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Extracto hidroalcohólico liofilizado de *Passiflora edulis* y *Zea mays* L, como potencial hipotensor arterial e hipocolesterolemia en *Mus musculus* hipertensos inducidos

Lyophilized hydroalcoholic extract of *Passiflora edulis* and *Zea mays* L, as potential arterial hypotension and hypocholesterolemia in hypertensive *Mus musculus* induced hypertension

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Article Data

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Abstract

The leaves of *Zea mays* L and *Passiflora edulis* have multipurpose for conventional medicine for their bioactive compounds, however, their use in animal models lacks demonstration and biomedical validation, hence the objective was to evaluate the effect of lyophilized extract of *P. edulis* Sims and *Z. mays* L as a potential arterial hypotensive and induce hypocholesterolemia in hypertensive Swiss albino mice. Forty-eight 8-week-old Swiss albino mice were used by dividing into 4 groups: G_1- passion fruit (50 mg [n= 4], 100 mg [n= 4], and 200 mg [n= 4]), G_2-purple corn (50 mg [n= 4], 100 mg [n= 4], and 200 mg [n= 4]), and G_3-controls: negative control (distilled water [n= 12]), G_4-positive control (N-nitro-L-arginine methyl ether (L-NAME) [n= 12]). Mice were fasted to assess systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), glucose and cholesterol at baseline and post induction with L-NAME by indirect method. At 4 weeks of study the animals of G_1-passion fruit and G_2-purple corn showed significant antihypertensive and hypocholesterolemia effect ($p<0.05$) resulting the concentration 200 mg as optimal reducer and stabilizer of SBP, DBP, MAP, glucose and cholesterol. In conclusion, the lyophilized extract of *P. edulis* (passion fruit) and *Z. mays* L (purple corn) leaves at 200 mg concentration showed excellent antihypertensive and hypocholesterolemia effects in hypertensive Swiss albino mice

Resumen

Las hojas del *Zea mays* L y *Passiflora edulis* tienen multipropósito para la medicina convencional por sus compuestos bioactivos, sin embargo, su uso en modelos animales carece de demostración y validación biomédica, de ahí el objetivo fue evaluar el efecto del extracto liofilizado de *P. edulis* Sims y *Z. mays* L como potencial hipotensor arterial e inducir la hipocolesterolemia en ratones albino suizo hipertensos. Se utilizaron 48 ratones albino suizos de 8 semanas dividiéndose en 4 grupos: G_1- maracuyá (50 mg [n= 4], 100 mg [n= 4] y 200 mg [n= 4]), G_2- maíz morado (50 mg [n= 4], 100 mg [n= 4] y 200 mg [n= 4]) y G_3-controles: control negativo (agua destilada [n= 12]), G_4-control positivo (N-nitro-L-arginina metíl éter (L-NAME) [n= 12]). Los ratones fueron sometidos en ayunas para evaluar la presión arterial sistólica (PAS), presión arterial diastólica (PAD), presión arterial media (PAM), glucosa y colesterol en estado basal y post inducción con L-NAME mediante método indirecto. A 4 semanas de estudio los animales del G_1-maracuyá y G_2-maíz morado mostraron efecto antihipertensivo e hipocolesterolemia

Palabras clave:

Antihipertensivo, colesterol, glucosa, maracuyá, maíz morado, ratones.

significativo ($p<0.05$) resultando la concentración 200 mg como óptimo reductor y estabilizador de PAS, PAD, PAM, glucosa y colesterol. En conclusión, el extracto liofilizado de hojas de *P. edulis* (maracuyá) y *Z. mays* L (maíz morado) a 200 mg de concentración demostraron ser excelentes antihipertensivos e hipocolesterolemia en ratones albino suizo hipertensos.

Introduction

Arterial hypertension (AHT) is a very prevalent disease in public health (45 % in the elderly)[1,2], however, in companion and production animals it is usually similar, to acute myocardial infarction, heart failure[3], and is associated as a risk factor in pathologies of renal failure[4], atrial fibrillation, diabetes mellitus and nephropathies[5].

In the scientific literature, AHT is a complex pathology, and its therapeutic treatment is not effective[5,6], which additionally causes an increase in production costs in animal husbandry, as well as being unnoticed by breeders, despite its clinical and veterinary pathological importance[7].

Beta-blockers, nitrates, ACE inhibitors and ARA II are commonly used in the treatment of AHT, however, they cause various adverse effects, and the cost of treatment limits the patient's ability to continue with therapy, with the possibility of resulting in precursors of multidrug resistance[5,8], which is why most drugs are not designed for the veterinary clinic[9,10].

The practice of complementary medicine is recommended by the World Organization for Animal Health (OIE) and the World Health Organization (WHO) for its various properties[11,12]. Therefore, the use of medicinal plants (MP) would be a therapeutic alternative for patients with hypertensive pathologies[13-15], in addition to the scarce biomedical and veterinary studies, despite the fact that the world and Latin American countries such as Peru have a great biodiversity of MPs that have economic and social benefits[9,16].

It has been described that *Z. mays* L and *P. edulis* leaves reduce cholesterol and blood pressure[11], stabilize and protect arterial capillarity[17,18], reduce LDL, increase HDL, reduce obesity and insomnia[19,20], due to their bioactive principles such as antioxidants, flavonoids and luteolin in their leaves and flowers[21].

It has been reported that the ethanolic extract of *P. edulis* Sims and *Z. mays* exhibited antihypertensive activity in laboratory animals, however, there are no reports that reported the concentration and time of action as antihypertensive and hypocholesterolemic stabilizers of these plant species. Therefore, the aim of the study was to evaluate the effect of freeze-dried extract of *P. edulis* and *Z. mays* L as a potential arterial hypotensive and hypocholesterolemic agent in hypertensive Swiss albino mice, which could contribute as an effective immunomodulatory and chemotherapeutic antihypertensive alternative in animal models.

Materials and methods

Scope of the study. The study was carried out at the Central Research Laboratory (LCI), Animal Health Area, where freeze-dried extracts of *P. edulis* Sims [passion fruit] leaves (MARA) and *Z. mays* L [purple maize] (MA) and the experimental model of Swiss albino mice in the minibiotherium of the Multidisciplinary Scientific Research Centre (CICMI)-National University of Huancavelica (UNH), located at

3860 m above sea level at temperatures ranging from 8.5 to 16º C.

Acquisition and adaptation of mice. For the study, 48 Swiss albino mice (Mus musculus), males, 2 months old, with an average weight of 28±3 g, were acquired from the Biotherium of the Vice-rectorate of Research of the Universidad Peruana Cayetano Heredia-Peru (certificates). The animals were installed and kept in the process of adaptation for 25 days in reference to ethical regulations for handling laboratory animals[22,23] in the CICMI mini-biotherium, with balanced rations and water ad libitum, maintained at a constant temperature of 22° C with a light/dark cycle of 12/12 h, supervised by the Ethics Committee (recognized by Resolution N° 1259-2021-CU-UNH) from the beginning to the end of the study, validated by means of a certificate.

Collection of plant material. MARA leaves were collected at the flowering stage from Pichanaqui-Junin Peru, and MA from Acoria District, Huancavelica - Peru in January 2021, after an authorization letter from the owner of the crop, collecting 10 kg of fresh leaves from both plants in manila envelopes, labeled and packed in technopor boxes and transferred to the Laboratory of Animal Health-UNH Peru.

Leaves from both plants were selected, and dehydrated (8 kg) for 18 days at room temperature in a ventilated shaded room until brittle to the touch[24]. The leaves were manually pulverized (1.0 cm) in diameter using a domestic mill (Corona, SKU:25113-001. Colombia) and sieved (600 g) using an Analytical Sieve Shaker (As 400 Control. Retsch. Germany) and packed in 3 amber jars (200 g) and stored at room temperature under shade for subsequent preparation of the lyophilized ethanolic extract[25,26].

Taxonomic study. Four complete seedlings of MARA and MA were selected and herborized according to the conventional method[26] and sent to the Herbarium - Museum of Natural History (MHN), Universidad Nacional Mayor San Marcos-Peru, for taxonomic identification.

Preparation of freeze-dried extracts. The pulverized leaves of both plants were macerated in hydroalcoholic solution (ethanol 97 %) as an initial solution (2:1:0.8) and kept in an agitation process with Orbitral Shaker (Labnique, 52150000)/1 h at 180 rpm for 8 days, then the extracts were dissolved with ethanol 70°, ultra-pure water at a ratio: 2:2:1:1.8, put in agitation for 5 days and purified through a quick filter (pores of 4. 7-4.6 µm)[21]. Prior to this process, the saturation point and apparent density of each plant species were determined using the mathematical formula: degree of alcohol in solution: axb=cxd (a: alcohol solution, b: degree of alcohol, c: solution, d: the new degree of alcohol), sample density: P= m v-1 in order to obtain the concentrations of solute and solvent to be tested.

The ethanolic solvents used were removed through an automated rotary evaporator (Büchi Rotavapor®, R-300) /4 h at 60°C) with 100 mmHg vacuum pressure, amber at 4° C[27,12] and by the boiling-cooling method, which consisted in subjecting the extracts to boiling in a water bath at 45°C/8 h under directed ventilation and cooling at 10°C/24 h in falcon tubes covered with aluminium foil and stabilized at room temperature/12 h continuously[28].

Finally, the MARA and MA extract obtained were centrifuged at 5000 rpm/10 min/3 times (Topscien, NextSpin-P1524. China), from which they were formulated for testing at concentrations of 50, 100, and 200 mg.

The extracts obtained from each plant species were hermetically packed in amber bottles and stored at 10°C/90 days' maximum in order not to alter their-

bioactive principles[27].

Measurement of antihypertensive activity. The 48 mice were registered according to study group and distributed in the CICMI minibiotherium in 4 groups: G_1-MARA (50 mg [n= 4], 100 mg [n= 4] and 200 mg [n= 4]), G_2-MA (50 mg [n= 4], 100 mg [n= 4] and 200 mg [n= 4]) and G_3-PC positive control (L-NAME [n= 12]), G_4-PC negative control (distilled water [n= 12]).

Table 1 Means and standard deviation of baseline and post L-NAME induction SBP, DBP, MAP in Swiss albino mice (n= 48)

Study groups	Dose mg	N 48	Basal (mmHg)			Post induction (mmHg)		
			PAS	PAD	PAM	PAS	PAD	PAM
	50	4	119.0 ±1.8	77.2±1.9	136.6±1.7	126.5±4.7	77.2±0.5	140.5±2.6
G_1-MARA	100	4	126.0±0.2	78.5± 0.8	141.5±0.1	128.0±3.1	76.0±4.8	137.0±4.6
	200	4	118.0±1.7	74.6±0.7	139.6±1.5	123.0±5.5	74.0±2.6	135.5±5.2
	50	4	117.7±0.5	79.0±1.6	137.8±1.6	119.7±5.1	76.7±5.5	136.6±4.1
G_2-MA	100	4	123.7±1.7	78.2±0.9	140.1±0.8	122.7±5.3	77.5±6.1	138.8±4.0
	200	4	123.2± 1.5	74.7±1.3	136.3±1.0	126.0±2.0	77.0±5.2	140.0±5.5
	50	4	125.0±1.6	81.2±1.2	143.7±0.4	127.5±4.3	80.5±4.3	144.2±4.2
G_3-CP	100	4	125.2±0.9	82.5±0.5	145.1±0.8	128.0±2.8	81.0±1.4	145.0±3.5
	200	4	126.7±0.7	81.2±1.0	144.6±1.1	128.2±3.9	80.7±4.5	144.8±1.3
	50	4	120.2±1.1	76.0±0.2	136.1±1.8	126.5±5.0	76.5±5.6	139.7±5.8
G_3-CN	100	4	123.7±0.9	75.2±0.9	137.1±1.1	126.5±2.7	76.7±0.9	140.0±0.7
	200	4	123.2±0.9	76.0±1.8	137.6±1.4	127.2±3.9	76.5±2.3	140.1±2.7

Statistical difference within columns ($p<0.01$), MARA = passion fruit, MA = purple corn, PC = positive control, NC = negative control, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure.

Table 2 Means and standard deviation of Glucose (mg/dL), Cholesterol (mg/dL) concentration at baseline and post L-NAME induction in Swiss albino mice (n= 48)

Study groups	Dosis mg	N 48	Basal		Post induction - L-NAME	
			Glucose	Cholesterol	Glucose	Cholesterol
	50	4	102.0±1.6	183.0±5.4	139.7±2.9	196.0±4.8
G_1-MARA	100	4	106.0±1.3	183.2±5.9	132.0±1.7	196.7±1.2
	200	4	76.6±7.5	165.3±2.1	139.3±4.7	212.3±4.9
	50	4	80.2±12.6	180.0±1.8	94.7±3.4	194.0±3.9
G_2-MA	100	4	99.0±2.9	181.0±2.5	95.0±3.1	206.2±7.5
	200	4	96.5±8.8	183.2±4.7	98.5± 1.5	206.5±1.3
	50	4	98.7±3.9	183.0±3.9	129.0±1.6	199.5±6.2
G_3-CP	100	4	93.0±4.2	184.7±1.7	137.5±6.4	198.2±1.7
	200	4	96.7±1.5	181.0±1.8	140.0±2.2	197.0±1.8
	50	4	91.7±3.0	181.0±2.1	106.0±1.2	185.2±9.2
G_3-CN	100	4	90.2±3.8	181.2±0.9	109.5±6.4	192.5±3.1
	200	4	91.7±3.0	182.2±2.3	105.2±4.5	189.0±40

Statistical difference within columns ($p<0.01$), MARA= passion fruit, MA= purple corn, PC= positive control, NC= negative control.

For measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), glucose, and cholesterol, all mice were fasted for 12 h, after which baseline values were recorded (Tables 1 and 2), HT was induced in all groups by administering N-nitro-L-arginine methyl ether (L-NAME) at a concentration of 30 mg/kg/w/v diluted at a ratio of 1: 3 orally for 8 continuous days[29], from which baseline values of SBP, DBP, MAP, glucose and cholesterol were taken in order to have the

reference indicators to expose the antihypertensive effect of lyophilized ethanolic extracts of MARA and MA at different concentrations.

The blood pressure (BP) of the animals was measured by an indirect method using an indirect pressure measuring device (Panlab: LE5007). The animals were placed in a bait without trauma with a 6 mm diameter pulse transducer and subjected to a tempering process (temperature 28° C/30 min) for tail vasodilatation[30,31].

Glucose and cholesterol (hypercholesterolemia) were measured using the Glucometer (Accu-Chek-Active) and Reflotron Single Channel (Mission Cholesterol) equipment, for which a drop (0.6 mL) of blood was extracted from the lateral caudal vein of the mouse with lancet number 25, placed on test strips, readings were taken and recorded on a record card[30].

To evaluate the antihypertensive effect and hypercholesterolemia, the mice in groups G_1-MARA and G_2-MA were administered lyophilized ethanolic extracts of MARA and MA at concentrations of 50, 100 and 200 mg, while the G_3-CP group was administered L-NAME (30 mg/kg/pv) and G_4-CN (distilled water) orally ad libitum (drinking troughs), The results of the study were recorded during the daytime (6:00 am) for 6 weeks, with a mixed diet (balanced and forage) and biosecurity management as established by the National Research Council Committee[22,23], SBP, DBP, MAP, glucose and cholesterol values were recorded during the daytime (6:00 am) during 6 weeks of the study, as well as control of the presence of collateral signs in the animals without any clinical manifestation.

At the end of the study, all animals from G_1-MARA, G_2-MA, G_3-CP, and G_4-CN were killed by desensitization by denudation and the carcasses were buried under strict biosecurity management according to the protocols established by Fuentes Paredes et al.[22].

Validation of study quality and statistical analysis. Significance difference contrasts between groups were compared by ANOVA ($p<0.05$) using the SPSS v. 20 statistical programs, using a 4*3[32] multifactorial array design.

Results

At 4 weeks of study, a significant decrease and stability ($p<0.05$) of SBP, DBP, and MAP were observed in the hypertensive mice of G_1-MARA and G_2-MA, with the highest antihypertensive effect at 200 mg concentration (SBP 113.3±2.9, 114.5±2.1 mmHg), DBP (66.6±4.7, 66.5±2.9 mmHg) and MAP (123.3±2.2, 122.7±3.3 mmHg), while G_3-CP increased SBP, DBP and MAP values and G_4-CN showed values within the basal range, from the fifth week onwards G_1-MARA and G_2-MA showed increased blood pressure and hypertension and obesity were observed in the mice (Table 3).

With respect to hypercholesterolemia, the Swiss albino mice of G_1-MARA and G_2-MA showed statistical differences of significance ($p\geq0.05$) in stabilizing glucose and cholesterol at 4 weeks of study, with 200 mg concentration proving to be an efficient glucose stabilizer (89.0±1.0, 90.0±2.4 mg/dL) and cholesterol (192.6±1.2, 195.0±1.2 mg/dL), while in G_3-CP glucose and cholesterol values increased, in G_4-CN values within the basal range were observed. From the fifth week onwards, hypercholesterolemia was observed in G_1-MARA and G_2-MA mice, and obesity and diabetes were apparently observed in the mice (Tables 3 and 4).

Table 3 Means and standard deviation of systolic, diastolic and mean blood pressure at 6 weeks of treatment in hypertensive Swiss albino mice (n= 48)

Groups	Dose †	Week 1			Week 2			Week 3		
		PAS*	PAD*	PAM*	PAS*	PAD*	PAM*	PAS*	PAD*	PAM*
G_1-MARA	50	119.7± 2.8	77.2±4.9	136.6±5.7	119.5±2.0	71.0±6.0	130.7±5.6	122.0±4.5	74.7±2.0	135.7±3.4
	100	126.0± 4.2	78.5±2.8	141.5±2.1	122.7±2.7	70.5±3.1	131.3±3.6	114.7±5.3	74.5±3.1	131.8±3.4
	200	130.0±1.7	74.6±4.7	139.6±5.5	119.6±2.5	71.6±7.0	131.5±6.2	123.3±5.5	75.3±5.5	137.0±6.5
G_2-MA	50	117.7±0.5	79.0±1.6	137.8±1.6	118.0±3.3	70.2±2.6	129.2±3.8	124.7±5.4	72.0±5.7	134.3±8.2
	100	123.7±4.7	78.2±4.9	140.1±3.8	120.5±5.0	70.5±4.3	130.7±6.5	121.5±8.1	72.0±4.2	132.7±5.6
	200	123.2±4.5	74.7±3.3	136.3±5.0	119.7±2.7	70.5±4.2	130.3±4.1	116.2±6.6	72.2±4.7	130.3±8.0
G_3-CP	50	125.0±6.6	81.2±2.2	143.7±4.4	126.2±3.0	78.7±3.5	141.8±3.5	124.7±5.1	73.0±5.0	135.3±7.3
	100	124.0±0.8	79.0±0.8	141.0±1.2	126.7±0.5	80.5±0.8	143.8±1.3	126.2±0.9	75.5±1.2	138.6±1.5
	200	120.0±0.8	80.7±0.9	140.7±1.1	128.0±0.8	79.7±0.5	143.7±1.8	126.2±1.7	75.7±1.7	138.8±1.4
G_4-CN	50	120.2±6.1	76.0±5.2	136.1±6.8	121.5±3.1	70.0±3.5	130.7±4.3	115.5±4.6	72.5±4.6	130.2±3.2
	100	122.5±1.2	79.5±1.2	140.7±0.8	124.0±0.8	69.0±0.8	131.0±1.0	92.2±5.2	72.2±0.9	118.3±5.8
	200	121.5±2.3	79.2±0.9	140.0±1.3	121.7±1.2	67.5±0.5	128.3±0.9	116.2±1.8	71.5±1.9	129.6±4.2

Statistical difference of means within columns ($p<0.05$), Legend: MARA= passion fruit, MA= purple corn, PC= positive control with L-NAME, NC= negative control without L-NAME, * mmHg, † mg, SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure.

Table 3 Means and standard deviation of systolic, diastolic and mean blood pressure at 6 weeks of treatment in hypertensive Swiss albino mice (n= 48). (Continued)

Groups	Dose†	Week 4			Week 5			Week 6		
		PAS*	PAD*	PAM*	PAS*	PAD*	PAM*	PAS*	PAD*	PAM*
G_1-MARA	50	117.7±1.7	67.0±1.6	125.8±2.7	119.7±7.6	69.7±3.8	121.6±4.4	122.2±5.5	69.5±3.8	122.6±5.8
	100	115.2±1.3	70.5±2.1	140.6±2.2	124.2±6.6	74.0±1.4	123.1±2.2	126.0±7.6	78.5±3.0	120.5±3.7
	200	113.3±2.9	66.6±4.7	123.3±2.2	123.0±2.0	71.3±1.5	122.8±1.5	129.6±1.1	92.3±3.5	124.1±3.0
G_2-MA	50	118.5±4.1	69.2±4.7	128.5±1.8	124.5±1.7	94.0±2.4	129.2±2.7	127.5±2.6	88.0±3.1	127.7±2.2
	100	116.0±6.9	69.7±6.8	127.7±2.7	118.5±3.5	67.7±5.1	123.0±5.6	128.5±3.4	68.0±3.5	123.7±3.3
	200	114.5±2.1	66.5±2.9	122.7±3.3	117.0±4.5	67.0±4.7	121.5±5.5	131.0±3.9	89.7±1.2	127.7±2.5
G_3-CP	50	128.0±6.1	82.7±4.4	120.7±5.8	125.0±7.1	80.2±2.7	125.2±6.1	124.0±5.2	81.0±2.1	125.5±4.6
	100	127.0±2.8	93.2±2.7	122.7±1.1	128.2±1.3	91.2±0.9	126.3±1.4	128.7±0.9	69.2±0.9	128.6±1.2
	200	129.7±1.7	91.5±3.9	120.8±2.1	127.5±1.2	98.2±0.9	128.0±0.7	127.7±1.7	68.5±1.2	127.3±3.0
G_4-CN	50	116.0±6.4	68.2±1.2	126.2±4.7	114.5±4.9	66.5±4.7	123.7±4.8	116.0±4.0	67.5±2.3	125.5±2.8
	100	119.2±0.9	68.5±4.7	128.1±0.6	118.0±0.8	67.7±1.2	126.7±1.0	118.0±1.8	67.7±0.5	126.7±0.2
	200	116.5±5.7	69.0±4.3	127.2±1.1	118.0±0.8	67.5±0.5	126.5±0.7	118.7±0.5	68.0±0.8	127.3±0.8

Statistical difference of means within columns ($p<0.05$), Legend: MARA= passion fruit, MA= purple corn, PC= positive control with L-NAME, NC= negative control without L-NAME, * mmHg, † mg, SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure.

Discussion

The results showed a reduction and stability of SBP, DBP, and MAP at 4 weeks of treatment in G_1-MARA and G_2-MA mice, with 200 mg, while G_3-CP increased BP values and G_4-CN maintained the basal value, these results indicate that the leaves of MARA and MA contain available flavonoids[18,20], nitric oxide, anthocyanins[17,19], luteolin-6-C-chinovoside[33,34] which are precursors of vasodilators, diuretic action, urine flow, glomerular filtration and excretion of Na^+ and K^+ and in lyophilized forms are more effective[35]. Arroyo et al.[36] reduced SBP, DBP, and MAP in hypertensive rats with 1000 mg of hydroalcoholic extract of *Z. mays* L, Shindo et al.[34] reduced BP in hypertensive rats by administration of MA, purple sweet potato, and red radish, Flores Luna[15] reported significant changes ($p>0.05$) in SBP and DBP values in albino rats due to the effect of *P. edulis* and *Petroselinum sativum* leaves, our results are similar to those reported and differ from others. The novelty of the study was that the concentration (200 mg) and optimum time of stabilizing antihypertensive action of MARA and MA leave under the mixed maceration-lyophilization method, which appears to be an.

alternative for controlling hypertension in public and veterinary health, as long as controlled preclinical clinical studies are carried out in other animal species.

Table 4 Means and standard deviation of glucose and cholesterol concentration at 6 weeks of treatment in Swiss albino mice (n= 48)

Groups	Week 1			Week 2		Week 3		Week 4		Week 5		Week 6	
	Dose†	GLU*	COLE*	GLU*	COLE*	GLU*	COLE*	GLU*	COLE*	GLU*	COLE*	GLU*	COLE*
	50	139.7±2.9	196.0±4.8	121.0±2.4	194.2±4.7	109.5±2.5	189.2±7.9	99.2±3.0	196.5±1.2	108.5±1.5	181.2±1.9	110.2±1.5	197.2±1.1
G_1-MARA	100	132.0±1.7	196.7±1.2	121.2±1.7	192.5±1.5	116.5±1.3	198.5±4.5	98.2±2.1	181.7±1.5	111.5±1.3	194.5±1.5	116.0±2.7	199.5±2.5
	200	139.3±4.7	212.3±4.9	131.3±1.0	206.6±1.1	128.0±1.0	196.0±4.3	89.0±1.0	192.6±1.2	113.0±1.0	198.0±1.3	115.0±2.0	201.6±2.1
	50	94.7±3.4	194.0±3.9	99.5±1.1	192.2±4.7	96.7±1.3	201.2±8.9	90.7±2.9	194.0±2.8	96.7±2.3	200.2±1.9	98.7±3.9	202.2±2.7
G_2-MAÍZ	100	95.0±3.1	206.2±7.5	94.0±3.2	192.2±5.1	94.7±1.2	203.2±5.9	93.5±1.1	198.2±1.8	97.7±1.2	201.2±1.9	99.5±2.1	205.2±1.0
	200	98.5± 1.5	206.5±1.3	94.0±1.9	192.0±4.3	92.7±6.2	195.0±5.2	90.0±2.4	195.0±1.2	98.7±3.2	197.0±3.2	101.0±1.4	202.0±3.3
	50	129.0±1.6	199.5±6.2	123.2±1.2	208.0±6.4	116.0±1.2	204.2±1.0	103.0±3.2	191.7±2.1	108.0±1.2	202.2±2.0	110.0±2.2	204.0±3.4
G_3-CP	100	137.5±6.4	198.2±1.7	119.2±1.2	209.5±1.9	115.0±0.8	205.5±4.0	110.7±2.2	195.2±0.9	118.0±0.8	208.5±2.0	119.7±1.2	209.5±2.9
	200	140.0±2.2	197.0±1.8	119.5±2.0	212.7±2.6	108.7±1.7	198.0±2.1	115.2±2.5	195.7±2.0	117.7±1.7	203.0±2.1	118.2±2.0	205.7±2.6
	50	106.0±1.2	185.2±9.2	95.2±1.2	186.2±3.5	91.0±1.0	188.7±9.7	88.2±1.2	185.7±1.0	89.0±1.0	182.7±1.7	87.2±2.2	181.2±1.5
G_4-CN	100	109.5±6.4	192.5±3.1	93.5±3.0	186.2±1.5	91.2±3.3	188.2±1.7	90.2±1.4	186.5±2.3	89.2±1.3	180.2±1.3	91.2±1.2	182.2±1.3
	200	105.2±4.5	189.0±4.0	96.2±5.1	188.0±2.1	93.5±5.8	186.7±2.2	94.0±2.2	186.0±1.4	93.5±1.8	185.7±1.2	94.1±2.0	186.0±1.1

Statistical difference of means within columns ($p<0.05$), Legend: MARA= passion fruit, MA= purple maize, PC= positive control with L-NAME, NC= negative control without L-NAME, GLU = glucose, COLE = cholesterol, * mg/dL, †

A palliative decrease in glucose and cholesterol was observed from the second to the third week in G_1-MARA and G_2-MA, the fourth week it decreased significantly and stabilized at normal values (basal), resulting in 200 mg with greater effectiveness in both groups, the G_4-CN remained within the normal-basal value and in G_3-CP after induction of L-NAME, no adverse effects were evident and would be related to the content of phenolics, salicylic acid, fats, resins and saponins[17,18] which are oxygen free radical scavengers and contribute as stabilizers to hypercholesterolemia and hyperglycemia, a critical role in the pathogenesis of cardiovascular disease[13,17,37].

Ravi et al.[38] reported lipid-lowering activity in *Eugenia jambolana* extract, Arroyo et al.[36], observed cholesterol and glucose lowering with *Z. mays* L extracts in hypercholesterolemic rats, Gorinstein et al.[39], reduced plasma lipids in rats treated with phenolic compounds and Numan Ahmad & Rabah Takruri Numan[40] reduced serum glucose and lipids with wheat bran in rats, results very similar to those obtained in this study, being very dependent on the concentration and time of action found, which would justify the flavonoids present in both plants studied (MARA and MA), leading to a decrease in the formation of free radicals by inhibiting NADPH oxidase and increasing the activity of nitric oxide synthase (eNOS), increasing nitric oxide-promoted vasodilation and providing the ability to respond to endothelial damage by increasing intracellular calcium, which stimulates vasodilation, thus explaining the antihypertensive activity in hypertensive mice.

The study showed a progressive increase in SBP, DBP, MAP, glucose, and cholesterol from the fifth week onwards in mice in the G_1 and G_2 groups, with extreme values in the sixth week with a greater effect at 200 mg, with hypercholesterolemic tendencies, hypertension, body mass development and adverse effects (vomiting, nervousness, allergy, and diarrhea), warranting discontinuation of treatment, similar behavior in G_3-CP (positive) and G_4-CN normal state, such results could argue for prolonged treatment, concentrations and routine doses that would imply a negative bioactive functionality of antioxidants, flavonoids as reported in Hesperidin and glucosyl hesperidin[40,41], inducing hypercholesterolemia and hypoglycemia in animal models[39,42].

Liu et al.[43], stabilized plasma glucose and lipids by supplementing chitosan in hypercholesterolemic rats, contradictorily resulting at 21 weeks in elevated body weight, para epididymal fat mass, and retroperitoneal fat mass, Ahmad & Amr[44], reported significant increases in very low-density lipoprotein-cholesterol (VLDL-C), atherogenic Index (AI) and serum total cholesterol (TC)/triglycerides (TG) by feeding defatted cocoa to obese rats at 10 weeks, Liu et al.[45], improved glucose and lipid metabolism in obese rats with *Gelidium amansii* extract, Yang et al.[46] with *Plantago ovata* peels optimized metabolic alterations in obese Zucker rats and contradictory, after 10 weeks of treatment, these scientific communications are similar to those reported in the research, indicating that freeze-dried extracts of MARA and MA leaves are precursors of cardiac hypotension and hypercholesterolemia in Swiss albino mice prolonged over 5 weeks of treatment.

Therefore, the research indicated that the lyophilized extract of *P. edulis* and *Z. mays* L, manifested to be excellent antihypertensive and hypercholesterolemia reducers and stabilizers, resulting in 200 mg with greater effectiveness in hypertensive Swiss albino mice, however, contradictory action was evidenced after 5 weeks. This research provides a possible therapeutic model for the use of MA and MARA leaves as antihypertensive and hypocholesterolemic stabilizers in veterinary medicine to counteract hypertension and minimize the indiscriminate use of drugs.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical considerations

The authors declare that they have considered the Code of Ethics for animal experiments, as described in the regulations: http://ec.europa.eu/environ-ment/

chemicals/lab_animals/legislation_en.htm, and have been supervised by the institutional ethics committee.

Contribution of the authors in the article

Carhuapoma Delacruz Víctor, methodological preparation, execution and writing of the article. *Capcha Huamani Mery*, acquisition and care of mice. *Valencia Mamani Nicasio*, data recording and processing. *Esparza Mario*, article quality assessment and translation.

Research limitations

There were no limitations to the research.

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