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Research Article

Analgesic Effect of the Chloroformic Extract of *Aniba canelilla* "canelon" Bark in BALB/c Mice

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ABSTRACT

Background. Some diseases can cause intense pain, where pharmacological treatment with opioid analgesics is necessary, as in cancer. Despite advances in cancer treatment, pain is still a common symptom. Treatment is usually based on the use of opioids, but there is still some rejection because of their adverse effects or because of the delay in access to them. To evaluate the analgesic effect of *Aniba canelilla* "canelon" bark in mice to validate the above and consider it an alternative to existing palliative treatment in cancer patients. **Methodology.** The analgesic effect was evaluated according to the method of Koster et al. using 50 BALB/c mice distributed in groups of 07 mice each. Comparison was made with the standards Tramadol 50 mg/kg and Paracetamol 500 mg/kg administered orally, and acetic acid 0.8% was used intraperitoneally as a pain inducer. **Results.** The potent analgesic effect of the chloroformic extract of *Aniba canelilla* at 200mg/kg was observed, with an analgesic percentage of 98.87% with a mean number of writhes of 28.29 ± 5.44, being statistically significant to the other treatments ($p<0.01$). **Conclusions** The analgesic effect of the chloroformic extract of *Aniba canelilla* at 200mg/kg was determined.

Keywords: Pain, *Aniba canelilla*, Analgesic, Palliative.

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INTRODUCTION

Pain is a semiological aspect of the nervous system, indicating something is going wrong in the organism. It can feel like pricking, tingling, burning, or discomfort and can be acute or chronic, recurring or intermittent. It may be localized to one part of the body or widespread[1].

It is a symptom that helps diagnose a pathology; however, it can become a more complex situation involving the patient physically and emotionally, affecting their quality of life. Approximately 60% of the population lives with a type of pain, which does not distinguish between age or sex, affecting the individual, especially those who suffer from it permanently[2].

There is nociceptive pain, a consequence of a visceral lesion; neuropathic pain, derived from a lesion and alteration of the transmission of nociceptive information; post-surgical pain; pain in rheumatic patients where non-pharmacological and pharmacological therapy is applied, rationally using drugs such as Acetaminophen and NSAIDs, which allow the treatment to be carried out, but in the long term does not prevent adverse reactions such as gastrointestinal lesions, cardiovascular or renal discomfort; and pain in neoplastic patients, where opioid analgesia is used in most cases, also presenting discomfort due to its use, such as nausea and vomiting [3].

Progress is currently being made in learning more about pain due to its high frequency. Therefore, it is no longer seen as another sign of medicine but as a whole discipline. Thus, important research is being carried out to improve its management, and new analgesic drugs are being developed.

In the context of the use of natural products to relieve pain, many medicinal plants have shown to have important properties, for example, the widely used acetylsalicylic acid is extracted from willow, colchicine (*Colchicicum aulummnale*) used for the treatment of gout, coca (*Erythrotoxyum*) from which cocaine is derived, opium (*Papaver somniferum*) and cat's claw (*Uncaria tormentosa* and *Uncaria guyanensis*) [3]. *Aniba canelilla* "canelon" is a species of the Lauraceae family; it is an evergreen tree with aromatic bark and reddish-yellow flowers, typical of the Amazon region, being the main producer [4]. Among the natives of Rio Negro in Brazil, the bark is widely used as a stimulant, digestive, and antispasmodic agent, and is even useful for treating anemia. The Lauraceae family presents important components such as polyphenols, lignans, triterpenes, steroids, and many alkaloids [5].

This study was aimed at evaluating the analgesic effect of the chloroformic extract of *Aniba canelilla* "canelon" bark in BALB/c mice.

METHODOLOGY

Collection of the plant species *Aniba canelilla* "canelon"

The plant species *Aniba canelilla* "Canelon" was collected in the Madre de Dios region, Tahuamanu province, Iñapari district (10°56′42″S 69°34′38″W), located at 139 m.a.s.l. The plant sample was approximately 4 kg of stem. *Aniba canelilla* is a medium-to-large tree that can reach up to 35 m in height, with coriaceous and glabrous leaves, yellow flowers, fruit, and a berry. This tree produces excellent wood for construction and has a very aromatic bark for medicinal use[4,5].

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Chloroformic maceration of *Aniba canelilla* "canelon" bark

Aniba canelilla "canelon" bark was pulverized and placed in an amber glass bottle with 1.5 L chloroform; it was covered and macerated for 7 days with daily stirring. After this time, the solution was filtered using filter paper and cotton; the solution obtained was poured into a glass container (pyrex) and placed on a stove at 40°C for 7 days, thus obtaining a dry extract, which was stored and labeled for later experimental study.

Preliminary qualitative analysis of the chloroformic extract of *Aniba canelilla* "canelon" bark

Six test tubes were used, and approximately 2 mg of the sample was placed in each tube with ethanol (minimum amount). The staining and precipitation reagents were added, using approximately 1mL of reagent in the reactions of Bertrand, Dragendorff, Mayer, Popoff, Sonnenschein, and Wagner, to determine alkaloids for their promising effects in pain relief.

Pharmacological Method

The method of Koster et al. [6] was used to determine the analgesic effect of the chloroformic extract of *Aniba canelilla* "Canelon" bark.

Study Groups

Fifty BALB/c mice of both sexes, weighing 25 - 35 g (biological material) will be used. They will fast for 24 hours before starting the experiment, leaving them only with water *ad libitum*. These mice will be randomly distributed in groups of 07 mice each, as follows: (3 females and 4 males)

- Group 1 blank: Treated only with distilled water orally.
- Group 2 control: Treated only with acetic acid 0.8% intraperitoneally.
- Group 3 standard: Treated with Tramadol 50 mg/kg orally, then with acetic acid 0.8% intraperitoneally.
- Group 4 standard: Treated with Paracetamol 500 mg/kg orally, then with acetic acid 0.8% intraperitoneally.
- Group 5: Treated with chlorformic extract of *Aniba canelilla* "canelon": 50 mg/kg orally, then with acetic acid 0.8% intraperitoneally.
- Group 6: Treated with chlorformic extract of *Aniba canelilla* "canelon": 100 mg/kg orally, then with acetic acid 0.8% intraperitoneally.
- Group 7: Treated with chlorformic extract of *Aniba canelilla* "canelon": 200 mg/kg orally, then with acetic acid 0.8% intraperitoneally.

The inducing agent was acetic acid 0.8%. First, the drugs Paracetamol and Tramadol were administered orally to each mouse in their respective groups; after 10 minutes, the inducing agent was applied intraperitoneally; after 30 minutes (after using the acetic acid), the number of writhes that occurred in each mouse was counted. In the same way, the different concentrations of the chloroformic extract of *Aniba canelilla* "canelon" bark will be administered orally to each mouse in their respective groups; after 10 minutes, the inducing agent will be applied intraperitoneally; after 1 minute as a control point and 30 minutes as a reference point, the number of writhes presented in each mouse will be counted [7].

Finally, the mice will be sacrificed by cervical dislocation.

The results obtained will be used to calculate the percentage of inhibition, using the following formula:

Inhibition % = [Mean no of writhes(control) – mean no of writhes (test)/ Mean no of writhes (control)]× 100

Acute toxicity study

The mice were divided into groups of 2: a control group and an ethanolic extract group with doses of 2000 mg/kg. The animals were fed ad libitum, while the negative control group received only isotonic water. The animals were evaluated at 72 hours (liver and kidney) and the extracts were administered every 8 hours [8]. Any change in behavior or mortality was observed, and the animals were finally sacrificed to determine histological changes in the study groups.

Statistical analysis

The normality of the quantitative variable (number of writhes in 30 minutes) was evaluated using the statistical program SPSS version 27. Since the sample size per group was 7 mice, the Shapiro-Wilk model was used, and it was concluded to use a parametric test due to the normality distribution of quantitative variables with a $p<0.05$. Therefore, the ANOVA test with Bonferroni's post hoc with a $p<0.05$ was used for analyzing the relationship between treatments and the number of writhes.

Ethical Aspects

The experiment followed the guidelines of the "Guide for the Management and Care of Laboratory Animals" from the National Center for Biological Products of the National Institute of Health, adhering to the principle of the three Rs: Reduce, Replace, and Refine. The animals received the best care during the experiment, including a suitable and clean environment and access to water and food [9,10]. The study was approved by the Pharmacology research course 01-0623 Norbert Wiener University.

Euthanasia

The pharmacological method was used for euthanasia. Consequently, Pentobarbital was used intraperitoneally at a dose of 150 mg/kg, which induced depression of the central nervous system leading to anesthesia and subsequently death. This method was used because it is the fastest and least painful[11-13].

RESULTS

As observed in Table 1, the 200/kg *Aniba canelilla* extract showed the best analgesic effect related to the lowest number of writhes, even compared to the positive control, such as Tramadol 50mg/kg.

As shown in Table 2, a significant difference was observed at 30 minutes ($p<0.01$) between the extract of *Aniba canelilla* at 200mg/kg and all the other treatments, with a notable analgesic effect that was shown as the lower number of abdominal writhes. Concerning the comparison of the same treatments at one minute and 30 minutes, a significant difference ($p<0.01$) was observed in all treatments, except for the treatment of *Aniba canelilla* at 200mg/kg, which corroborates the potent analgesic effect of *Aniba canelilla* at 200mg/kg. In the table, the high analgesic percentage (98.87%) of the *A. canelilla* extract at 200mg/kg is noteworthy.

$^{a, b, c, d, e}$ Represent a $p<0.01$ vertically between treatments.

* Represents a $p<0.01$ in each treatment horizontally.

As shown in Table 3, all tests for alkaloids were positive, corroborating the presence of alkaloids in the chloroformic extract of *A. canelilla*.

Table 1. Descriptive statistics of the treatments 30 minutes after the administration of acetic acid.

	N	Media	Standard deviation
Acetic Acid	7	2502.86	641.995
Tramadol	7	664.29	85.607
Paracetamol	7	1714.29	63.471
Ca. Ex.50	7	1898.57	172.957
Ca. Ex.100	7	1911.43	37.607
Ca. Ex. 200	7	28.29	5.438

Table 2. Analysis of Variance between treatments.

Group	Dose (mg/kg)	Treatment (After 1 minute of acetic acid administration)	Treatment (After 30 minutes of acetic acid administration)	Percentage of inhibition (After 30 minutes of acetic acid administration)
Acetic acid	0,8%	83.43± 21.40 *	2502.86 ± 641.10 [a]	
Tramadol	50mg/kg	22.14±2.85*	664.29 ± 85.61 [a, b, *]	73,46%
Paracetamol	500/kg	57.14±2.12 *	1714.29 ± 63.47 [a, b, c, *]	31,51%
Aniba canelilla Extract	50mg/kg	63.29±5.77 *	1898.57 ± 172.96 [a, b, d, *]	24,17%
Aniba canelilla Extract	100mg/kg	63.71±1.25 *	1911.43 ± 37.61 [a, b, e, *]	23,63%
Aniba canelilla Extract	200mg/kg	1.14±0.38	28.29 ± 5,44 [a, b, c, d, e]	98,87%

Table 3. Preliminary qualitative profile of the chloroformic extract of *Aniba canelilla* "canelon" bark.

N°	Trial	Metabolite	Result
1	Dragendorff	Alkaloids	(+)
2	Mayer	Alkaloids	(+)
3	Popoff	Alkaloids	(+)
4	Wagner	Alkaloids	(+)
5	Bertrand	Alkaloids	(+)
6	Sonnenschein	Alkaloids	(+)

Note. Presence (+); Absence (-)

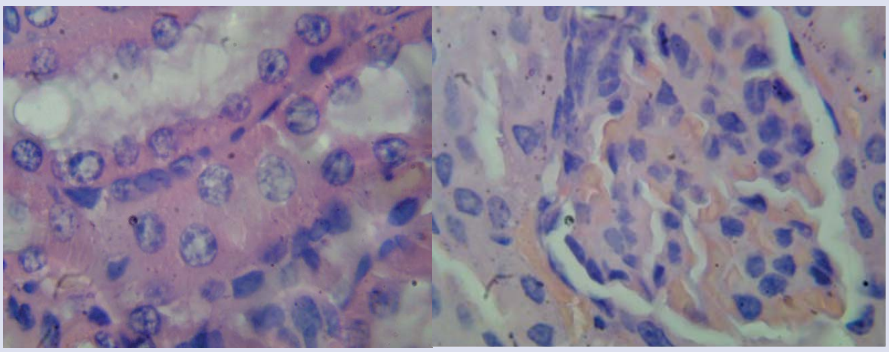

Figure 1. Kidney slides at 72 hours. The figure at the left represents a blank control group section without modifications at 400X. The figure at the right represents the experimental group (*Aniba canelilla* 2000mg/kg) section without modifications at 400X.

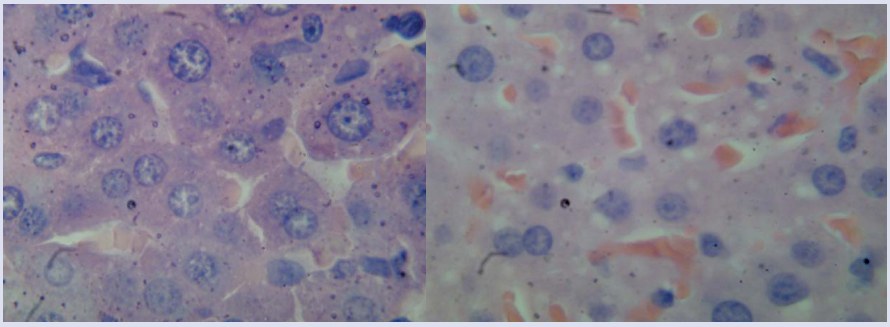

Figure 2. Liver slides at 72 hours. The figure at the left represents a blank control group section without modifications at 400X. The figure at the right represents the experimental group (*Aniba canelilla* 2000mg/kg) section without modifications at 400X.

DISCUSSION

Regarding the result obtained from the analysis of the qualitative profile of the chloroformic extract of *Aniba canelilla* "canelon" bark, the presence of alkaloids was evidenced in the 6 methods that corroborated its presence (Table 1), because alkaloids are related to the analgesic effect. It is deduced that alkaloids in *A. canelilla* had an analgesic effect. The results obtained agree with the study carried out by Souza et al. regarding the ethnobotanical and phytochemical properties of *Aniba canelilla*, belonging to the Lauraceae family, whose study showed that this plant species presents secondary metabolites, such as the alkaloid 1-nitro-2-phenylethane[14].

In the evaluation of the analgesic effect of the chloroformic extract of *Aniba canelilla* "canelon" bark in which the method of Koster et al. was used, which induces pain by applying acetic acid intraperitoneally[6], this chemical substance causes pain in the abdominal region. This effect has been visualized through writhes in C53/CNPB mice. The analgesic effect was evidenced with tramadol or paracetamol treatment with a $p<0.01$ compared to the negative control (acetic acid 0.8%) and, mainly, in the extract of *Aniba canelilla* "canelon" at a dose of 200 mg/kg, which was statistically significant to all treatments having the lowest number of writhes, and, therefore, the best analgesic effect. Other plants of the genus *Pereskia* sp. [15,16] have shown an analgesic effect, although, in our case, the action of *A. canelilla* at 200 mg/kg was markedly noticeable.

Previous studies on ethanolic extracts of *Pereskia lychnidiflora* and *Ficus iteophylla* leaves showed analgesic effects at 20 minutes and 15 minutes, respectively, between 30mg/kg to 400 mg/kg, showing among their constituents, i.e., alkaloids, tannins, triterpenes, sterols, steroids, saponins, and flavonoids[7,17]. In contrast, our study had the greatest effect at 200mg/kg, with a significant value compared to the other treatments ($p<0.01$) of 28.29 ± 5.44 at 30 minutes, with a percentage of inhibition of withers and, therefore, a high analgesic percentage of 98.87% after the application of acetic acid.

The remarkable analgesic effect of *A. canelilla* would be accompanied by an anti-inflammatory effect since the acetic acid test generates prostaglandin-mediated inflammation in the area of exposure[18]. A previous study has shown therapeutic properties in traditional medicine to treat digestive, respiratory, inflammatory diseases, pain, and central nervous system disorders, administered mainly orally, as tea[19]. A study on the chemistry of natural products has mentioned that the infusion of *A. canelilla* bark has shown therapeutic effects on inflammation and pain[20]. Lipophilic compounds, such as 1-Nitro-2-Phenylethane (1N2PE) and Methyleugenol, have demonstrated analgesic and anti-inflammatory effects by applying abdominal writhes and carrageenan models [21-23]. It is important to note that in this study an extract of *A. canelilla* of lipophilic nature was used, using the chloroformic solvent in which a remarkable analgesic effect was observed that would be supported by the findings of the alkaloids, 1N2PE and Methyleugenol, according to the present study and previous studies[21-23].

Regarding toxicity in the histological analyses at the level of kidney and liver tissues, no pathological alterations were observed to report, both at the level of the blank or negative control and the tissues of the mice, to which the dose of 2000mg/kg was administered (figure 1 and figure 2). During the follow-up of the administration of the chloroformic extract of *Aniba canelilla*, no mortality was reported in murine mice, so it could be placed in the fifth category of toxicity, which consists of presenting a value greater than DL50 > 2000 mg/kg concerning body weight. Additionally, the essential oil of *A. canelilla* has not shown any toxic effect at the cellular and tissue level, being, therefore, classified as low toxicity[24,25]. The toxicological test used in this study is indispensable to extrapolating collateral effects in human trials and, in addition, it is a unique test due to its In Vivo model that could be replaced by In Vitro trials[26,27].

CONCLUSIONS

The analgesic effect of the chloroformic extract of *Aniba canelilla* "canelon" bark was determined, verifying that the dose of 200 mg/kg is the one with the best analgesic effect that achieved the decrease of abdominal writhes in BAB/c mice.

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AUTHOR CONTRIBUTIONS

The study was conceived and designed by JCF, JEV, AMA, RMS, SCZ, and JRJ. Data collection was conducted by JCF and JRJ. Data analysis was carried out by ER-Z, JCF, and JR-J. The manuscript was drafted by JCF, JEV, AMA, RMS, SCZ, and JRJ and was critically reviewed by JCF and JR-J. All authors approved the final version of the manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The data generated or analyzed during this study are included in this publication.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Pharmacology research course 01-0623 Norbert Wiener University.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare no competing interest.

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