Pharmacogn. Commn. 2016; 6(2) 64-71
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
www.phcogcommn.org

Original Article

Study on the Temperature, respiratory rate, heart rate and Electrocardiogram of concomitant administration of *Maytenus macrocarpa* "Chuchuhuasi" and Propranolol in escalating doses

Zambrano-Huailla Rommel[1,2], Zambrano-Huailla Alexander[1,2], Wong-Peréz Karelya[1], García-Berrocal Jorge[1,2], Velit-Bassino Tiara[1], Zevallos-Gonzáles Dayana[1], Mujica-Calderón José[1], Salazar-Granara Alberto[1,2*]

[1]Research Centre of Traditional Medicine and Pharmacology of Facultad de Medicina Humana de la Universidad de San Martin de Porres (FMH-USMP), Avenida El Corregidor 1531, Urbanización Los Sirius, Las Viñas, La Molina, Lima, Perú. Extension 151, SOUTH AMERICA.
[2]Sociedad Científica de Estudiantes de Medicina de la Universidad de San Martin de Porres (SOCIEM-USMP), El Corregidor Avenue, Las Viñas, La Molina, Lima, Peru, SOUTH AMERICA.

ABSTRACT

Background: Previous studies of *Maytenus macrocarpa* "Chuchuhuasi" and linked species have corroborated their biological effects related to cardiovascular, respiratory, and others systems. This research has focused on evaluating the effect in the corporeal temperature, respiratory rate, heart rate and electrocardiogram of concomitant administration of "Chuchuhuasi" and propranolol in escalating doses. **Methods:** Albino rats were divided randomly into four control groups and five experimental groups. Temperature was measured by a digital thermometer, respiratory rate by direct-counting and electrocardiogram and heart rate by a Grass Polygraph. Rhythmic and arrhythmic electrocardiographic patterns were identified by a mathematical modeling of autocorrelation. The outcomes were acquired in periods of time but were analyzed using the average of the whole of the experiment. The result was applied to the following statistical tests: one-way ANOVA, Tuckey, Shapiro-Wilk, Pearson Correlation and Chi square with Yate's correction test. **Results:** The comparison between control and experimental groups showed a profile of raise in the corporeal temperature, then, for the respiratory rate the bias was to increase, in contrast, it was showed trend to decrease of the heart rate and an increase of voltages of p and r wave, also, an increment of p-r interval and presences of arrhythmias. **Conclusion:** This study revealed effects of concomitant administration of propranolol and *Maytenus macrocarpa* on temperature, respiratory rate, heart rate and electrocardiogram. In addition, it showed abnormalities in the electrocardiogram which were associated with arrhythmia patterns Thus, the usage of propranolol and *Maytenus macrocarpa* may negatively impact several aspects of the health of users of these drugs.

Key words: Chuchuhuasi, Propranolol, Heart rate, Respiratory rate, Temperature, Arrhythmia.

Correspondence:
Alberto Salazar Granara,
Avenida El Corregidor 1531, Urbanización Los Sirius, Las Viñas, La Molina, Lima, Perú. 511 3652300 Extension 151, Research Centre of Traditional Medicine and Pharmacology of Facultad de Medicina Humana de la Universidad de San Martin de Porres (FMH-USMP), Peru, SOUTH AMERICA.
Phone no: +51 983153407

E-mail: asalazarg@usmp.pe
DOI : 10.5530/pc.2016.2.3

INTRODUCTION

Maytenus macrocarpa is a medicinal plant belonging to genus Maytenus. This genus is distributed mainly in tropical and subtropical areas of America, Asia and Africa,[1] particularly Bolivia, Colombia, Ecuador and Peru. In the American countries in which M macrocarpa grows, it is important due to its medicinal properties.[2–5] In Peru, this plant is commonly called "Chuchuhuasi", and its medicinal properties are used by population of Peruvian Amazon as an anti-rheumatic, analgesic, anti-inflammatory, anti-diarrheal, anti-pyretic, anti-parasitic drug amongst other uses.[3,6–12] Its traditional uses are principally reported in native communities such as Cocama, Quechua, Shipibo-Konibo and Bora-Bora. In these communities, an infusion of the bark, root and leaves of "Chuchuhuasi" are one of the main forms of use for their medicinal needs.[2,3,6,7,9–14]

Several *in vivo* animal studies have shown different effects of Maytenus spp. Several species such as M. forsskaoliana, M. krukovii, M. ilicifolia, M. emarginata, M. heterophylla, M. senegalensis, M. obscura, M. rigida, M. undata etc have demonstrated biological effects on the central nervous system, respiratory rate, heart rate, blood pressure, temperature, diuresis, inflammation, pain, diarrhea, gastric ulcers and affect the development of pathogenic microorganisms.[15-27] Various studies report the effects of *M. macrocarpa* on nociception, intestinal motility, reproductive system, temperature, respiratory rate, heart rate and decrease of voltage of p wave and an increase of p-r interval of electrocardiogram.[28-31] Thus, an understanding about this medicinal plant has been growing in recent years. Its phytochemistry has been examined and it is known to contain multiple constituents including flavonoids, tannins, alkaloids, triterpenes and sesquiterpenes.[2,12,32–34]

However, some studies have shown fatal outcomes after intake of medicinal plants with drugs. For example, concomitant use of warfarin and plants such as ginkgo biloba and ginseng are contraindicated in order to reduce the number of deaths by bleeding.[35] In addition, a previous study has shown that concomitant administration of propranolol and Allium sativum (garlic) produce a decrease on blood pressure.[36] This result suggests a harmful effect of propranolol in cotreatments with these medicines. Other studies have demonstrated interactive effects between medicinal plants and drugs.[35-38] In this context, people who consume "Chuchuhuasi" and common drugs may ignore potential risks in reduction of therapeutic effectiveness, adverse reactions or even death.

Up to now, there is no research about the concomitant use of *M. macrocarpa* and propranolol. For this reason, this study has focused on evaluating the effects of concomitant administration of *Maytenus macrocarpa* and propranolol in escalating doses on the corporeal temperature, respiratory rate, heart rate, and electrocardiogram in albino rats.

MATERIALS AND METHODS

Study type

The experimental study was performed at the Research Centre of Traditional Medicine and Pharmacology of Facultad de Medicina Humana de la Universidad San Martin de Porres (FMH-USMP).

Plant material

M. macrocarpa plant material was collected in the Department of Ucayali (Pucallpa) by using the criteria of the Cerrate method:[39]

1. The vascular plant was collected at 08:00 hrs
2. It was put immediately into a field press
3. It was subsequently dried

Berta Loja, (biologist of The Research Centre of Traditional Medicine and Pharmacology, FMH-USMP) authenticated the identity of the plant by macroscopy and microscopy. The outcome was corroborated by specimens in the herbaria of the Universidad Nacional Mayor de San Marcos (USM) and Missouri Botanical Garden (MO). The identification as *Maytenus macrocarpa* was further verified by reference to Peruvian[40–42] and South American[43,44] flora references.

Animals

Wistar male albino rats were obtained from the Experimental Animal Centre of Universidad Peruana Cayetano Heredia, Peru. The average weight was 300 g for each animal. Rats were housed 2 per cage and maintained at ambient in the following conditions: temperature 22°C, humidity between 30 and 70%, 12 hrs light/dark cycles and noise levels less than 70 db. They were provided with balanced food and water *ad libitum*. Animals were deprived of food 12 h before the experiment. Individual animals were divided randomly between the groups.

All rodents were intraperitoneally treated. Six rodents were included for each experimental group; the groups were:

– GC or control group; pentobarbital sodium 30 mg/kg.
– GA or positive control or heart stimulant group; atropine sulphate 0.3 mg/kg.
– GPr or negative control or heart depressor group; propranolol 5 mg/kg.
– GM or *M. macrocarpa* group; ethanolic extract of *M. macrocarpa* 1500 mg/kg.

Experimental groups were:

- G1: *M. macrocarpa* 1500 mg/kg+propranolol 7 mg/kg
- G2: *M. macrocarpa* 1500 mg/kg+propranolol 9 mg/kg
- G3: *M. macrocarpa* 1500 mg/kg+propranolol 11 mg/kg
- G4: *M. macrocarpa* 1500 mg/kg+propranolol 13 mg/kg
- G5: *M. macrocarpa* 1500 mg/kg+propranolol 15 mg/kg

Experimental materials

Atropine sulphate (blister) 1 mg/1ml, code ISPF-13505/04, expiration 04/2013; propranolol (tablets) 40 mg, code EG-2406, expiration 04/2013; pentobarbital sodium (blister) 6.5%, code F.23.01.N.0042, expiration 07/2013; distilled water (blister), code 82100 613 990.

Preparation of aqueous solution of *Maytenus macrocarpa* ("Chuchuhuasi")

The collected leaves of *M. macrocarpa* were washed and sun dried in the shade for several days. The dried leaves were powdered in an electrical grinder. The powdered leaves were extracted with 70% ethanol at room temperature. The extractions were kept at room temperature and allowed to stand for several 7 days with occasional shaking and stirring. The extract thus obtained was filtered through filter paper (Whatman Fitter Paper No. 1). The filtrate was dried in an oven for 2 days. It was prepared as an aqueous solution (40%) of the filtrate of *Maytenus macrocarpa* by adding the appropriate volume of distilled water. The whole aqueous solution was mixed at 50°C (6 rpm) for half an hour. The resultant solution was divided into two components (solid and fluid). The solid component was filtered and removed. The fluid component was used for this research.[45]

Measurement of the physiological parameters

The measurement of physiological parameters was by standard techniques as described by Huaccho *et al*[31] Briefly:

– Each rodent was anesthetized with 30 mg/kg of pentobarbital sodium then placed in an incubator at an average temperature of 20°C.
– The Grass Polygraph (model 98k04826) was used to capture the electrical heart signals (lead II); these were processed by an application in Matlab with the following filters: Notch with a cut-off frequency of 60 Hz, a high pass with a cut-off of 0.2 Hz and low-pass with a cut-off of 40 Hz. The results were applied to the mathematical modelling of autocorrelation which was considered as digital processing of periodicity. We obtained two types of electrocardiographic patterns: rhythmic and arrhythmic. Rhythmic electrocardiography patterns were used to determinate the heart rate, electrocardiographic waves and p-r interval (Figure 1).
– We followed periods such as pre-dose (baseline), at 0, 5, 10, 15, 20, 25, 30, 45, and 60 min. For each period of time, the following tests were performed:

- Three measurements of corporeal temperature by a digital medical thermometer (non-contact) NC 100.
- Respiratory rate was measured by counting the number of respiratory movements for one minute.
- Captured heart electrical signals by the Grass Polygraph.

Ethics and research

This study was approved by the Institute of Research of FMH-USMP, which followed strictly the principles of research with laboratory animals: International Guiding Principles for Biomedical Research Involving Animal (1985).[46]

Statistical analysis

Quantitative variables were analyzed using one-way ANOVA, Tuckey, Shapiro-Wilk and Pearson Correlation. Qualitative variables were analyzed using chi square with Yate's correction test. Significance was defined as $p<0.05$, with a 95% confidence interval using the statistical package Graph Pad Prism 5.01.

RESULTS

Effects on temperature

All experimental groups showed variation on temperature. The Shapiro-Wilk test determined a Gaussian distribution. ANOVA and Tukey test showed statistical differences, particularly, between the next groups: GC compared to G 1 and 5; GA compared to G 1, 2, 4 and 5; GPr compared to G 3, 4 and 5; GM compared to G 3, 4 and 5 (Table 1). With respect to G5, it showed the greatest increase on temperature and G4 showed the greatest decrease on temperature.

Effects on respiratory rate

With reference to data from respiratory rate, the Shapiro-Wilk test determined a Gaussian distribution. ANOVA and Tukey test showed $p<0.05$,

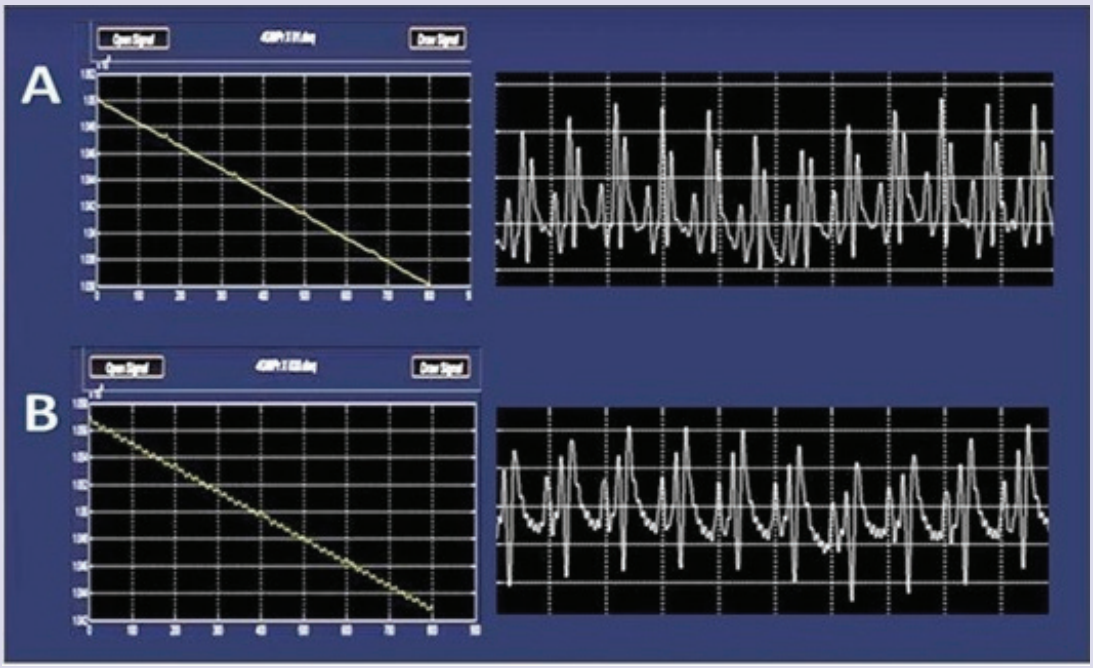


Figure 1: Digital processing of periodicity. Rhythmic electrocardiography patterns (A) and arrhythmic electrocardiography patterns (B)

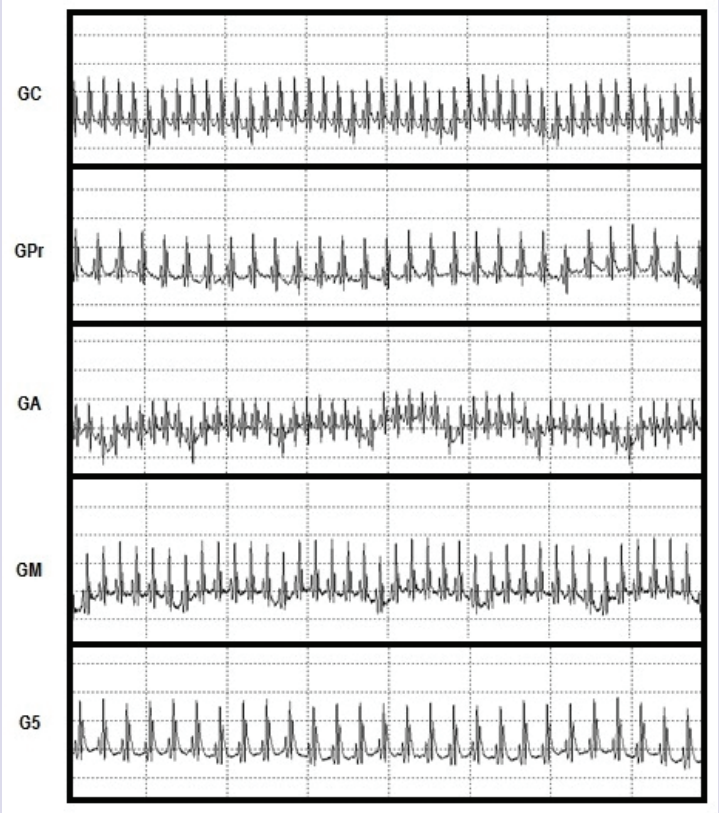


Figure 2: Comparison of heart rate in 8 sec. Control group, pentobarbital sodium 30 mg/kg (GC); propranolol group, propranolol 5 mg/kg (GPr); atropine group, atropine sulphate 0.3 mg/kg (GA); *Maytenus macrocarpa* group, ethanolic extract of *Maytenus macrocarpa* 1500 mg/kg (GM) and *Maytenus macrocarpa* + propranolol V group, ethanolic extract of *Maytenus macrocarpa* 1500 mg/kg and propranolol 15 mg/kg (G5)

Table 1: Comparison of Temperature, Respiratory rate and Heart rate means between experimental groups

Experimental groups	Temperature*	Respiratory rate†	Heart rate‡
	Mean ± SD	Mean ± SD	Mean ± SD
G1	31.19 ± 0,12	53.50 ± 2.95	272 ± 40.69
G2	30.96 ± 0.16	49.17 ± 1.94	294 ± 23.64
G3	30.59 ± 0.23	52.09 ± 4.01	275 ± 35.37
G4	30.24 ± 0.26	49.83 ± 1.61	267 ± 29.70
G5	31.37 ± 0.20	52.44 ± 3.52	259 ± 29.28
Control Group (GC)	30.53 ± 0.25	47.43 ± 2.23	305 ± 22.46
Atropine Group (GA)	30.60 ± 0.21	52.32 ± 1.50	346 ± 9.52
Propranolol Group (GPr)	30.92 ± 0.19	41.81 ± 3.20	309 ± 31.99
***Maytenus macrocarpa* Group (GM)**	30.91 ± 0.12	51.61 ± 3.26	338 ± 10.97

*ANOVA, $p<0.05$; Tukey, $p<0.05$, GC versus G1 and 5; GA versus G 1, 2, 4 and 5; GPr versus G 3, 4 and 5; GM versus G 3, 4 and 5.

† ANOVA, $p<0.05$; Tukey, $p<0.05$, GC versus G 1, 3, 4 and 5; GPr versus G 1, 2, 3, 4 and 5.

‡ ANOVA, $p<0.05$; Tukey, $p<0.05$, G5 versus GC, GPr, GA and GM.

Table 2: Comparison of arrhythmia and p and r waves and p-r interval

Experimental groups	Arrhythmia	P wave†	R wave‡	p-r interval¶**
		Mean ± SD	Mean ± SD	Mean ± SD
G1	YES*	0.12 ± 0.05	0.71 ± 0.14	0.0436 ± 0.0022
G2	NO	0.15 ± 0.05	1.01 ± 0.22	0.0466 ±0.0040
G3	NO	0.10 ± 0.05	0.75 ± 0.08	0.0420 ± 0.0019
G4	NO	0.08 ± 0.03	1.19 ± 0.12	0.0513 ± 0.0063
G5	NO	0.12 ± 0.02	0.77 ± 0.07	0.0470 ± 0.0014
Control Group (GC)	NO	0.05 ± 0.01	0.89 ± 0.03	0.0435 ± 0.0017
Atropine Group (GA)	NO	0.14 ± 0.02	0.68 ± 0.04	0.0426 ± 0.0017
Propranolol Group (GPr)	NO	0.09 ± 0.02	0.84 ± 0.11	0.0432 ± 0.0019
***Maytenus macrocarpa* Group (GM)**	NO	0.12 ± 0.02	0.74 ± 0.05	0.0417 ± 0.0016

* Chi-square test with Yates' correction=5.486. 1; $p=0.0192$, G1 versus GA.

† ANOVA, $p<0.05$; Tukey, $p<0.05$; GC versus G 1, 2, and 5.

‡ ANOVA, $p<0.05$; Tukey, $p<0.05$; G4 versus GC, GA, GPr and GM.

¶ ANOVA, $p<0.05$; Tukey, $p<0.05$; G4 versus GC, GP, GA, GPr and GM; G5 versus G.

**Pearson's correlation, $p<0.05$, $r=0.1210$.

specially, between the following groups: GC compared to G 1, 3, 4 and 5; GPr compared to G 1, 2, 3, 4 and 5 (Table 1). G1 showed the largest increase in respiratory rate.

Effects on heart rate

The Shapiro-Wilk test showed a Gaussian distribution for groups G 3 and 4. ANOVA and Tukey test showed $p<0.05$, particularly, the following groups: G5 compared to GC, GPr, GA and GM (Table 1). G5, particularly, showed the greatest decrease on heart rate. (Figure 2)

Effects on electrocardiographic patterns

From thirty minutes to the end of the experiment, arrhythmic patterns were registered in the electrocardiogram (Figure 1); Chi-square with Yates correction test showed $p<0.05$ between GA compared to G1 (Table 2). These results suggest that this concomitant administration could cause arrhythmia on rats.

Regarding the p wave, ANOVA and Tukey test showed $p<0.05$ for the following groups: GC compared to G 1, 2, and 5 (Table 2). All experimental groups showed an increase of voltage of p wave. With regard to r wave, the Shapiro-Wilk test showed non-Gaussian distribution for the following groups: G 3, 5 and GC. ANOVA, Kruskal-Wallis, and Tukey tests showed $p<0.05$, particularly in the following groups: G4 compared to GC, GA, GPr and GM. According to this outcome, G4 showed the greatest increase of voltage of r wave (Table 2). In relation to p-r interval, the Shapiro-Wilk test showed Gaussian distribution. The increase of p-r interval was correlated with doses of experimental groups, this was proved by Pearson correlation test; $r=0.1210$, $p<0.05$. ANOVA and Tukey test showed $p<0.05$ in the following groups: G4 compared to GC, GA, GPr and GM; and G5 compared to GM (Table 2). Both experimental groups showed the largest increase of p-r interval.

DISCUSSION

"Chuchuhuasi", a traditional medicine plant that is well known in the Peruvian Amazon, is used for its reported effects on pain, rheumatism, ulcers, etc.[6–14] Previous studies of "Chuchuhuasi" have shown outcomes such as anti-nociception,[28] stimulating intestinal motility,[29] bradycardia[31]

and several others biological effects.[30,31]

In recent years, there has been an increasing amount of literature on the interaction between some drugs and medicinal plants and its adverse reactions[35–38] However, there is no evidence that *Maytenus macrocarpa* could have effects with concomitant administration of drugs such as propranolol.

Studies have reported a dual effect of propranolol on temperature.[47–49] In contrast, "Chuchuhuasi" and other Maytenus spp. have shown a decrease of corporeal temperature.[15,31] In the present study, G4 showed a decrease of temperature, possibly due to a hypothermic effect carried out by propranolol and its effect on the thermogenesis of rats.[50] In contrast, G5 induced an increase of temperature. This result may partly be explained by a decrease in tail blood flow by propranolol, which could decrease an effective mechanism in heat loss of rats.[50] In both outcomes, the effect of propranolol could be influenced by "Chuchuhuasi".

It has been reported that "Chuchuhuasi" and propranolol reduce respiratory rate[31,51] In contrast, the result of G1 presented the largest increase of respiratory rate. This result is likely to be related to an increase of temperature of propranolol and "Chuchuhuasi". Both mechanisms could increase respiratory rate in order to maintain normal temperature range in rats.[50]

The negative chronotropic effects of propranolol on the heart are well known.[52] According to several studies, M. krukovii, *M. macrocarpa* and M. Forsskaoliana have similar effects.[15,16,31] In contrast, individual this study has demonstrated an opposite effect. Nonetheless, all experimental groups showed a decrease in heart rate in our study. The observed decrease in heart rate could be attributed to sympatholytic effect of propranolol, which may be influenced by "Chuchuhuasi". A possible explanation for this might be the regulation of some potassium channels in heart by some terpenoids which may be present in this medicinal plant.[12,34,53,54]

The results obtained from the electrocardiogram were noteworthy because they could present a possible deleterious effect. An increase of voltage of p wave was observed in all experimental groups. This increase in p wave voltage indicates an intensification of the auricular pressure systole,[55] which could be a consequence of a negative chronotropic and inotropic effect produced by propranolol, and possibly also by "Chuchuhuasi".[15,16,51,52] If we compared the human intake, it could mean that the concomitant administration could increase the cardiac output and could be harmful to the people who suffer a heart disease.

Propranolol and "Chuchuhuasi" decrease the voltage of r wave.[31] In our research, G4 showed the largest increase of r wave, suggesting a possible positive inotropic action. This hypothesis might be explained by the activation of baroreflex and secretion of catecholamines carried out by propranolol, and also by "Chuchuhuasi", on peripheral vascular resistance.[15,16,51,52]

Another outcome was an increase of p-r interval for G4 and G5. This finding was unexpected and suggests a decrease of electrical conduction induced by propranolol on the heart.[52] For "Chuchuhuasi", a similar effect may have been produced by sesquiterpenes.[12,34,53,54] This observation may support the hypothesis that the concomitant administration of propranolol and "Chuchuhuasi" could have deleterious effect on heart because an increase of p-r interval which is typical in heart block[56] could produce arrhythmias.[57] Moreover, the electrocardiogram revealed readings compatible with arrhythmia in G1 (Table 2). These have not been analysed further.

The study was principally focused on determining the possible effect of concomitant administration of "Chuchuhuasi" and propranolol. The study makes no attempt to specify the component of *Maytenus macrocarpa* that could produce the possible interaction with propranolol, and as a result, the adverse effects on rats. Our hypotheses were based on previous studies of *M. macrocarpa*. Future research should focus on a phytochemical analysis of the *M. macrocarpa* extract.

One of the limitations with this research is that it does not measure blood pressure. Furthermore, it does not analyze others waves and intervals in electrocardiogram. Both measurements would be more useful to understand the effects on cardiovascular system and further studies are needed to address this. In spite of this, our findings enhance understanding of the effects of concomitant administration of medicinal plants and drugs. The most striking result to emerge from the data is the arrhythmic electrocardiography patterns. A work needs to be done to classify it. In summary, these findings are useful for understanding about possible adverse effects of the concomitant administration of "Chuchuhuasi" and propranolol. These effects could be more severe in people with cardiovascular disease. The current findings add to a growing body of literature on risk of the concomitant intake of medicinal plants and drugs,[35–38] further experimental investigations are needed to promote the rational use of the herbal medicine.

CONCLUSION

The present research has shown the effects of concomitant administration of propranolol and *Maytenus macrocarpa* on temperature, respiratory rate, heart rate and the electrocardiogram. Also, it revealed abnormalities in the electrocardiogram such as arrhythmias. These interactions may have adverse effects on the health of people who are co-administering propranolol and *Maytenus macrocarpa*. Further research is required to clarify the mechanism of each effect.

AUTHORS' CONTRIBUTIONS

Author contributions to the study and manuscript preparation are as follows. ZHR, ZHA, MCJ, and SGA conceived and designed the study. ZHR, ZHA, WPJ, GBJ, and ZGD performed the experiments. SGA and MCJ carried out the process of capture of heart electrical signals. WPJ, GBJ, VBT, and ZGD acquired of data. Statistical analysis: ZHR, ZHA, and SGA. All authors analyzed and contributed to data interpretation. SGA drafted the manuscript. All authors revised and approved the final manuscript.

ACKNOWLEDGMENTS

This research was supported by the authors and FMH-USMP. We would like to express our appreciation and thanks to Dr. Frank Lizaraso Caparo (Dean of the FMH-USMP), Dr. Benjamin Castañeda Castañeda (Past Director of the Research Institute of the FMH-USMP), Professor Angel Alvarado Yarasca and Professor Berta Loja Herrera (Research Centre of Traditional Medicine and Pharmacology of FMH-USMP), and technician Carlos Pante Medina (Laboratory of Pharmacology of FMH-USMP) for their collaborations.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ABBREVIATIONS USED

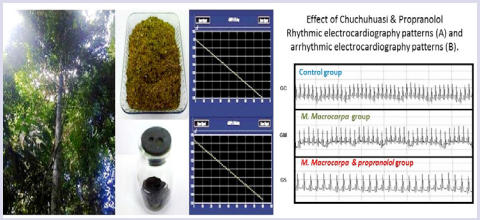
ANOVA: Analysis of variance; **GC:** Control group; **GA:** Atropine group; **GPr:** Propranolol group; **GM:** *Maytenus macrocarpa* group; **G1:** M. macrocarpa 1500 mg/kg+propranolol 7 mg/kg group; **G2:** *M. macrocarpa* 1500 mg/kg+propranolol 9 mg/kg group; **G3:** *M. macrocarpa* 1500 mg/kg+propranolol 11 mg/kg group; **G4:** *M. macrocarpa* 1500 mg/kg+propranolol 13 mg/kg group; **G5:** *M. macrocarpa* 1500 mg/kg+propranolol 15 mg/kg group.

REFERENCES

1. McKenna MJ, Simmons MP, Bacon CD, Lombardi JA. Delimitation of the Segregate Genera of Maytenus s. l. (Celastraceae) Based on Morphological and Molecular Characters. Syst Bot. 2011;36(4):922-32.
2. Pinedo MP. CHUCHUHUASI. In: Instituto de Investigaciones de la Amazonía Peruana, Editor. Plantas medicinales de la amazonia peruana: estudio de su uso y cultivo. 1st ed. Iquitos: Imprenta del Ejército; 1997. p.107-108.
3. Salazar-Granara A, Loja B, Rabanal A, Mestanza S, Heringman K, Pinedo D, *et al.* Comparación de los usos del chuchuhuasi (*Maytenus macrocarpa*) entre indígenas Bora-Bora de Loreto y chamanes de Lima (Perú). Rev Fitoter. 2013;13(1):149-57.
4. Moraes MR. Plantas medicinales de los Andes ecuatorianos. In: Botánica Económica de Los Andes Centrales, Editor. 1st ed. San Andres: Universidad Mayor de San Andrés; 2006:285-93.
5. Gonzalez J, Delle G, Delle F, Marini-Bettolò GB. Chuchuhuasha-A drug used in folk medicine in the amazonian and andean areas. A chemical study of maytenus Laevis. J Ethnopharmacol. 1982;5(1):73-7.
6. Stagegaard, J, Sørensen M, Kvist LP. Estimations of the importance of plant resources extracted by inhabitants of the Peruvian Amazon flood plains. Perspect Plant Ecol Evol Syst. 2002;5(2):103-22.
7. Sanz-Biset J, Campos-de-la-Cruz J, Epiquién-Rivera MA, Cañigueral S. A first survey on the medicinal plants of the Chazuta valley (Peruvian Amazon). J Ethnopharmacol 2009;122(2):333-62.
8. Jernigan K. Plants with histories: The changing ethnobotany of Iquito speakers of the Peruvian Amazon. Econ Bot. 2012;66(1):46-59.
9. Kvist LP, Andersen MK, Stagegaard J, Hesselsøe M, Llapapasca C. Extraction from woody forest plants in flood plain communities in Amazonian Peru: use, choice, evaluation and conservation status of resources. For Ecol Manag. 2001; 150(1):147-74.
10. Sanz-Biset J, Cañigueral S. Plant use in the medicinal practices known as "strict diets" in Chazuta valley (Peruvian Amazon). J Ethnopharmacol. 2011;137(1):271-88.
11. Polesna L, Polesny Z, Clavo MZ, Hansson A, Kokoska L. Ethnopharmacological inventory of plants used in Coronel Portillo Province of Ucayali Department, Peru. Pharm Biol. 2011;49(2):125-36.
12. Mejia K, Rengifo E. Chuchuhuasi. In: Instituto de Investigaciones de la Amazonia Peruana, Editor. Plantas Medicinales de Uso Popular En La Amazonia Peruana, 2nd edition. Lima: Agencia Española de Cooperación Internacional para el Desarrollo; 2000. p. 71-2.
13. Schultes RE, Raffauf RF. The Healing Forest: Medicinal and Toxic Plants of the Northwest Amazonia. Environ Conserv. 1990;3:284-5
14. Kvist LP, Nebel G. A review of peruvian flood plain forests: ecosystems, inhabitants and resource use. For Ecol Manag. 2001;150(1):3-26.
15. El Deeb KS, Al-Haidari RA, Mossa JS, Ateya A-M. Phytochemical and pharmacological studies of Maytenus forsskaoliana. Saudi Pharm J. 2003;11(4):184-91.
16. Salazar A, Milla D, Morales V, Velarde L, Villanueva A, Segura K. Evaluación de la actividad hipotensora del Maytenus krukovii (chuchuhuasi) en rata consciente. Rev Horiz Méd. 2008;8(2):41-7.
17. Crestani S, Rattmann YD, Cipriani TR, de Souza LM, Iacomini M, Kassuya CAL. A potent and nitric oxide-dependent hypotensive effect induced in rats by semi-purified fractions from Maytenus ilicifolia. Vascul Pharmacol. 2009;51(1):57-63.
18. Leme TS, Prando TB, Gasparotto FM, de Souza P, Crestani S, de Souza LM. Role of prostaglandin/cAMP pathway in the diuretic and hypotensive effects of purified fraction of Maytenus ilicifolia Mart ex Reissek (Celastraceae). J Ethnopharmacol. 2013;150(1):154-61.
19. Vineela P, Sandhya M. Evaluation of antipyretic activity of polyphyto leaf extract of *Cocculus hirusitus* and Maytenus emarginata. Int J Pharm Technol. 2012;4(3):4825-30.
20. Da Silva G, Taniça M, Rocha J, Serrano R, Gomes ET, Sepodes B, *et al. In vivo* anti-inflammatory effect and toxicological screening of Maytenus heterophylla and Maytenus senegalensis extracts. Hum Exp Toxicol. 2011;30(7):693-700.
21. Alajmi MF, Alam P. Anti-inflammatory activity and qualitative analysis of different extracts of Maytenus obscura (A. Rich.) Cuf. by high performance thin layer chromatography method. Asian Pac J Trop Biomed. 2014;4(2):152-7.
22. Martins MV, Estevam CDS, Santos ALLM, Dias AS, Cupertino-da-Silva YK, Araújo-Júnior JX. Antinociceptive effects of an extract, fraction and an isolated compound of the stem bark of Maytenus rigida. Rev Bras Farmacogn. 2012;22(3):598-603.
23. Ahmed AS, McGaw LJ, Eloff JN. Evaluation of pharmacological activities, cytotoxicity and phenolic composition of four Maytenus species used in southern African traditional medicine to treat intestinal infections and diarrhoeal diseases. BMC Complement Altern Med. 2013;13(1):1-15.
24. Jorge R, Leite JP, Oliveira A, Tagliati C. Evaluation of antinociceptive, anti-nflammatory and antiulcerogenic activities of Maytenus ilicifolia. J Ethnopharmacol. 2004;94(1):93-100.
25. De Deus FAPN, de Fátima SGD, de Jesus CJ, Del CG, Salazar M, Duarte LP. Estudo fitoquímico do decocto das folhas de Maytenus truncata Reissek e avaliação das atividades antinociceptiva, antiedematogênica e antiulcerogênica de extratos do decocto. Quim Nova. 2007;30(4):842-7.
26. Mokoka TA, McGaw LJ, Mdee LK, Bagla VP, Iwalewa EO, Eloff JN. Antimicrobial activity and cytotoxicity of triterpenes isolated from leaves of Maytenus undata (Celastraceae). BMC Complement Altern Med. 2013;13(1):1-9.
27. Malebo HM, Wiketye V, Katani SJ, Kitufe NA, Nyigo VA, Imeda CP. *In vivo* antiplasmodial and toxicological effect of Maytenus senegalensis traditionally used in the treatment of malaria in Tanzania. Malar J. 2015;14(1):1-7.
28. Robles-Pizarro V, Tarqui-Cabrera L, Rodríguez-Collazos N, Morales-Chau A, De La Cruz-Manyari J, Ríos-Melgar K. Efecto antinociceptivo del extracto etanólico de las hojas de *Maytenus macrocarpa* (Ruiz and Pav.) Briq."chuchuhuasi" mediante la prueba de contorsiones abdominales en ratones. Rev Horiz Méd. 2014;14(1):6-10.
29. Uscamaita AA, Palomares FC, Ramírez AA, Liñán MC, Huamán C, Castro JMM. Acción del extracto etanólico de las hojas de *Maytenus macrocarpa* (Ruiz. Pav.) Briq."chuchuhuasi" sobre la motilidad intestinal. Rev Horiz Méd. 2013;13(2):6-11.
30. Acosta LG, Vásquez J, Núñez V, Pino J, Shiga B. Efecto de *Maytenus macrocarpa* Chuchuhuasi en el sistema reproductor masculino del ratón (Mus musculus). Rev Peru Biol 2013;20(3):223-6.
31. Huaccho JJ, Cavero ES, Quezada MA, Lara AM, Lluen SE, Paragulla AA. Efectos sobre la temperatura, frecuencia respiratoria, frecuencia cardiaca y electrocardiograma de *Maytenus macrocarpa* (Ruiz and Pav.) Briq.(chuchuhuasi). Rev Cubana Plant Med. 2012;17(3):233-43.
32. Brack A. In: Brack A, Editor. Diccionario enciclopédico de plantas útiles del Perú. Cuzco, 1st ed. Lima: Centro de Estudios Regionales Andinos Bartolomé de las Casas; 1999. p. 556.
33. Spivey AC, Weston M, Woodhead S. Celastraceae sesquiterpenoids: biological activity and synthesis. Chem Soc Rev. 2002;31(1):43-59.
34. Niero R, de Andrade SF, Cechinel FV. A review of the ethnopharmacology, phytochemistry and pharmacology of plants of the Maytenus genus. Curr Pharm Des. 2011;17(18):1851-71.
35. Hussin AH. Adverse effects of herbs and drug-herbal interactions. Malays J Pharm. 2001;1(2):39-44.
36. Asdaq SM, Inamdar MN. Pharmacodynamic and Pharmacokinetic Interactions of Propranolol with Garlic (Allium sativum) in Rats. Evid Based Complement Alternat Med. 2011;2011:1-11.
37. Fugh-Berman A. Herb-drug interactions. Lancet. 2000;355(9198):134-8.
38. Izzo AA. Interactions between Herbs and Conventional Drugs: Overview of the Clinical Data. Med Princ Pract. 2012;21(5):404-28.
39. Cerrate E: Manera de preparar plantas para un herbario. Lima: Museo de Historia Natural, Universidad Nacional Mayor de San Marcos; 1969.
40. Brako L, Zarucchi JL. Catalogue of the Flowering Plants and Gymnosperms of Peru. Volume. 45;1993.
41. Macbride JF. Celastraceae, Flora of Peru. Publ Field Mus Nat Hist Bot Ser. 1951;13(02):259-70.
42. Vásquez Martínez R: Flórula de Las Reservas Biológicas de Iquitos, Perú: Allpahuayo-Mishana, Explornapo Camp, Explorama Lodge. Volume 63; 1997.
43. Funk VA, Hollowell TH, Berry PE, Kelloff CL, Alexander SN. Checklist of the Plants of the Guiana Shield (VENEZUELA: Amazonas, Bolivar, Delta Amacuro; GUYANA, SURINAM, FRENCH GUIANA). Contributions from the United States National Herbarium, Volume 55; 2007.
44. Killen TJ, Schulenberg TS. Conservation International, Washington, DC (EUA). Dept. of Conservation Biology: A biological assessment of Parque Nacional Noel Kempff Mercado, Bolivia. Washington, DC (EUA); 1998. [RAP Working Papers-Conservation International (EUA), vol. 10]
45. Vizcaino RLM, Torres CDIR, Pérez AM. Actividad antifungica del extracto total en etanol de la hojas frescas de Pedilanthus tithymaloides L Poit (ULTIMORRIAL). Sci Tech. 2007;13:155-9.
46. Institute for Laboratory Animal Research (U.S.) (Ed): Appendix D: International Guiding Principles for Biomedical Research Involving Animals (1985). In The development of science-based guidelines for laboratory animal care: proceedings of the November 2003 international workshop. Washington, D.C: National Academies Press; 2004:240-8.
47. Fregly MJ, Rowland NE, Cade JR. Relationship between drinking and increase in tail skin temperature of rats treated with L-5-hydroxytryptophan. Pharmacology. 1996;52(2):69-77.
48. Lin MT, Chandra A, Chern YF, Tsay BL. Effects of DL-propranolol on the thermoregulatory responses of rats at different ambient temperatures. Experientia. 1981; 37(4):370-1.
49. Horwitz BA, Hanes GE. Propranolol and pyrogen effects of shivering and nonshivering thermogenesis in rats. Am J Physiol. 1976;230(3):637-42.
50. Gordon CJ. Thermal biology of the laboratory rat. Physiol Behav. 1990;47(5): 963-91.
51. Zawoiski EJ. Central antihypertensive activity of propranolol. Arch Int Pharmacodyn Thérapie. 1980;243(1):111-31.
52. Brunton L, Chabner B, Knollman B. Agonistas y antagonistas adrenérgicos. In Goodman & Gilman: Las bases farmacológicas de la terapéutica. 12th edition. Edited by Westfall TC, Westfall E. México D.F.: McGraw Hill; 2011:310-20.

53. Calderone V. Large-conductance, ca(2+)-activated k(+) channels: function, pharmacology and drugs. Curr Med Chem. 2002;9:1385-95.
54. Imlach WL, Finch SC, Miller JH, Meredith AL, Dalziel JE. A Role for BK Channels in Heart Rate Regulation in Rodents. PLoS ONE. 2010;5(1):1-7.
55. Luna AB. Basic Electrocardiography: Normal and Abnormal ECG Patterns. Massachusetts: John Wiley and Sons. 2008.
56. Dubin D. Rapid Interpretation of EKG's: An Interactive Course. Florida: Cover Publishing Company; 2000.
57. Lorenzo-Velázquez B. Fármacos antiarrítmicos. In Farmacología: básica y clínica. 18th edition. Edited by Delpón E, Cosio FG, Caballero R. Buenos Aires: Ed. Médica Panamericana. 2008:374.

PICTORIAL ABSTRACT



SUMMARY

- Concomitant administration of propranolol and Maytenus macrocarpa produced changes on temperature, an increase of respiratory rate, a decrease of heart rate.
- Concomitant administration of propranolol and Maytenus macrocarpa produced changes in electrocardiogram such as an increase of voltages of p and r wave, an increase of p-r interval and arrhythmias.
- This study revealed effects of concomitant administration of propranolol and Maytenus macrocarpa on temperature, respiratory rate, heart rate and electrocardiogram. In addition, it showed abnormalities in electrocardiogram which was associated with arrhythmia patterns.

ABOUT AUTHORS

Rommel Zambrano Huailla: Is a Junior Researcher and student currently at 7th year of Medical School at Universidad de San Martin de Porres. He is member of the SOCIEDAD CIENTIFICA DE ESTUDIANTES DE ME-DICINA HUMANA (SOCIEM-USMP), which's main goal is to promote research. His clinical practices are at Hospital NacionalGuillermo Almenaralrigoyen. His research interests include the pharmacological effects of the Peruvian medicinal plants, especially cardiologic system, in order to improve existing information about the plants of common use in communities. He is also interested in cardiology, and hopes to keep developing researches in the following years of her medical education.

Alexander Zambrano Huailla: Is a Junior Researcher and student currently at 7th year of Medical School at Universidad de San Martin de Porres. He is member of the SOCIEDAD CIENTIFICA DE ESTUDIANTES DE ME-DICINA HUMANA (SOCIEM-USMP), which's main goal is to promote research. His clinical practices are at Hospital Jorge Voto Bernales C. His research interests include the pharmacological effects of the Peruvian medicinal plants, especially central nervous system, in order to improve existing information about the plants of common use in communities. He is also interested in neurology, and hopes to keep developing researches in the following years of her medical education.

Karelya Wong Peréz: Is a Junior Researcher and student currently at 7th year of Medical School at Universidad de San Martin de Porres. Her clinical practices are at Hospital NacionalDaniel AlcidesCarrión. Her research interests include the pharmacological effects of the Peruvian medicinal plants, especially central nervous system, in order to improve existing information about the plants of common use in communities. She is also interested in Internal Medicine, and hopes to keep developing researches in the following years of her medical education.

Jorge García Berrocal: Is a Junior Researcher and student currently at 7th year of Medical School at Universidad de San Martin de Porres.He is member of the SOCIEDAD CIENTIFICA DE ESTUDIANTES DE ME-DICINA HUMANA (SOCIEM-USMP), which'smain goal is to promote research. His clinical practices are at Hospital NacionalMaria Auxiliadora. His research interests include the pharmacological effects of the Peruvian medicinal plants, especially central nervous system, in order to improve existing information about the plants of common use in communities. He is also interested in Traumatology, and hopes to keep developing researches in the following years of her medical education.

Tiara Velit Bassino: Is a Junior Researcher and student currently at 7th year of Medical School at Universidad de San Martin de Porres. Her clinical practices are at Hospital NacionalDaniel AlcidesCarrión. Her research interests include the pharmacological effects of the Peruvian medicinal plants, especially central nervous system, in order to improve existing information about the plants of common use in communities. She is also interested in Internal Medicine, and hopes to keep developing researches in the following years of her medical education.

Dayana Zevallos Gonzáles: Is a Junior Researcher and student currently at 7th year of Medical School at Universidad de San Martin de Porres. Herclinicalpractices are at Instituto Nacional de Salud del Niño. Her research interests includ e the pharmacological effects of the Peruvian medicinal plants, especially central nervous system, in order to improve existing information about the plants of common use in communities. She is also interested in Gastroenterology, and hopes to keep developing researches in the following years of her medical education.

José Mujica Calderón: He is an electronic engineer and a Researcher at the Centro de Investigación de Medicina Tradicional y Farmacología of the Facultad de Medicina Humana de la Universidad de San Mar¬tin de Porres, Lima, Peru. His research interests are the signals processing, development alternatives of software for teach pharmacology and explore the pharmacological effects of the Peruvian medici¬nal plants.

Alberto Salazar Granara: Is a Professor in Pharma¬cology and Researcher at the Centro de Investigación de Medicina Tradicional y Farmacología of the Facultad de Medicina Humana de la Universidad de San Mar¬tin de Porres, Lima, Peru. His research interests are the pharmacological effects of the Peruvian medici-nal plants, especially central nervous system effects, anti-inflammatory and analgesic properties. He is also interested in discover off-label effect from the common antihypertensive, antidiabetic, antidepres¬sants and analgesic drugs. He is also interested in exploring the pharma¬cogenetic and pharmacokinetic highlight markers in Peruvian population, applied in important pathologies like Peruvian tuberculosis, hypertension, diabetes and others.