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Hypolipidemic activity of *Phaseolus vulgaris* (Fabaceae) in mice

Actividad hipolipemiante de *Phaseolus vulgaris* (Fabaceae) en ratones

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Abstract

Objective: To evaluate the lipid-lowering activity of an aqueous extract obtained from the seeds of *Phaseolus vulgaris* in male mice using the hyperlipidemia induction model with Triton X-100. Methods: the chemical quality of the extract obtained was characterized by quantifying the total polyphenols (Folin Ciocalteu method) and total anthocyanins (colorimetric method) as well as their antioxidant activity by their ferric ion reducing capacity (FRAP, TPTZ method). Results: The data obtained show that the aqueous extract contains a large amount of total polyphenols (415 mg EAG / 100g of seed) and total anthocyanins (43EMG / 100 g of seed) and significant antioxidant activity (11.080.83 of Fex / g of seed). Administration of the aqueous extract to hyperlipidemic mice improved their lipid profile, especially by reducing the serum value of total cholesterol (144 mg/dL) and triglycerides (147 mg/dL) and increasing HDL values (67 mg/dL) in the group that received a dose of 300 mg of extract / kg of weight. Conclusion: These results show that the aqueous extract of *P. vulgaris* exerts an antioxidant activity in vitro and a lipid-lowering effect in mice.

Dyslipidemia, Antioxidant, Anthocyanins

Resumen

Objetivo: Evaluar la actividad hipolipemiante un extracto acuoso obtenido a partir de las semillas de *Phaseolus vulgaris* en ratones macho usando el modelo de inducción de hiperlipidemia con Tritón X-100. Métodos: se caracterizó la calidad química del extracto obtenido mediante la cuantificación de los polifenoles totales (método de Folin Ciocalteu) y antocianinas totales (método colorimétrico) así como su actividad antioxidante por su capacidad reductora de iones férrico (FRAP, método de TPTZ). Resultados: Los datos obtenidos demuestran que el extracto acuoso contiene una gran cantidad de polifenoles totales (415±mg EAG/ 100g de semilla) y de antocianinas totales (43±EMG/ 100 g de semilla) y una actividad antioxidante significativa (11.08±0.83 de Fex/ g de semilla). La administración del extracto acuoso a los ratones hiperlipidémicos mejoró su perfil lipídico, especialmente al reducir el valor sérico del colesterol total (144 mg/dL) y trigicéridos (147 mg/dL) e incrementar los valores de HDL (67 mg/dL) en el grupo que recibió una dosis de 300 mg de extracto/ kg de peso. Conclusión: Estos resultados demuestran que el extracto acuoso de *P. vulgaris* ejerce una actividad antioxidante in vitro y un efecto hipolipemiante en ratones.

Dislipidemia, antioxidante, antocianinas

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Introduction

Obesity is a risk factor for contracting various diseases that compromise the patient's life; the higher the overweight index, the higher the amount of fat in the body and the higher the dyslipidaemia, characterised by an increase in triglycerides, production of low-density lipoprotein (LDL) particles and a reduction in high-density cholesterol (HDL), increasing the risk of vascular accidents; In addition, there is an increase in blood glucose because fat provides energy to muscle to the detriment of glucose, this state causes the pancreas to secrete excess insulin in an attempt to reduce hyperglycaemia but fails to compensate for this balance causing peripheral insulin resistance which can lead to the development of diabetes[1-4].

Hyperlipidaemia has a high predictive value as a risk factor for atherosclerosis and cardiovascular and cerebrovascular accidents, characterised by elevated serum levels of total cholesterol and LDL and decreased serum levels of HDL; treatment of hyperlipidaemia is therefore one of the best therapeutic models for slowing down the process of atherogenesis [5-7]. One measure taken to control the imbalance present in dyslipidaemias, in addition to pharmacotherapy and physical exercise, is a healthy, balanced diet with functional foods that help to improve the patient's metabolic status [5, 8, 9]. Beans (also known as beans in other regions of the Americas), whose scientific name is *Phaseolus vulgaris*, in addition to providing macronutrients to the diet, the whole bean, and nutrients such as non-heme iron, fibre, folic acid, thiamine, potassium, magnesium and zinc, provide substances beneficial to the health of the consumer such as various phenolic acids (ferulic, p-coumaric and gallic acid), flavonoids and anthocyanins 10-13. Previous studies have shown that aqueous extracts of *P. vulgaris* exert beneficial biological activity by stabilising blood levels of glucose and lipids, because polyphenolic compounds facilitate the binding of insulin to its receptors, affect the digestibility of carbohydrates, for example by inhibiting amylase, among other proposed mechanisms [10, 14, 15].

However, there are not enough studies demonstrating the effectiveness of *P. vulgaris* in the treatment of dyslipidaemia, so the aim of the present study was to determine the lipid-lowering activity of the aqueous extract of lyophilised *P. vulgaris* seed powder in hyperlipaemic mice treated with Triton X-100 to estimate the pharmacological and biotechnological potential of the plant.

Material and Methods

Black bean (*Phaseolus vulgaris*) samples were collected in the region of Hopelchén, Campeche State (Mexico) and their taxonomic identity was corroborated; the seeds obtained were dried at room temperature and stored in plastic containers refrigerated at 4 °C; prior to extraction, the seeds were ground to obtain a powder that was subjected to an extraction process by static maceration, for which 100 g of powder were deposited in 2. 0 L beakers and 1.0 L of sterile distilled water was added, left to stand for 8 h and the supernatant was separated by filtration. For quantification, an aliquot of 100 mL was taken for the determination of total polyphenolic compounds by the Folin Ciocalteu method, anthocyanin quantification and ferric ion reducing power by the TPTZ method. The rest of the extract was subjected to a freeze-drying process (13.3 Pa for 72 h) to obtain the dry extract for bioassays, the freeze-dried extract was kept refrigerated at 4 °C in amber vials until evaluation [29-31].

Determination of Total Polyphenolic Compounds [29-31]

100L of the extract was added to 500L of water in a test tube and then 100L of Folin-Ciocalteu's reagent was added, left to react for 30 min and then 500L of Na_2CO_3 20% was added, incubated at room temperature for 30 min, and finally read in a spectrophotometer at 760 nm. A calibration curve was performed with a standard solution of gallic acid 250 ppm to determine the concentration of polyphenols present in the extract, the test was performed in triplicate.

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Quantification of anthocyanins [29,30]

The test was performed in triplicate by acidifying the solution with 0.1 M HCl and finally filtering the solution to recover the supernatant. The absorbance of the acid solution was measured at 540 nm and the anthocyanin concentration was estimated by the following formula (proposed by Di Stefano):

$$Anthocyanins\ \frac{mg}{L} = A_{540\ nm} * 16.7 \qquad (1)$$

Where is the absorbance of the acid solution at 540 nm and 16.7 is the conversion factor considering the absorbance of malvidin-3-glucoside.

Determination of Ferric Ion Reductive Antioxidant Power (FRAP) [30,31,38]

The test was performed using TPTZ (2,4,6-tripyridyl-S-triazine) reagent as a ferrous ion complexing agent; first the FRAP reagent was prepared by mixing 25 mL of 300 mM sodium acetate buffer, 2.5 mL of 10 mM TPTZ (2,4,6-tripyridyl-S-triazine) solution and 2.5 mL of 20 mM ferric chloride solution. Subsequently, 100 µL of the bean extract was added to 1000 µL of a freshly prepared solution of FRAP reagent, mixed thoroughly, allowed to react for 60 min and the ferrous-tripyridyltriazine complex formed was measured at 590 nm in a spectrophotometer; a calibration curve was performed with ferrous sulphate as a standard.

Lipid-lowering activity in albino mice [32-35]

Ten-week-old male albino mice (Mus musculus) weighing more than 25 g (range 25-30 g) and pre-conditioned for one week, maintained at 30°C and 50% relative humidity, with water and purina® food ad libitum, with 12-hour light-dark cycles, were used. Following the standard indications of mouse caretakers and breeders and the instructions of the Mexican Official Standard NOM-062-ZOO-1999 that dictates the technical specifications for the reproduction, care and use of laboratory animals.

Hyperlipidaemia was induced by intraperitoneal administration of the surfactant Triton X-100 (a non-ionic detergent) in freshly prepared saline (100 mg/kg) to mice, after an overnight 18-hour fast, to cause elevation of plasma cholesterol and triglycerides (1).

After 72 hours of triton administration, the animals were randomly divided into groups of six and treatments were initiated as shown in table 1, the substances were administered orally for 7 days.

Group	Name	Induction Hyper-lipidemia	Treatment
1	Witness	No	Saline solution
2	Control Negative	Yes	Saline solution
3	PV1	Yes	Aqueous extract of *P. vulgaris*, dosage 100 mg/kg
4	PV2	Yes	Aqueous extract of *P. vulgaris*, dose 200 mg/kg
5	PV3	Yes	Aqueous extract of *P. vulgaris*, dose 300 mg/kg
6	Positive Control	Yes	Atorvastatin in 0.5% aqueous methylcellulose, dose 10 mg/kg

Table 1 Experimental protocol used to determine the hypolipidemic activity of *P. vulgaris*, hyperlipidaemia was induced with Triton X-100 (i.p.) and after 72 hours the treatments were started for 7 days, orally
Source: Own elaboration

On the eighth day of treatment and after an 18 h fasting period, the animals were anaesthetised to obtain blood samples by intracardiac puncture. Sera were separated by centrifugation at 3000 rpm for 10 min for determination of blood parameters (total cholesterol, triglycerides, HDL) using commercial enzyme kits. Cholesterol was determined by the enzymatic method of the enzyme cholesterol ester hydrolase which hydrolyses all serum cholesterol esters present in the sample and then using the enzyme cholesterol oxidase which oxidises the free cholesterol generating hydrogen peroxide, which by the action of peroxidase reacts with chromogen to produce a coloured compound. The experimental procedure for the determination of total cholesterol was done with 1.0 mL of commercial total cholesterol reagent and 10 L of serum, mixed well and incubated for 10 minutes at 37°C, after which the absorbances were read at a length of 505 nm in a spectrophotometer. A calibration curve was also determined with the cholesterol standard provided by the Bayer® commercial kit (1).

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For the determination of triglyceride concentration, the enzymatic method was used which hydrolyses serum triglycerides to glycerol and fatty acids, the glycerol produced is phosphorylated by the action of the enzyme glycerol kinase and the glycerol-1-phosphate generated is oxidised by the enzyme glycerol phosphate oxidase which produces hydrogen peroxide, which in the presence of peroxidase and chromogens produces a coloured compound. The experimental procedure was carried out with 1.0 mL of the working reagent and 10 L of serum was added, mixed well and incubated for 10 minutes at 37ºC, finally, the absorbance was measured at 505 nm in a spectrophotometer. A calibration curve was performed with the standard provided in the commercial kit (1).

For the determination of HDL cholesterol, the method based on the precipitation of VLDL and LDL lipoproteins with phosphotungstate in the presence of magnesium ion was used, then the remaining cholesterol in the serum was determined with the total cholesterol enzyme reagent. LDL-cholesterol concentration was estimated by the Friedelwlad equation:

$$LDL = CT - \left(HDL + \frac{TG}{5}\right) \quad (2)$$

Where LDL is the concentration of LDL cholesterol, TC is the concentration of total cholesterol, HDL is the concentration of HDL cholesterol and TG is the concentration of triglycerides (all expressed in mg/dL).

On the other hand, the atherogenic index expresses at a mathematical level the ratio or proportion between total cholesterol levels and high-density lipoprotein levels and serves to find the risk of atherosclerosis, a value equal to or lower than 3.5 represents a low risk, an atherogenic index between 3.5 and 4.5 implies a moderate risk and a value higher than 4.5 means a maximum risk of atherosclerosis. The Castelli formula was used to calculate the atherogenic index:

$$IA = \frac{CT}{HDL} \quad (3)$$

Where AI is Castelli's atherogenic index, TC is total cholesterol concentration and HDL is HDL cholesterol concentration, expressed in mg/dL.

Statistical analysis

Statistical analysis of the data was performed using SPSS V25.0 statistical software, the descriptive statistics with which the values are reported are the mean and one standard deviation; the results of each test were analysed for significant statistical differences by a one-way Analysis of Variance (ANOVA), followed by a multiple range test employing Tukey's multiple comparison of means method by the least significant difference LSD procedure, with a confidence level of 95% (=0.05).

Results

The chemical characterisation of the aqueous extract of Phaseolus vulgaris is shown in table 2, these results reveal that the extract contains a high concentration of polyphenolic compounds and anthocyanins, in addition the extract presents a good ferric ion reducing capacity.

Total polyphenols	415±15 mg EAG/ 100g of seed.
Anthocyanins	43±1 EMG/ 100g of seed.
FRAP	11.08±0.83 of Fe^{2+}/ g of seed.

Table 2 Polyphenol and anthocyanin content and ferric iron reducing activity of Hopelchén bean seed acidic aqueous extracts. EAG= gallic acid equivalents, EMG= malvidin-3-glucoside equivalents, results are shown as X SD, n=3.
Source: Own elaboration

The values of cholesterolemia and triglyceremia were elevated with Triton X-100 treatment, if the results of the control group (not treated with Triton) are compared with those of the negative control group (who received Triton and saline); however, the individuals treated with the aqueous extract of *Phaseolus vulgaris* had a lower serum concentration of cholesterol and triglycerides than the negative control group, thus observing the hypolipidemic action of the extract of *P. vulgaris* (Graphic 1).

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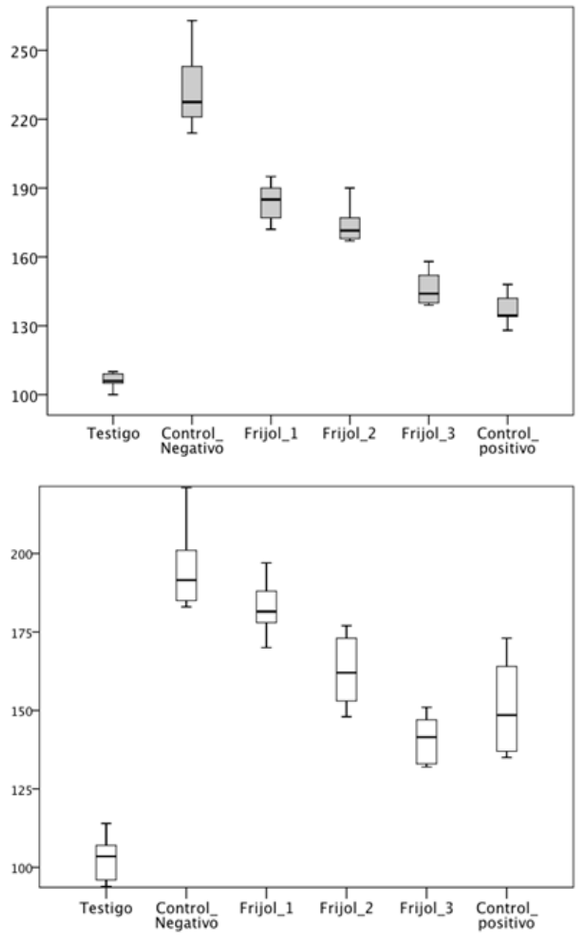

Graphic 1 On the left, the serum cholesterol values of the groups studied. On the right, serum triglyceride values (n=6), different letters in each group indicate significant differences. In both graphs the y-axis indicates the concentration expressed in mg/dL
Source: Own elaboration

Likewise, the other lipid profile data are shown in table 3, together with the atherogenic index; these results show that the administration of the aqueous extract of *P. vulgaris* increased HDL values in contrast to the negative control group. LDL values and the atherogenic index decreased in the mice treated with the extract, which is beneficial because it decreases the risk of vascular accidents. It can be It can be seen that the increase in HDL and decrease in LDL was a dose-dependent effect.

Group	HDL	LDL	Atherogenic index
Control	$49\pm7^{a,c,d}$	36 ± 5^{a}	2.19 ± 0.27^{a}
Negative control	36 ± 4^{b}	157 ± 18^{b}	6.51 ± 0.92^{b}
PV 1	40 ± 3^{a}	107 ± 8^{c}	4.58 ± 0.38^{c}
PV 2	$57 \pm 8^{c,d}$	84 ± 10^{s}	3.08 ± 0.38^{d}
PV 3	67 ± 3^{c}	51 ± 9^{e}	2.19 ± 0.16^{e}
Positive control	55 ± 4^{d}	52 ± 6^{e}	2.51 ± 0.14^{e}

Table 3 Serum HDL and LDL values and atherogenic index of the different study groups. Results are presented as X SD, n=6, different letters in the same column represent differences (<0.005) statistic
Source: Own elaboration

Discussion

The model used in this research to induce hyperlipidaemia was the administration of Triton X-100 which causes elevation of serum total cholesterol, LDL and triglyceride values, as well as a reduction in HDL levels, which is a major risk because it increases the atherogenic index 5,[22-24]. The mechanism by which non-ionic surfactants produce hyperlipidaemia in mice appears to be the accelerated induction of hepatic cholesterol synthesis, post-administration of the chemical compound which increases the activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA) which is the enzyme involved in cholesterol biosynthesis. In addition, triton inhibits lipoprotein lipase, an enzyme that hydrolyses triglycerides to fatty acids and glycerol, thereby increasing plasma triglyceride levels[36,37].

In this study, an increase in lipidaemia levels was observed in the negative control group compared to the control group, corroborating the success of the model used to induce hyperlipidaemia [32,35,37]; in the positive control group (to which the lipid-lowering drug was administered) a decrease in serum lipid values (cholesterol and triglycerides) was observed and in the problem groups the lipidaemia levels were significantly lower than in the negative control group, which demonstrated that the aqueous extract of *P. vulgaris* aqueous extract exerted a dose-dependent lipid-lowering effect.

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Since the proposed mechanism of action for the induction of hyperlipidaemia by triton X-100 is the induction of lipid biosynthesis, it can be assumed that if a plant extract exerts a lipid-lowering effect it may be because it contains metabolites that interfere with cholesterol biosynthesis; Furthermore, the drug used as a reference treatment in this research was atorvastatin, a member of the statin group that acts as a competitive inhibitor of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCoA), which is responsible for hepatic cholesterol biosynthesis [25-28]; the group treated with the drug showed a decrease in serum cholesterol and triglyceride levels. Accordingly, the atherogenic index in the mice treated with aqueous bean seed extract decreased with respect to the negative control group, as there was an increase in HDL levels and a decrease in LDL concentration in the problem group mice; The decrease in the atherogenic index is beneficial because values lower than 4 do not represent a cardiovascular compromise or risk, and when it is higher than 4 (as in the negative control group) there is a greater probability that atheroma plaque will form in the arteries and cause atherosclerosis [4-6, 22-24]. In addition to inducing hyperlipidaemia by increasing HMG-CoA reductase activity and inhibiting lipoprotein lipase, triton increases the production of free radicals, causing oxidative damage, especially in liver tissue; this oxidative damage is also observed in patients with dyslipidaemia [35-37].

Therefore, the content of polyphenolic compounds in the extract could exert a synergistic action with its lipid-lowering activity, as the antioxidant activity of the bean extract correlates with its high polyphenol content and may be beneficial in dyslipidaemias because these clinical conditions are associated with oxidative stress, which is implicated in the aetiopathogenesis of cardiovascular diseases [18, 19]; Although the present study did not evaluate the antioxidant activity in vivo, these results could support future research to show whether there is a protective association due to *P. vulgaris* extract against oxidative damage in vivo under this same model because it has been established that Triton causes lipoperoxidation and that malonylaldehyde levels increase and endogenous antioxidant levels decrease, compromising the health status of the individual and increasing the risk of vascular accidents [18-21, 39].

The presence of polyphenolic compounds, especially anthocyanidins, in the aqueous extract of these results are in agreement with the values expected for *P. vulgaris* according to different studies published in the scientific literature [13, 16, 17]; phenolic compounds are excellent transition metal chelators, which play a fundamental role in the formation of radicals and influence lipid peroxidation40. In addition, the mechanism by which polyphenols exert their action is based on modulation of enzyme activity; it has been shown that they can inhibit enzymes related to inflammatory or oxidative activity [13-15, 40]. Consequently, the ferric iron reducing action of the aqueous extract of *P. vulgaris* could be beneficial in vivo in individuals with hyperlipidaemia because hyperlipidaemia generally causes oxidative stress and in obese patients it is an intermediary in the development of metabolic syndrome, and it has also been observed that adipose tissue is the main source of reactive oxygen species [9, 5, 18, 19, 41].

The advantage of bean consumption in the diet is based on the contribution of polyphenolic compounds with antioxidant activity and its beneficial effect on the consumer's serum biochemistry due to its hypoglycaemic and lipid-lowering properties, which give it its nutraceutical character [9, 16, 25, 39, 41]; it would be necessary to study whether its pharmacological activity is preserved in decoction (bean broth).

Conclusions

Phaseolus vulgaris extract showed a dose-dependent lipid-lowering activity by reducing total cholesterol and triglycaemia levels, as well as a protective action by increasing HDL cholesterol concentration and decreasing the atherogenic index in the groups treated with the extract.

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