

Anti-Inflammatory and Neurobehavioral Effects of the Leaves from *Maytenus macrocarpa* (Ruiz and Pavón) Briquet in Mice

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ABSTRACT

Context: *Maytenus macrocarpa* (Chuchuhuasi) has long been employed in Peru as a traditional alternative therapy for several diseases, including cancer, arthritis and diarrhea. Recent studies show that several species of *Maytenus* have effects on nociceptive and inflammatory signaling, as well as toxic effects on behavioral neuronal pathways. **Aims:** The aim of this study is to evaluate the anti-inflammatory effects and neurobehavioral side manifestations of the leaf of *Maytenus macrocarpa* (Ruiz and Pavón) Briquet. **Methods and Materials:** Experimental study, double blind. 60 male albino mice strain BALB/c were divided in ten groups and each group, was orally feed with different doses of ethanolic extracts of *Maytenus macrocarpa* (500, 750, 1000, 1250 and 1500 mg/kg), others group received distilled water, caffeine 32 mg/kg, diazepam 32 mg/kg, diclofenac 15 mg/kg and the last group without substance. Neurobehavioral effects were assessed by the Irwin test. The anti-inflammatory activity was measured by the Carrageenan paw oedema test. Statistical analysis was performed with ANOVA test and Fisher exact test. **Results:** Anti-inflammatory effects of *M. macrocarpa* were observed in a non-significant trend of dose dependent form. *M. macrocarpa* displayed an anti-inflammatory effect at 1250 mg/kg and these effects were higher in comparison with diclofenac (74.14% vs 58.62%, one way ANOVA, $p < 0.05$). Neurobehavioral side effects secondary to *M. macrocarpa* therapy were also identified, these included excitation, abnormal gait, abdominal cramps, piloerection, stereotypes and scratching (Fisher exact, $p < 0.05$, CI 95%). **Conclusion:** *M. macrocarpa* leaves presented anti-inflammatory activity and concomitants neurobehavioral side effects.

Key words: *Maytenus*, Leaves, Anti-inflammation, Neurobehavioral manifestations, Diclofenac, Mice.

INTRODUCTION

Traditional use of the specie *Maytenus macrocarpa* (*M. macrocarpa*) is common among natives of the Amazon region in Peru. These populations describe therapeutic effects of *M. macrocarpa* against dysentery, hemorrhoids, rheumatism, arthritis, cleft nipples, sexual impotence, lumbago, bronchitis, diarrhea, flu and helminthic infections.¹⁻²

In Peru, *M. macrocarpa* is commonly known as “Chuchuhuasi”.² This plant has secondary metabolites like alkaloids, weak acids, catechins, coumarins and phenols.³

Studies in rodents treated with *M. macrocarpa* showed activity on intestinal motility,⁴ also on cardiovascular, respiratory and thermoregulatory systems.⁵ Other species how *M. heterophylla* and *M. senegalensis*, have shown anti-inflammatory activity,⁶⁻⁸ also antibacterial activity of *M. Blepharodes*,⁹ analgesic effect of *M. ilicifolia* and *M. aquifolium*.¹⁰⁻¹¹ and hypotensive action of

M. krukovii.¹² Moreover, *Maytenus*'s species such as *forsskaoliana* and *Blepharodes*, have shown to produce neuro-toxic effects like sedation and decreased respiratory rate.¹³

There are also experimental models to evaluate the anti-inflammatory activity, as carrageenan's plantar oedema test,^{6,14} and to evaluate the behavior of the rodent as Irwin test.¹⁵⁻¹⁷

Additionally, the guidelines of the recent strategic plan of the World Health Organization, about traditional medicine indicate that nations must increase the scientific evidence¹⁸ of medicinal plants. Overall the evidence is consistent with the anti-inflammatory role of *M. macrocarpa*, but also suggests the possibility of concomitant neurological side effects. This study aim focuses on exploring the anti-inflammatory and neurobehavioral activity of the ethanolic extract of the leaves of *Maytenus macrocarpa* in mice.

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SUBJECTS AND METHODS

Chemical and reagents

Diclofenac sodium, ampule of 75 mg/3 mL, Lot: 1031702, sanitary registration (SR) N°EG2537, Farmaindustria Company. Diazepam, ampule 10 mg/2mL, Lot: 10312081, SR N°535, Sanderson S.A. Laboratory. Caffeine CA205, CAS. 58-08-2, Spectrum Chemical Mfg. Corp. Carrageenan, SIGMA, type 4, 25g, Lot: 80K1334.

Plant material

Leaf from *M. macrocarpa* were collected in Madre de Dios (South-east, Peru). The plant was identified by Dra. Berta Loja Herrera (Centro de Investigación de Medicina Tradicional y Farmacología, FMH-USMP, Lima, 12, Perú). A voucher specimen was deposited at the Herbarium Vargas CUZ from the Universidad Nacional San Antonio Abad del Cuzco, numbers 3547 and 3653.

Ethanol extract preparation

The extract was prepared following the described methodology.¹⁹ Briefly, first, the ground dried leaf of *M. macrocarpa* (Ruiz and Pav.) was macerated in ethanol 70% for a week. Second, macerated was filtered and placed in an evaporator. Third, a product obtained was dried in an oven for a period of 48 hours and stored in airtight containers in the refrigerator. Forth, the final product was dissolved in distilled water at concentrations which ensured a volume of oral administration that did not exceed 0.25 mL.²⁰

Animals

60 male albino mice (*Mus musculus*) strain BALB/c were acquired from the National Health Institute's vivarium (Lima-Peru). Mice were kept at the vivarium of the School of Medicine of The Universidad de San Martín de Porres following the statements of the guidelines of Bioethics International Guiding Principles for Biomedical Research Involving Animals²⁰ and the guide management and care of laboratory animals from the National Health Institute of Peru.²¹ A couple of mice were isolated in cages, at a temperature of $22 \pm 3^\circ\text{C}$, humidity between 40 to 70%, cycles light/darkness of 12 h, the average noise level lower than 70 dB, with free access to water and were provided with feed, in amounts of 5 g per mouse, 2 times daily.

In vivo experiments

The study was approved by the Research Institute of the School of Medicine at the Universidad de San Martín de Porres, following the principles and guidelines for animal research laboratory referred by the International Guiding Principles for Biomedical Research Involving Animals²⁰ and the Declaration on the use of animals in Biomedical Research.²²

Irwin Test in mice

The test was conducted as an adaptation of the previously described.¹⁷ The substance was administered to mice in a double-blind manner. Subsequently, the animals were observed during a one hour in time ranges of 15, 30, 45 and 60 min. The endpoints analyzed were the presence or absence of the following: lethality, convulsions, Straub tail, sedation, agitation, abnormal gait (rolling or toes), jumps, motor incoordination, piloerection, abdominal cramps, stereotypies (sniffing, chewing or head movements), head shaking, itching and abnormal breathing. Moreover, a training process was performed, regarding of the explored manifestations, by the use of the Pharmacology Lab Virtual Software²³ and Microlabs,²⁴ and by an *in vivo* pilot.

Carrageenin-induced paw edema in mice

This was performed as previously indicated.¹⁴ The carrageenan 0.2% was injected subcutaneously into the mice plantar aponeurosis. The volume of the injected paw was measured before and after each injection with a LETICA digital plethysmometer (LE-750). Observations were made on 6 periods: pre-test (before the time of administration), 1, 2, 3, 4 and 5 hours after administration. The inhibitory activity was calculated using the formula:²⁵

$$\text{Percent inhibition (\%)} = \frac{((Ct - Co) \text{ control} - (Ct - Co) \text{ treated}) \times 100}{(Ct - Co) \text{ control}}$$

Ct = volume of the foot at the measurement point.

Co = paw volume before carrageenan administration (pre-test)

Experimental groups

Ten experimental groups were included, each made up of 6 mice. Group 1, did not receive any substance. Group 2, received distilled water orally at 0,1ml/10g of body weight. Group 3, received caffeine 32mg/kg p.o. Group 4 received diazepam 32 mg/kg p.o. Group 5 received diclofenac 15 mg/kg p.o. Groups 6 to 10 received ethanolic extracts of the leaf of *M. macrocarpa* at escalating doses of 500, 750, 1000, 1250 and 1500 mg/kg respectively.

Statistical analysis

For quantitative variables the following statistics were applied: 1 tail ANOVA test, paired Tukey test and Pearson Correlation Coefficient. For qualitative variables, Fisher's statistic was applied. It was considered statistical significance for $p < 0.05$ value and a confidence interval of 95%. It was used like informatics support Microsoft Office Excel 2013 and the Graph Pad Prism Software version 5.01.

RESULTS

M. macrocarpa effects on neurobehavioral

In general, the neurobehavioral presented by the effect of the leaf of *M. macrocarpa* were excitation, abnormal gait, abdominal cramps, piloerection and scratching. (See details in Table 1)

Furthermore, statistical significance (Fisher test, $p < 0.05$ and CI95%) were observed in specific doses when crossover with the control groups, so, It was observed excitation with leaf of *M. macrocarpa* at doses of 1250 and 1500 mg/kg, abnormal gait with *M. macrocarpa* at 750 mg/kg, abdominal cramps with *M. macrocarpa* at 1500 mg/kg, piloerection by *M. macrocarpa* at 750, 1250 and 1500 mg/kg and finally, scratching at 500, 1000 and 1500 mg/kg.

Anti-inflammatory activity of the leaf of *M. macrocarpa*

According to the paw edema, leaf of *M. macrocarpa* started their anti-inflammatory activity at first hour at doses of 1000 and 1500 mg/kg and this is maintained through the 5 hours, in addition, in the second, third and four hours were showed an anti-inflammatory effect at a dose of 1250 mg/kg. (See details in Table 2)

The method of the paw edema establish to analyze the third and fifth hour, because, in these checkpoints usually are presented the best efficacy, in this sense, in the third hour it was observed anti-inflammatory effect of the leaf of *M. macrocarpa* at doses of 1250 and 1500 mg/kg, but, in the fifth hour it was showed anti-inflammatory activity at doses of 1000, 1250 and 1500 mg/kg, inclusively, it was presented better effect than diclofenac at doses of *M. macrocarpa* of 1250 and 1500 mg/kg. (See details in Figure 1)

Also, there was calculated the percentage of the inflammatory inhibition, so, It was shown inflammatory inhibition with all doses of the leaf of

Table 1: Statistical significance of the Irwin Test.

Variables Grupos	Control	Placebo	Caffeine	Diazepam	Ethanollic extract from the leaves of <i>Maytenus macrocarpa</i>				
					500 mg/kg	750 mg/kg	1000 mg/kg	1250 mg/kg	1500 mg/kg
Excitation	NO	NO	YES	NO	NO ^a	NO	NO ^a	YES ^b	YES ^b
Abnormal march	NO	NO	NO	NO	NO	YES ^c	NO	NO	NO
Abdominal cramps	NO	NO	NO	NO	NO	NO	NO	NO	YES ^d
Piloerection	NO	NO	YES ^e	YES ^e	YES ^f	NO	NO	YES ^e	YES ^e
Estereotypes	YES ^g	YES ^g	YES ^g	NO	YES ^g	YES ^g	YES ^g	YES ^g	YES ^g
Scratch	NO	NO	YES ^h	NO	YES ^h	NO	YES ^h	NO	YES ⁱ

Excitation: (a) $p < 0.05$, Caffeine vs. *M. macrocarpa* 500 and 1000 mg / kg. (b) $p < 0.05$, Diazepam vs *M. macrocarpa* 1250 and 1500 mg / kg. **Abnormal march:** (c) $p < 0.05$, *M. macrocarpa* 750 vs control and placebo. **Abdominal cramps:** (d) $p < 0.05$, *M. macrocarpa* 1500 mg / kg vs control and placebo. **Piloerection:** (e) $p < 0.05$, placebo vs Caffeine, Diazepam, *M. macrocarpa* 1250 and 1500 mg / kg (f) $p < 0.05$ *M. macrocarpa* 500 mg / kg vs caffeine, control and placebo. **Stereotypes:** (g) $p < 0.05$ Diazepam vs control, placebo, caffeine, *M. macrocarpa* 500, 750, 1000, 1250 and 1500 mg / kg. **Scratching:** (h) $p < 0.05$ Control vs Caffeine, *M. macrocarpa* 500 and 1000 mg / kg (i) $p < 0.05$ *M. macrocarpa* 1500 mg / kg vs Diazepam.

Table 2: Anti-inflammatory activity of the ethanollic extract of *Maytenus macrocarpa* leaves

TRATAMIENTO	DOSE (mg/kg)	PRE-TEST	1H	2H	3H	4H	5H	% Inhibition Percentage
Control	-	0,147 ± 0,03	0,215±0,02*	0,235±0,05***	0,253±0,07***	0,242±0,07***	0,243±0,06***	-
Placebo	0,1ml/10g	0,152 ± 0,02	0,208±0,02**	0,247±0,03***	0,255±0,03***	0,253±0,03***	0,247±0,03***	-
Diclofenac	32	0,172 ± 0,02	0,225±0,04***	0,215±0,04**	0,222±0,02**	0,212±0,04	0,212±0,02*	58,62
<i>M. macrocarpa</i>	500	0,147 ± 0,02	0,202±0,03	0,215±0,04**	0,245±0,06***	0,230±0,07**	0,215±0,04**	29,31
<i>M. macrocarpa</i>	750	0,155 ± 0,02	0,180±0,04	0,200±0,03	0,247±0,04***	0,237±0,04***	0,213±0,03***	39,66
<i>M. macrocarpa</i>	1000	0,158 ± 0,03	0,215±0,05**	0,235±0,03***	0,260±0,06***	0,238±0,07***	0,225±0,05***	31,03
<i>M. macrocarpa</i>	1250	0,172 ± 0,04	0,195±0,06	0,217±0,05**	0,207±0,05*	0,213±0,04*	0,197±0,06	74,14
<i>M. macrocarpa</i>	1500	0,153 ± 0,03	0,237±0,04***	0,237±0,06***	0,230±0,05**	0,215±0,03*	0,218±0,02**	32,76

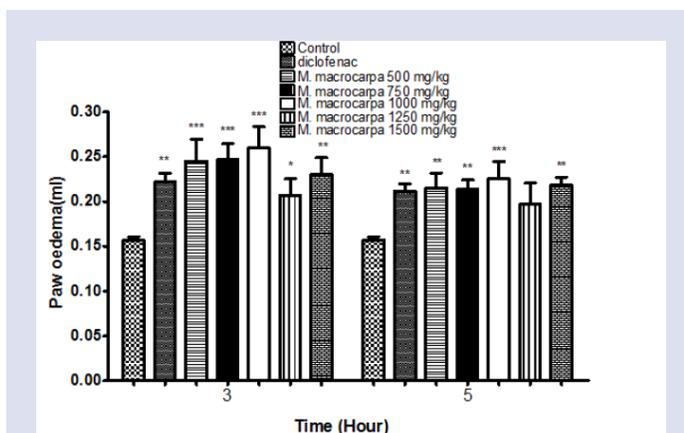


Figure 1: Anti-inflammatory activity of the ethanollic extract of the leaves of *M. macrocarpa*. n = 6, Values expressed as mean ± standard deviation * $p < 0.05$, ** $p > 0.01$ and *** $p < 0.001$ when compared to the control group.

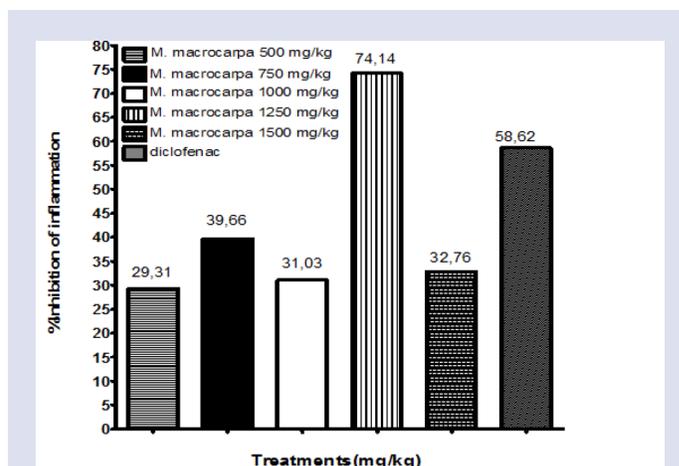


Figure 2: % inhibition of inflammation 5 hours after injection of Carageenan in the plantar region of the mouse.

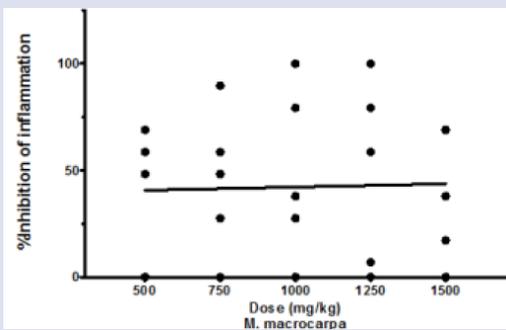


Figure 3: Correlation between the% inhibition of inflammation and the dose of *M. macrocarpa* mg / kg. ($r = 0.3214$) ($p = 0.86$) ($r^2 = 0.001$).

M. macrocarpa, moreover, at doses of 1250 mg/kg presented the best percentage of inflammatory inhibition, more than diclofenac. (See details in Figure 2)

Although it was not statistically significant, it was observed a trend of positive correlation in the inhibitor of the inflammation and escalated doses of the leaf of *M. macrocarpa*. (See details in Figure 3)

DISCUSSION

Investigations in species of *M. senegalensis*, *M. dark* and *M. heterophylla*,^{6,8,26} have demonstrated their anti-inflammatory effect in experimental rodent models. This study confirms the anti-inflammatory efficacy of the genus *Maytenus* and extends this to the leaves of *Macrocarpa* species.

The anti-inflammatory activity of the *macrocarpa* species could be due to its secondary metabolites, in this regard, previous studies report the presence of flavonoids, phenols, diterpenes, triterpenes and sesquiterpene and spermidinics alkaloids, among others.^{3,13,26-29} Subsequent studies are required to prove the possible anti-inflammatory effects of these molecules.

Contrasting the anti-inflammatory effectiveness of the genus *Maytenus*, model studies in carrageenan plantar edema, show a percent inhibition of swelling of 95% for *M. rigida* at doses of 750 mg/kg,³⁰ 55.9% for *M. dark* at 200 mg/kg,²⁶ *M. heterophylla* 51% at 120 mg/kg and 35% for *M. senegalensis* at 120 mg/kg,⁶ in contrast, this study shows maximum inhibition of 74.14% at 1200 mg/kg; these findings show variability in this pharmacological property, which could be due to the different origin of the species, the source region, the part of the plant used or the presence of a specific secondary metabolite.

As the carrageenan experimental model is initiated by tissue injury and activation of the arachidonic acid cascade,³¹ our findings suggest a peripheral mechanism for the action of the ethanolic extract from the leaves of *M. macrocarpa*.

In this study, it was observed that *M. macrocarpa*, induced behavioral effects in the rodent, which could be explained by blood-brain barrier cross-over of the metabolites.³²⁻³³ The neuro behavioral expressions by the action of the *M. macrocarpa* put on a state of alert the use of the plant as a natural anti-inflammatory medicine and present phenotypic characteristics of conventional drugs, where most, presents side effects are considered therapeutic.

In this regard, between the neurological manifestations observed, we can highlight the abnormal gait, which expresses an impairment of motor coordination system of the brain, typical of drugs such as anesthetics, benzodiazepines, alcohol, among others;³⁴ this is why, despite having confirmed an anti-inflammatory pharmacological property of *M. macro-*

carpa, with an important traditional root and scientific support, is advisable to alert the community, that they should consider common precautions of the drug, for the use of this medicinal plant.

CONCLUSION

The study probes the anti-inflammatory effect of the leaf of *M. macrocarpa* and concomitant neurobehavioral activity. Also, the therapeutic anti-inflammatory effect was observed in a range of doses at 1000 to 1500 mg/kg.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

ABBREVIATIONS

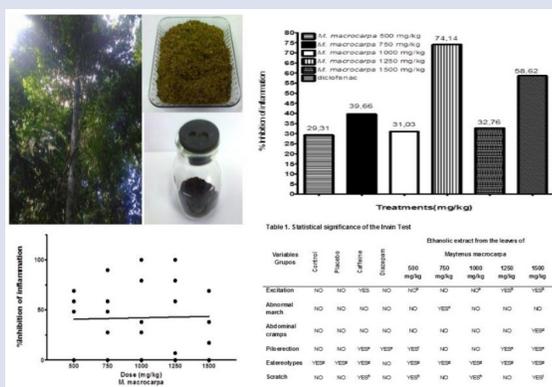
Maytenus macrocarpa: *M. macrocarpa*, Chuchuhuasi; **Maytenus heterophylla:** *M. heterophylla*; **Maytenus senegalensis:** *M. senegalensis*; **Maytenus ilicifolia:** *M. ilicifolia*; **Maytenus blepharodes:** *M. blepharodes*; **Maytenus aquifolium:** *M. aquifolium*; **Maytenus krukovii:** *M. krukovii*; **CT:** Volume of the foot at measurement point; **CO:** paw volume before carrageenan administration (pre-test); **Maytenus dark:** *M. dark*; **Maytenus rigida:** *M. rigida*.

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GRAPHICAL ABSTRACT



SUMMARY

- *Maytenus macrocarpa* leaves presented anti-inflammatory activity
- *Maytenus macrocarpa* leaves presented concomitants neurobehavioral side effects
- There is a need for further research in order to discover new effects and determine the safety of the plants.
- The anti-inflammatory effect of *Maytenus macrocarpa* was superior to diclofenac

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