Pharmacogn J. 2018; 10(6) Suppl: s33-s37
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
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*Original Article*

# Antidepressant and Antipsychotic-like Activity of the Ethanolic Extract of the Leaves of *Maytenus macrocarpa*

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**ABSTRACT**

**Introduction:** *Maytenus macrocarpa* (Chuchuhuasi) is an Amazonian Peruvian traditional plant, traditionally used as anti-inflammatory, antipyretic, antihemorrhagic and antidiarrheic agent. Also, chuchuhuasi is known as a master plant, attributing to it properties in the central nervous system. In addition, depression is a disorder of the mood that cause disability to millions of people around the world. For this reason, the aim of this study was to determinate the antidepressant and antipsychotic-like activity of the ethanolic extract of *Maytenus macrocarpa*. **Methods:** It was used the ethanolic extract of the leaves of *Maytenus macrocarpa* (EELMM) in female mice at the experimental model of the Forced Swim Test described by Porsolt. As control, it was used distillate water, fluoxetine and haloperidol. **Results:** The immobility time of the groups of EELMM has a mean of 38.26 ± 21.57, 84.32 ± 26.68 and 32.17 ± 25.55 for the doses of 750, 1000 and 1250 mg/Kg respectively; and the immobility time had a median of 7.5 [4.07 – 20.3] and 20.93 ± [17.63 – 23.75] for the doses of 500 mg/Kg and 1500 mg/Kg. It was seen a positive dose-response between the dose of 500 to 1000 mg/Kg (Pearson correlation of r=0.8339 and R=0.6954) and a negative dose-response between the dose of 1000 to 1500 mg/Kg. (Pearson correlation of r= -0.7590 and R= 0.5760). **Conclusion:** It was demonstrated the antidepressant-like activity of the ethanolic extract of the leaves of *Maytenus macrocarpa* with a dose of 500 mg/kg and an antipsychotic-like activity with a dose of 1000 mg/kg.

**Key words:** Chuchuhuasi, Depression, Forced swim test, Haloperidol, Fluoxetine.

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**History**
- Submission Date: 21-04-2018;
- Review completed: 28-06-2018;
- Accepted Date: 07-09-2018

**DOI : 10.5530/pj.2018.6s.6**

**Article Available online**
http://www.phcogj.com/v10/i6s



## INTRODUCTION

The medicinal plants are ancestrally used, they belong to the therapies with medication according to the document of Strategies about Traditional Medicine 2014-2023 of the World Health Organization. Also, at the same document, it is urged the promotion of research on traditional medicine with the purpose of achieve its rational and safe use.[1]

One of the native Peruvian medicinal plants is "chuchuhuasi", whose scientific name is *Maytenus macrocarpa* (Ruiz and Pav.) Briq.[2] which is one of the 4400 peruvian species of medicinal plants.[3] Chuchuhuasi has a big tree from the *Celastraceae* family and is native of the amazon. Its branches are whorled and its leaves coriaceous, oblong-lanceolate or elliptical, acuminate, emarginated and glossy in the beam that have 10 to 20 cm. long and it has axillary inflorescence. It is traditionally used for its analgesic, antipyretic, antidiarrheic and antihemorrhagic at postpartum properties among others.[2,4-5] Also, Chuchuhuasi is part of a selected group of Peruvian plants named master plants, as ayahuasca, coca, among other. These plants are used to heal a person by taking it to high levels of the consciousness, coming into contact with the spiritual world; this is why these plants are probably attributed effects at central nervous systems as psychotropic and hallucinogens.[6–9]

Laboratory studies in rodents have confirmed biological effects of *Maytenus macrocarpa*, having reported intestinal stimulant activity, analgesic activity, bradycardia, decrease on the p-wave voltage at the electrocardiogram and alteration of sperm morphology.[10–13] Also, there is a study in rodents of the bark of *Maytenus macrocarpa* in which it was demonstrated neuroleptic effect, sedation and stereotypes, on the other hand, in another study of the root of *Maytenus obtusifolia* it was demonstrated the potential depressant effect over the central nervous system.[14-15]

Depression is a disorder of the mood that causes disability and affects more than 300 million people around the world. In Peru the prevalence of depression is at the range of 18, 2% to 21, 4%. The treatment of depression involves the use of antidepressant drugs, that currently have variable efficacy and adherence due to their adverse effects and pharmacology interactions; situation that promotes the search for new antidepressant.[16–18] There is an experimental model in rodents to evaluate the antidepressant and

**Cite this article:** Tácuna-Calderón AL, Huaccho-Rojas JJ, Zimic-Zare C, Pante-Medina C, Salazar-Granara A. Antidepressant and Antipsychotic-like Activity of the Ethanolic Extract of the Leaves of *Maytenus macrocarpa.* Pharmacog J. 2018;10(6)Suppl:s33-s37.

neuroleptic effect of chemical substance, which is called Forced Swim Test or Porsolt's test.[19-21] Many drugs were validated using this test, like fluoxetine, amitriptyline and haloperidol.[22-23] For this reason, this study was centered on exploring the antidepressant or antipsychotic-like activity of the ethanolic extract of the leaves of *Maytenus macrocarpa* in a model of forced swim in rodents.

## MATERIALS AND METHODS

### Type of Study, Space and temporality

It was a quasi-experimental double-blind study that was conducted at Traditional Medicine and Pharmacology Research Center.

### Vegetal Sample

Leaves of *Maytenus macrocarpa* was collected in the region of Madre de Dios (Sur-east, Peru). The plant was identified by a specialist from the Research Center. Voucher specimens are deposited at the Herbarium Vargas CUZ from the Universidad Nacional San Antonio Abad del Cuzco, numbers 3547 and 3653.

### Preparation of the Ethanolic extract of the leaves of *Maytenus macrocarpa* (EELMM)

The ethanolic extract was prepared with the following methodology:[24] the leaves collected were macerated for one week with ethanol at 70%. Then the mixture was filtrated and reduced at the rotavapor. The resulting was dried at the stove for 48 h and then stored at hermetic containers in the refrigerator for its future use. The final product was dissolved with distillate water at appropriate proportions for an administration volume less than 0.30 mL of the extract.

### Animal Sample

We used 88 female albino mice of BALB/c strain, with an average weight of 30g from the vivarium of the National Institute of Health of Peru.

The mice were prepared at the vivarium with the following conditions: a distribution of two mice per cage, cleaning cycles twice per day, a balanced diet, water *at libitum*, room temperature of 22°C (+/-1°C) or 71.6°F, humidity between 50 - 70%, light/darkness cycles of 12 h and noise levels less than 70 db.

### Chemistry Sample

Il was used Fluoxetine at tables of 20mg with S.R. NG-2276, Lab AC FARMA S.A., Series: 1060542, Exp.: 06-2015; Haloperidol ampoule of 5mg/1mL with S.R. Peru EG-674, Lab SANDERSON S.A., Series N°75FL2479, Exp.: 11-2016; and distillate water.

### Forced Swim Test in mice

This test was previously described by Porsolt and *col.*[22] The mice were carried to the laboratory two hours before the experimental. It was used transparent cylinders filled with water with 10 cm. depth; the temperature was set to 22°C (+/- 2°C). The cylinders were separated with dark panels. Sixty minutes before the swim, mice were administrated the respective substance orally. We placed to swim one mouse per cylinder at two cylinders simultaneously then we recorded six minutes of swimming, the first two of adaptation to the water and at the last four minutes was counted the immobility time.

### Design of experimental groups

We used 11 experimental groups with eight mice in each group. Group 1, was the control and didn't received any substance; group 2 was placebo and received 0.1ml of distillate water per each 10g of corporeal weight. The rest of the groups received the following substances: group 3, fluoxetine 40mg/Kg; group 4, fluoxetine 80mg/Kg; group 5, haloperidol 1mg/Kg; group 6, haloperidol 3mg/Kg; group 7, EELMM 500mg/Kg; group 8, EELMM 750mg/Kg; group 9, EELMM 1000mg/Kg; group 10, EELMM 1250mg/Kg; and group 11, EELMM 1500mg/Kg.

### Blind and control system

A double-blind system was applied in which the person that administrated the solutions and observed the reactions, didn't know the origin of these solutions.[25] Noise levels, humidity, room temperature and swimming tanks were monitored using VWR hygrometer model Thomas Traceable® Digital Humidity/Temperature Meter 35519-045 with a capacity to measure humidity from 60% to 82% and a temperature range from 5°C to 34°C, a sound level digital indicator Radio Shack 33-2055, able to measure from 60 to 120 Db, a insertion thermometer for water temperature of the forced swimming test, manufactured by Isolab with measurement capabilities from -50°C to 300°C, two fan heaters to maintain a stable temperature of the room, brand NF15C 1500 W Imaco with 2 heat intensities: 1000-2000W for an area of 15 $m^2$. Research assistants were trained to explore physical manifestations using the Pharmacology Lab Virtual Software[26] and Microlabs[27] and by an *in vivo* pilot.

### Ethics aspect of the research

The study was approved by the Research Institute of the FMH-USMP following the International Guiding Principles for Biomedical Research Involving Animals[28] and the Declaration of the Use of Animals in Biomedical Research.[29]

### Statistical Analysis

The immobility time was described as mean, median, standard deviation and interquartile range. It was applied the statistical test of Shapiro-Wilks to evaluate a normal distribution of the data, Kruskal-Wallis to evaluate difference between the experimental groups, Dunn's Multiple Comparison as a post hoc test and Pearson Correlation to set the curve dose-response of the EELMM. The Statistical significance was set for a p value <0.05 with a confidence interval of 95% (CI95%). It was used as informatics support Microsoft Excel 2010 and Graph Pad Prism 5.01 version.

## RESULTS

The immobility time of the groups of EELMM was 38.26 ± 21.57, 84.32 ± 26.68 and 32.17 ± 25.55 for the doses of 750, 1000 and 1250 mg/Kg respectively. In the groups that didn't have normal distribution the immobility time had a median of 7.5 [4.07 – 20.3] and 20.93 ± [17.63 – 23.75] for the doses of 500 mg/Kg and 1500 mg/Kg. (Table 1)

The Kruskal-Wallis Test, got a p<0.0001 with a CI95%. Later the groups were analyzed with the Dunn's multiple comparisons Test, finding a $p < 0.05$ for the following pairs of groups: control vs Fluoxetine, Control vs EELMM 500 mg/kg, Placebo vs Fluoxetine, Fluoxetine vs Haloperidol, Fluoxetine vs EELMM 1000 mg/kg, Haloperidol vs EELMM 500 mg/kg, EELMM 500 mg/kg vs EELMM 1000 mg/kg. For the rest of combinations, the Dunn's multiple comparisons Test got a $p > 0.05$ (CI95%) (Figure 1)

Pearson correlation showed a positive correlation between doses of 500 to 1000 mg/kg with an r=0.8339 and R=0.6954 with a CI95% (0.6689 a 0.9206) and a p<0.0001 (Figure 2). On the other hand, it was obtained a negative correlation between doses of 1000 and 1500 mg/Kg with an r= -0.7590 and R= 0.5760 with a CI of 95% (-0.8879 a -0.5196) and a p<0.001. (Figure 3)

## DISCUSSION

In this study, it was observed that extreme doses of 500 and 1500 mg/Kg of EELMM an effect similar to it was obtained with fluoxetine, while a

**Table 1: Descriptive data of the immobility time of the experimental groups.**

| Substance (mg/kg) | Mean ± SD* | Normal Distribution (SW test) * | Median [IQR]* |
|---|---|---|---|
| Blanco | 108.5 ± 24.46 | Yes | 103.4 [83.75 – 134.7] |
| Placebo | 62.22 ± 19.95 | Yes | 57.04 [48.45 – 77.55] |
| Fluoxetine 40 | 10.16 ± 11.05 | No | 6.02 [2.93 – 17.86] |
| Fluoxetine 80 | 5.08 ± 8.98 | No | 1 [0 – 6.5] |
| Haloperidol 1 | 113.53± 51.16 | Yes | 111.3 [79.72 – 163.7] |
| Haloperidol 3 | 109.90± 27.68 | Yes | 107.9 [87.47 – 127.6] |
| M. macrocarpa 500 | 12.15 ± 11.45 | No | 7.5 [4.07 – 20.3] |
| M. macrocarpa 750 | 38.26 ± 21.57 | Yes | 38.84 ± [19 – 54.29] |
| M. macrocarpa 1000 | 84.32 ± 26.68 | Yes | 84.34 ± [64.20 – 102.3] |
| M. macrocarpa 1250 | 32.17 ± 25.55 | Yes | 23.0 ± [9 – 61.13] |
| M. macrocarpa 1500 | 22.59 ± 8.12 | No | 20.93 ± [17.63 – 23.75] |

* SD: Standard deviation. SW test=Shapiro Wilks normality test. IQR=Interquartile range.

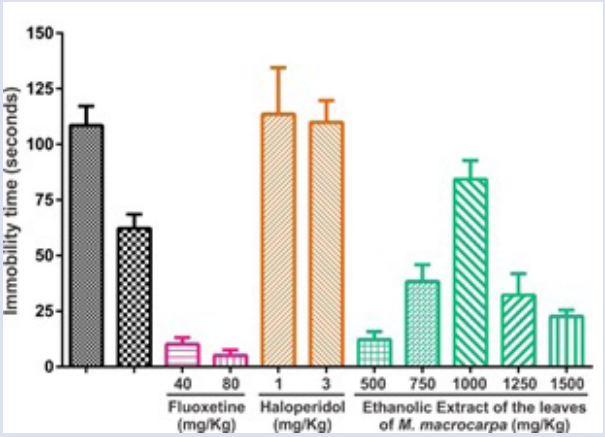


**Figure 1:** Immobility time of the Ethanolic Extract of the leaves of *M. macrocarpa* and control groups.

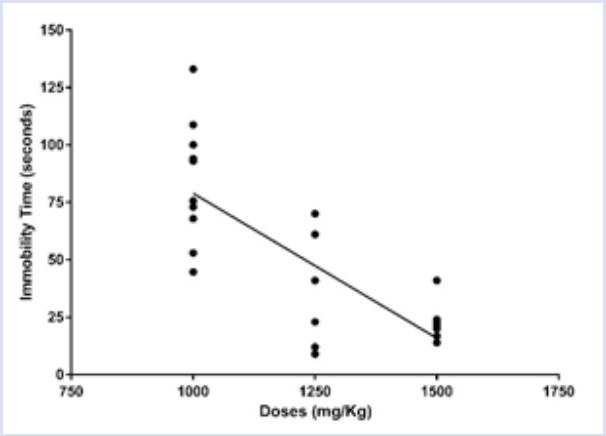


**Figure 3:** Doses-response of the immobility time of the Ethanolic Extract of the leaves of *M. macrocarpa* at doses of 1000 to 1500 mg/Kg.

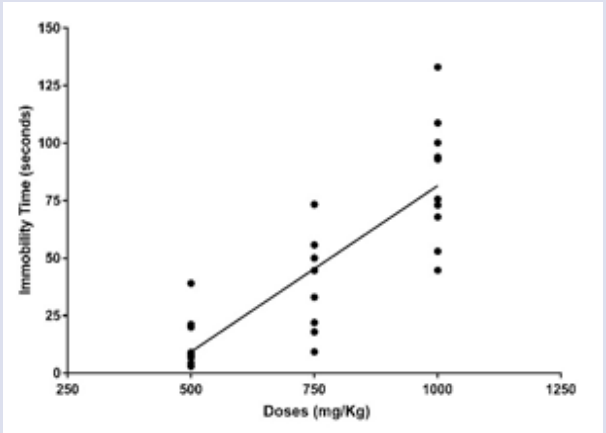


**Figure 2:** Doses-response of the immobility time of the Ethanolic Extract of the leaves of *M. macrocarpa* at doses of 500 to 1000 mg/Kg.

dose of 1000 mg/kg of EELMM the effect was similar to haloperidol. These results contrast with those obtained by a study conducted with an ethanolic extract of the bark of *M. macrocarpa* that evaluated the antipsychotic effect obtaining a negative dose-response curve, resulting that with the mayor dose of 1000 mg/kg the effect was similar to fluoxetine.[14] Also, at the study conducted with chloroform extract of the root of *Maytenus obtusifolia* MART, it was evidenced the neuroleptic activity at three experimental models with a unique dose of 125mg/kg, that differed with our study in which the lowest dose was similar to fluoxetine.[15] These changes could be to the multiple doses evaluation in a unique experimental model, that allowed us observed the dose- response curve of the EELMM. These results could expand the evidence of the Central Nervous system activity of the Maytenus genus and at the same time, the variability of this activity depending of the part of the plant that is use. (bark, leaves, root).[30]

The fluoxetine is a drug of the Selective Inhibitors of Serotonin Recaption family, whose site of action its located at the Synaptic cleft producing an increased and prolonged serotonergic transmission by stimulating many postsynaptic receptors.[31] Then, the antidepressant effect observed could be due to secondary metabolites present in the *Maytenus macrocarpa's* leaves, of which the most abundant are terpenes, among them the sesquiterpenes and terpenoids such as lupeol, friedeline and epifriedelinol,[32] which have been identified with antioxidant, anti-inflammatory, antinociceptive and antitumor properties, which will result in a neuroprotection effect of the central nervous system. Also, is was found that lupeol has medium activity of inhibition of the acetylcholinesterase, increasing the amount of this neurotransmitter and stimulating the secretion of other neurotransmitters such as catecholamines.[33–35]

In addition, the presence of other secondary metabolites as polyphenols[36] could support the antidepressant effect, because a study of polyphenols isolated front green tea demonstrated that these metabolites have an antidepressant effect (in the forced swim test and the tail suspension test) and that this effect was probably for and inhibition of the hypothalamic-hypophysis – adrenal axis by decreasing cortisol and ACTH levels.[37] On the other hand, the probably antipsychotic effect found at dose of 1000 mg/kg of EELMM could be to the action of a secondary metabolite unidentified yet, such the case of another plant of the family, the *Maytenus obtusifolia* MART and its metabolite linalool,[38] whose may decreased the

release of glutamate potassium dependent without the intervention of the basal release of glutamate, acting specifically at ionotropic receptor AMPA or NMDA type, which is the reason it would have a neuroleptic and anticonvulsant effect.[39–41]

The dual effect observed in our study according to the dose-response curve suggest us, that one of the secondary metabolites could have a selective affinity receptor dose-dependent, such is the case of the adrenaline that at low dose have major affinity to beta receptors and with higher doses major affinity to alfa adrenergic receptors.[42] Nevertheless, another theory to the dual effect, could be that recently it was described as part of the physiopathology of the depression and schizophrenia an increase of the proinflammatory component at the Central Nervous System, so that the application of anti-inflammatory therapies (effect attributed to metabolites of the EELMM) could be beneficial in this kind of diseases.[43-44]

### Limitations

The main limitation of our study was that we couldn't determinate the mechanism or specific place of action for the antidepressant and antipsychotic effects because there are a plenty of secondary metabolites present in *Maytenus macrocarpa*. For future studies, we suggest to evaluate the effect of each metabolite in the Central Nervous System as well as the specific mechanism of action by which these metabolites act.

## CONCLUSION

It was demonstrated a dual effect dose-dependent of the ethanolic extract of the leaves of *Maytenus macrocarpa* with a positive correlation between the dose of 500 to 1000 mg/kg and a negative correlation between the dose of 1000 to 1500 mg/kg. It was demonstrated the antidepressant-like activity of the ethanolic extract of the leaves of *Maytenus macrocarpa* with a dose of 500 mg/kg and an antipsychotic-like activity with a dose of 1000 mg/kg.

## ACKNOWLEDGEMENT

We want to thank the dean of our Medical School, Dr. Lizaraso Caparó; the past director, Dr. Castañeda; and the actual director of our Research Institute, Dr. Lizaraso Soto for their support to complete the present research work. Also, we are thankful to Professor Alvarado and Professor Loja for their help with the extract preparation and Botanical identification of the plant.

## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## ABBREVIATIONS

**EELMM:** Ethanolic Extract of the leaves of *Maytenus macrocarpa*; **SD:** Standard deviation; **SW test:** Shapiro Wilks normality test; **IQR:** Interquartile range.

## SUMMARY

The aim of the study was to determinate de antidepressant or antipsychotic-like effect of the ethanolic extract of the leave of *Maytenus macrocarpa*. For this reason, we used 88 albino female mice, at the experimental model of Porsolt, the Forced Swim Test. We used eleven experimental groups (one for blanco, one for distillated water, two for fluoxetine, two for haloperidol and five groups with the EELMM). The result was that at the dose of 500 mg/Kg of EELMM, we obtained an antidepressant-like effect and at the dose of 1000 mg/Kg of EELMM we observed an antipsychotic-like effect.

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**Cite this article:** Tácuna-Calderón AL, Huaccho-Rojas JJ, Zimic-Zare C, Pante-Medina C, Salazar-Granara A. Antidepressant and Antipsychotic-like Activity of the Ethanolic Extract of the Leaves of *Maytenus macrocarpa*. Pharmacog J. 2018;10(6)Suppl:s33-s37.