BIOU:NMRI)

Group	Initial phase	Induction phase	Treatment phase
	Day 0 Chol. (mg/dL)	Day 15 Chol. (mg/dL)	Day 30 Chol. (mg/dL)
Healthy	169	169	174
Control	224,38	281,94	216,61
Treatment 1	201,61	197,88	220,49
Treatment 2	292,65	293,14	195,28

Note: Chol.: cholesterol

Regarding the results of the non-parametric Kruskal-Wallis statistical test (Table 3) with a confidence level of 99% with a p-value ≤ 0.01, it was observed that there are statistically significant differences between the measurements taken at 15 and 30 days for the T2 group with respect to the group of healthy individuals; however, no statistically significant differences were found for these measurements in the Control group and T1, in relation to the healthy group.

Table 3 Contrast statistics (a,b)

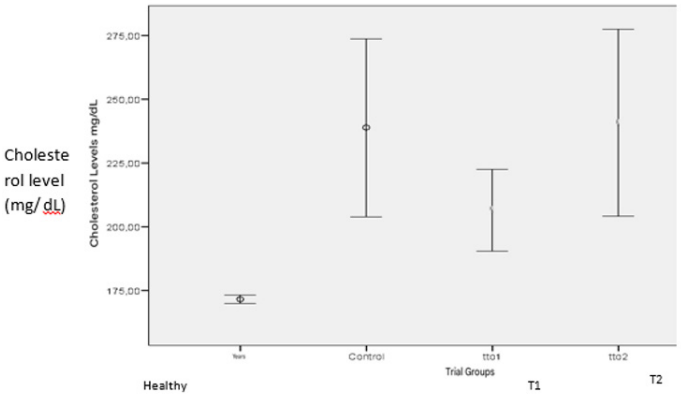
	mg/dL[b]
Chi-squared[a]	17,677
Df	3
Sig. asympt.	,001

Note:

[a] - Kruskal-Wallis Test.

[b] - Group variable: trial groups.

In reference to the administration of the pitaya-based nutraceutical as treatment, group T1 reported a value of 201.62 mg/dL after fifteen days and at the end reported a value of 213.99 mg/dL; that is, despite the modification in the diet and receiving the treatment, an increase in the biochemical values was observed at the end of the study (Graph 1).



Graph 1 Results of the cholesterol biochemical analyzes of mice (*Mus musculus* Line BIOU: NMRI) of the project.

Discussion

In relation to the results obtained from the group of mice belonging to the T1 group, it can be inferred that it would be necessary to let the nutraceutical product act for a period of time greater than that proposed (fifteen days for the treatment phase), in order to observe a decrease in cholesterol values; In this sense, it is worth mentioning that, generally, a drug with a lipid-lowering effect is left to act for a minimum time of 30 days[12] before evaluating its effects. However, regarding the modification of the diet as an intervening factor for the regulation of cholesterol levels, it is known that changing the diet is an important control option to reduce cholesterol levels, either by itself using various strategies to modify diet or in combination with drug therapy.[13]

A similar response to the hypocholesterolemic effect was exposed in the investigation by Hernawati[12], reporting that after the induction of the pathology (hypercholesterolemia), through a diet with a high fat content for a month and after administering powder of pitaya peel for a period of thirty days, the blood lipid levels of male mice (*Mus musculus* strain Balb-C) changed, reducing total cholesterol levels compared to the negative control. Similarly, Choo[14] reports a reduction in cholesterol levels in hypercholesterolemic rats that were fed for five weeks with dilutions of lyophilized red pitaya peel (*H. polyrhizus*) at different concentrations. It also reports the reduction of triglycerides and the level of LDL cholesterol. In this study, among the concentrations studied, the one that reported the greatest reduction in cholesterol was the one that contained 1.17% freeze-dried pitaya peel.

Other studies have reported the relationship between the content of total polyphenols and other antioxidant compounds present in the peel and pulp of red pitaya (H. *polyrhizus*), with the reduction of cholesterol levels. In this regard, Choo[14] reports that, when processing the pulp of red pitahaya (*H. polyrhizus*), above 95°C and more than

30 minutes, its content of total polyphenols and antioxidant capacity are significantly reduced and ability to regulate the lipid profile in rats, compared to fresh pulp. Not so the ability to control the level of triglycerides, which remains the same. Similarly, it is reported that the higher the temperature and time of thermal processing, the lower the hypocholesterolemic effect in rats, confirming the hypothesis that the cardioprotective efficiency of red pitahaya (*H. polyrhizus*) is associated with the antioxidant compounds present in the fruit pulp,[14] including peel and seeds.

The latter have a fatty acid profile that reveals a significant content of polyunsaturated fatty acids (PUFA), the intake of which, as has been shown in numerous investigations, has a regulatory effect on cholesterol levels and cardiac diseases. However, most studies have focused on red-skinned pitaya varieties (*H. polyrhizus and H. undatus*). Reports regarding the medicinal benefits of yellow pitaya (*H. megalanthus*) are scarce.[14] Results suggest that plant compounds of interest, are included at the edible and the non-edible part of the fruit, and would constitute a source of antioxidants applicable in the food industry.[15]

Conclusion

The effect of the nutraceutical product made from pitaya (Selenicereus megalanthus) on serum cholesterol levels in a Mus musculus model of hypercholesterolemia was verified through biochemical analysis. The results showed a statistically significant reduction ($p \leq 0.01$) in total cholesterol in the T2 group compared to the healthy group. These findings in an animal model suggest a potential hypocholesterolemic effect that warrants further investigation. However, extrapolation to humans should be made with caution, and clinical studies are necessary to confirm any effect in human populations.

Acknowledgements

We thank to Vitalis Clinical Analysis Laboratory for providing the equipment and reagents for quantification of the cholesterol content. We thank to Sensory Analysis Laboratory and Physicochemical Analysis Laboratory of the University of Los Andes for providing their facilities for the preparation of the nutraceutical and ensuing analysis.

Conflicts of interest

The authors declare that they have no conflicting interests.

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