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Antimalarial activity of aqueous extract from the species *Plectranthus amboinicus* (Lour.) Srpeng growing in Venezuela

Actividad antimalárica del extracto acuoso de la especie *Plectranthus amboinicus* (Lour.) Srpeng cultivada en Venezuela

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Abstract

Plectranthus amboinicus, a medicinal species belonging to the Lamiaceae family, currently classified under the scientific name *Coleus amboinicus* Lour, it is widely distributed and recognized worldwide. However, its exact origin remains uncertain, with both India and Africa frequently cited as potential sources. Extensive literature reports highlight the pharmacological activity of its extracts and essential oils, which have been studied in various regions and cultures. In Venezuela, this plant is used as a diuretic and is traditionally used to treat ailments such as fever, cough, digestive disorders, and headaches. Due to its pleiotropic effects, the antimalarial activity of an aqueous extract obtained by the decoction of its leaves was determined in mice infected with *Plasmodium berghei*, in addition to evaluating its risk-benefit balance through toxicological parameters that demonstrate that it has no hepatotoxic or hemotoxic effects. The results obtained in mice infected with *Plasmodium berghei* indicated that although a reduction in parasite density and an increase in post-infection survival was observed, this was not comparable to that observed in the control group treated with Chloroquine, suggesting that the aqueous extract does not have antimalarial properties. However, it could be used as an adjuvant with other conventional antimalarial drugs currently used in therapeutics.

Keywords: *Plectranthus amboinicus*, antimalarial activity, toxicity, biochemical parameters

Resumen

Plectranthus amboinicus, perteneciente a la familia Lamiaceae, cuyo nombre ha sido actualizado científicamente a *Coleus amboinicus* Lour, es una especie medicinal conocida a nivel mundial, aunque su origen es aún incierto, se usan frecuentemente las de India y África. Amplios reportes en la literatura dan cuenta de la reconocida actividad farmacológica de extractos y aceites esenciales obtenidos de diferentes lugares y culturas alrededor del mundo. En Venezuela se utiliza para la fiebre, tos, cefalea, trastornos digestivos y como diurético. Por sus efectos pleiotrópicos, se procedió a determinar la actividad antimalárica de un extracto acuosos obtenido por decocción de sus hojas en ratones infectados con *Plasmodium berghei*, además de evaluar su balance riesgo-beneficio a través de parámetros toxicológicos que demuestran que el mismo no tiene efectos hepatotóxicos ni hemotóxicos. Los resultados obtenidos en ratones infectados con *Plasmodium berghei*, indicaron que a pesar de que se observó una reducción de la densidad parasitaria y un incremento en los días de supervivencia post infección, no es similar a la observada en el grupo control tratado con cloroquina, sugiriendo que el extracto acuoso no tiene propiedades antimaláricas. Sin embargo, podría ser utilizado como coadyuvante con otros medicamentos antimaláricos convencionales utilizados en la terapéutica actual.

Palabras clave: *Plectranthus amboinicus*, actividad antimalárica, toxicidad, parámetros bioquímicos

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Introduction

Medicinal plants, known for their well-documented pharmacological properties, are found across the globe. In recent years, especially after the COVID-19 pandemic, the world has witnessed a resurgence of interest in traditional medicine. Millions of people have relied on these plants for survival, reaffirming the value of ancient healing knowledge (Al-Jamal et al., 2024; Mukherjee et al., 2022; Villena-Tejada et al., 2021). The scientific community must further investigate and validate the purported benefits of the hundreds of plant species commonly used by populations worldwide, particularly in regions where access to public healthcare remains inadequate.

Plectranthus amboinicus-whose origins are still debated, with some sources suggesting India or Africa- has spread globally, especially in tropical zones. Recently reclassified by botanists as *Coleus amboinicus* Lour., this species belongs to the Lamiaceae family, which is widely recognized for the medicinal properties of its secondary metabolites (Nascimento Martinez et al., 2020).

In Venezuela, *P. amboinicus* is used to treat various diseases and ailments, including asthma, colds, kidney stones, headaches, skin diseases, digestive and cardiovascular diseases, and fever. It is also a culinary condiment (Orsini, 2020; Orsini and Tillet, 2019). In other countries, its applications are even broader, encompassing antiviral, antifungal, antitumor, analgesic, anti-inflammatory, and wound-healing properties, as well as the treatment of genitourinary disorders, asthma, and skin diseases, among others. Despite its wide-ranging uses, few reviews in the literature document the pharmacological properties, phytochemistry, and applications of this remarkable species (Arumugan et al., 2016; Asiinwee et al., 2014; Chang et al., 2007; Kumar et al., 2020).

Phytochemical studies of this plant have revealed the presence of various secondary metabolites, including flavonoids, with flavones being the most common, as well as triterpenes, sterols, aromatic organic acids, and lignans (Ruan et al., 2019). The composition of its essential oil has been investigated in multiple regions, including Venezuela (Blasio et al., 2025; Gupta et al., 2024; Han et al., 2023; Valera et al., 2003). Key compounds identified in these studies include carvacrol, germacrene D, α-humulene, α-terpinene, p-cymene, thymol, terpinen-4-ol, and caryophyllene.

Malaria remains a major global health challenge, with approximately 40% of the world's population at risk of infection. Despite significant research efforts to develop effective treatments and preventive measures, including some notable successes factors such as vector resistance, the lack of new therapeutic targets, poor living conditions in endemic regions, and globalization continue to hinder malaria eradication (Daskum et al., 2021; Siqueira-Neto et al., 2023; Tse et al., 2021). Medicinal plants remain a valuable therapeutic source for longstanding and emerging diseases. The most successful antimalarial compounds, such as artemisinin and quinine, have been derived from plants. Additionally, synthetic drugs inspired by these natural products play a critical role in current therapies, saving millions of lives annually (Dhamaliya et al., 2023; Kretli et al., 2021).

In regions such as Africa, Asia, and South America, a wide variety of plants are traditionally used to treat malaria. Many of these plants have been scientifically investigated (Erhirhie et al., 2021; Ribeiro et al., 2023; Tajbakhsh et al., 2021; Wrigth, 2005; Uzor et al., 2020a, 2020b), and research in this field continues with the hope of discovering new potential treatments for the disease.

To contribute to the ongoing search for antimalarial sources and considering the pivotal role of plant-derived natural products in antimalarial drug discovery (Alkandahri et al., 2022; Pan et al., 2018), we investigated *Coleus amboinicus* (known as oregano orejón in Venezuela) for its antiprotozoal potential. Specifically, this study used Peter's test to evaluate the antiplasmodial activity of its aqueous leaf extract against *Plasmodium berghei* infection.

Materials and Methods

Plant material

The leaves of *C. amboinicus* were harvested in the city of Carrizal, Carrizal municipality, Miranda state, during the morning hours at a height of 1.50 cm from the ground. The leaves were then selected and taxonomically characterized. The plant was authenticated, and a voucher specimen was deposited at the Herbarium Victor Manuel Ovalles de la Facultad de Farmacia, Universidad Central de Venezuela under number 29535. Fresh leaves (30g) were cut into small pieces and submitted to decoction in an Erlenmeyer of 250 mL, using 50 mL of distilled water. The decoction process was kept for 15 minutes; the solution was filtered, cooled, and submitted to a lyophilization process to obtain a brown solid (1.56 g) reconstituted in distilled water at the moment of the experiment. This extract was named the aqueous extract of *Coleus amboinicus* (AE).

Qualitative phytochemical screening

The powdered extract was submitted to a phytochemical screening to detect the presence of the family of major secondary metabolites, such as flavonoids, alkaloids, and terpenes, using standard procedures (Solansky et al., 2019).

Chemical and reagent

The reagents used are of high analytical quality, available in the country and/or acquired from SIGMA-Aldrich Chemical Co and STANBIO Laboratory. Cloroquine (CQ) was purchased from SIGMA-Aldrich Chemical Co. Lote 109H109.

Experimental animals

Twenty male mice of the INH strain, weighing between 18 and 20 g, from the "Instituto Nacional de Higiene Rafael Rangel" were used. The animals were kept in cages with 12 hours of light/darkness, with water and food (ratarina®) *ad libitum*. The research complied with the bioethical standards contained in the Principles of Laboratory Animal Care Guide (Anonymous, 1985).

Dose to be used in Antimalarial Activity

The dose of CQ was selected based on an *in vivo* study in mice (Acosta and Gamboa, 2017), in which CQ has biological effects at

doses of 15 and 25 mg/Kg of body weight by i.p. The aqueous extract doses (EA dose) were 250, 500, and 1000 mg/Kg of body weight. The dose was selected based on an *in vivo* study in mice (Ramli et al., 2014).

Mice Infection

Mice were infected i.p. with 1 x 10^6 parasitized erythrocytes diluted in physiological solution (0.9% NaCl). The course of parasitemia was monitored through peripheral blood smears of infected animals stained with Giemsa and observed by light microscopy.

Preparation of peripheral blood smears and determination of parasitemia

A drop of blood was taken from a transverse incision at the end of the tail of the infected mouse and placed on a slide. Using another slide, a thin, uniform blood smear was made along the slide by sliding it at a 45° angle. The dried smear, fixed with methanol and heat, was stained with Giemsa (1:1) using the inversion technique for 20 minutes, washed with distilled water to remove excess stain, and allowed to dry. The slides were observed by light microscopy with a 100X objective in immersion oil. At least five fields were counted (approximately 500 red blood cells), and parasitemia was determined and expressed as a percentage (infected erythrocytes per 100 erythrocytes).

Antimalarial Activity

The treatment of animals with no patent infection was carried out using the Peter Test (1975).

The experimental design included the following groups.

Treatments	Doses
Healthy control	NaCl 0.9%
Infected control	NaCl 0.9%
Aqueos extract (AE) 250	250mg/Kg
Aqueous extract (AE) 500	500 mg/Kg
Aqueous extract (AE) 1000	1000 mg/Kg

Two hours after infection, four mice per group were treated once a day for five days with 0.1 mL of the indicated compound. On day 5 post-infection and post-treatment, parasite density was determined by microscopic examination of peripheral blood smears. Additionally, a record of post-infection survival days (PSD) was kept for 30 days.

Determination of reduced and oxidized glutathione (GSH/GSSG) levels

The method originally described by Tietzs (1969) was used, in which GSH reacts with dinitrobenzene (DTNB), forming a yellow complex that absorbs at 405 nm with the subsequent oxidation of NADPH.

Catalase determination

Catalase activity was determined according to Aebi's method (1982), following the degradation of H_2O_2 by catalase present in the sample. Briefly, in a quartz cell, 25 μL of the 1.33-fold diluted sample was placed in 10 mM phosphate buffer (pH 7), 725 μL of 7.7 mM H_2O_2 was added, and the absorbance change at 240 nm was immediately measured at 15 and 30 seconds. According to Aebi, the first-order reaction constant (k) was used as the unit of CAT activity, which was defined according to

the following formula: k = (1/t) (2.3 x log A1 / A2), where t is the measured time interval (sec), A1 and A2 are the H_2O_2 absorbances at times t1 and t2. The results were expressed as k/mg of protein.

Protein determination

The protein concentration was determined using the Lowry method (1951), which was adapted to 96-well microplates, to estimate the specific activity.

Determination of hepatotoxicity markers in serum

The activity of some specific liver isoenzymes, such as Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT), was determined in serum using kits from SIGMA-Aldrich Chemical Co.

Erythrocyte lysis assay

One toxicity assessment method is based on measuring hemoglobin efflux from suspended red blood cells. The ability of CQ and AE to induce red blood cell lysis was assessed as a marker of blood toxicity (Mehta et al., 1984). Erythrocyte lysis by plant extracts or compounds, is considered a standard protocol for assessing the *in vitro* toxicity of new substances and was determined by measuring the hemoglobin released at 550 nm, at the concentrations of the compounds to be tested (0.1, 1 and 10 μg/mL) at 37°C for 45 minutes. The results were expressed as a percentage of hemolysis of each concentration of the compounds tested. Hemolytic activity was evaluated using the following ranges: 0% - 9% = Non-toxic, 10% - 49% = slightly toxic, 50 – 89% = Toxic, and 90% to 100% = highly toxic.

Statistical Analysis

Results were presented as the mean ± standard error of the mean (X ± SEM). Data were analyzed using Prism v.8 software (Graph Pad, San Diego, CA, USA) using the unpaired Student t-test. *P* values <0.05 were considered statistically significant.

Results and Discussion

Evaluation of the antimalarial effect in a model of patent infection (Peter's test)

Table I shows the changes in the percentage of parasitemia on the fifth day post-infection and the survival of mice in the treatment groups compared to the infected and control groups.

Chloroquine significantly increased survival days and reduced parasitemia ($p<0.01$). At the three doses evaluated, treatment with AE significantly increased survival days ($p<0.05$) compared with the control healthy or infected groups, but less than the effect of CQ. Regarding parasitemia, AE at the three doses evaluated had a significantly decreasing effect ($p<0.05$) compared with the infected control group; however, the magnitude was smaller than the effect of CQ. It is suggested that AE is ineffective for treating malaria because it does not cure the infection and reduces the animal's survival days. Therefore, the test should be carried out in combination with conventional antimalarial drugs because, at all doses tested, the parasitemia was reduced, indicating that the AE may be effective as an adjuvant treatment.

Table I.
Modifications in the percentage of parasitemia and days of survival post-infection of mice infected with *Plasmodium berghei*, treated with CQ, and AE from the leaves of *Plecthantus amboinicus*

Treatments	Survivance days S.E.M	% of Parasitemia S.E.M
Healthy control	30.0	0.00
Infected control	7.5 ± 0.23**	90.4 ± 0.15
CQ (25 mg/Kg)	29.2 ± 0.53**	1.23 ± 0.25**
Aqueos extract (AE) (250 mg/Kg)	10.43 ± 0.24*	12.50 ± 0.27**
Aqueous extract (AE) (500 Kg/mg)	11.22 ± 0.56*	10.67 ± 0.25**
Aqueos extract (AE) (1000 mg/Kg)	13.35 ± 0.13*	9.65 ± 0.26**

**p<0.05; *p<0.001 in relation to the infected control

Determination of total Glutathione levels (GSH+GSSG)

Glutathione represents an essential defense mechanism of parasites against oxidative stress generated during infection. Table II shows the changes in blood levels of GSH, GSSG, and GSH+GSSG (total glutathione).

The total glutathione levels shown in Table II indicate that malaria infection produces a significant increase in GSH and GSSG values, which could represent compensatory mechanisms to control the oxidative trigger that occurs in the infection. AE at different concentrations reduced GSH and GSSG infection-induced values, obtaining similar levels to what is observed with healthy controls; that is, they had the capacity to normalize the blood glutathione levels of infected animals towards the values corresponding to healthy controls. The depleting effect of AE on GSH, GSSG, and total glutathione (GSH+GSSG) levels is also evident. Meanwhile, CQ had a slight effect on reducing concentrations of GSH and GSSG infection-induced values; however, this was statistically significant.

Determination of Catalase (CAT) levels

Table III shows the specific activity values of one of the first-line antioxidant defense enzymes, catalase, and its modifications

Table II.
Levels of reduced glutathione (GSH) and oxidized glutathione of mice infected with CQ and AE from the leaves of the *Plecthantus amboinicus*

Treatments	GSH (U/mg proteíns x 10^{-4} ± S.E.M)	GSSG (U/mg proteíns x 10^{-4} ± S.E.M)	Glutatión Total (U/mg proteína x 10^{-4} ± S.E.M)
Healthy control	0.95 ± 0.05	22.37 ± 0.15	23.32 ± 0.18
Infected control	1.95 ± 0.13**	49.13 ± 0.18**	51.08 ± 0.10**
CQ (25 mg/Kg)	1.25 ± 0.43	39.25 ± 0.23**	40.50 ± 0.25**
AE (250mg/Kg)	0.93 ± 0.14	23.48 ± 0.23	24.41 ± 0.25
AE (500 Kg/mg)	0.83 ± 0.02	27.07 ± 0.26	27.90 ± 0.25
AE(1000 mg/Kg)	0.99 ± 0.05	28.05 ± 0.20	29.04 ± 0.16

**p<0.05; *p<0.001 compared with healthy control

Table III.
Catalase (CAT) activity of mice infected with Plasmodium berghei, treated with CQ and AE from *Plecthantus amboinicus* leaves

Treatments	CAT (U/mg proteins x 10^{-2} S.E.M)
Healthy control	12.35 ± 0.15
Infected control	3.20 ± 0.10**
CQ (25 mg/Kg)	4.13 ± 0.33**
AE (250 mg/Kg)	4.33 ± 0.24**
AE (500 mg/Kg)	4.79 ± 0.22**
AE (1000 mg/Kg)	5.89 ± 0.15**

**p<0.05 compared with healthy control

due to the effects of both infection and treatments.

Plasmodium berghei infection produced a significant decrease in CAT levels. AE tends to counteract the inhibitory effect, similar to CQ, which could lead to a failure to promote the generation of hydroxyl radicals and consequently generate oxidative stress. However, the reduction of CAT levels was significant compared to the healthy group, indicating a very poor action of CQ or the three doses of the aqueous extract from the species *Plectranthus amboinicus* (Lour.) in restoring the antioxidant capacity.

Determination of AST, ALT and GGT

To evaluate the hepatotoxic effects of the different treatments, the levels of the liver damage marker enzymes (AST, ALT, and GGT) in the serum of the treated animals in relation to their *Plasmodium berghei* infection controls were assessed. The results obtained are expressed in Table IV.

The results show that malaria infection significantly increases serum AST, ALT, and GGT levels, so the damage to liver tissue during malaria infection is evident. Treatment of infected animals for 5 days with CQ reduced the levels of AST, ALT, and GGT in relation to the infected control. Evaluation of different concentrations of AE produces a decrease in the levels of AST, ALT, and GGT in relation to the infected control, observing values that tend to normalize in relation to the results obtained by the healthy control.

These data indicate that the aqueous extract from the species *Plectranthus amboinicus* (Lour.) significantly reduces the hepatotoxic effect of *Plasmodium berghei* infection and supports the notion that AE, *per se*, is not hepatotoxic.

Table IV.
Serum ALT, AST and GGT levels of *Plasmodium berghei*-infected mice treated with CQ and AE from the leaves of the *Plecthantus amboinicus* leaves

Treatments	ALT (UI) E.E.M	AST (UI) E.E.M	GGT (UI) E.E.M
Healthy control	59.10 ± 0,12	27.36 ± 0.25	36.84 ± 0.14
Infected control	149.60 ± 0.23**	59.10 ± 0.28**	86.97 ± 0.16**
CQ (25 mg/Kg)	71.25 ± 0.53	29.25 ± 0.53	37.25 ± 0.35
AE (250mg/Kg)	72.58 ± 0.24	32.54 ± 0.23	37.53 ± 0.15
AE 500 Kg/mg)	74.22 ± 0.22	39.21 ± 0.36*	38.67 ± 0.25
AE (1000 mg/Kg)	62.27 ± 0.23	40.87 ± 0.20*	40.15 ± 0.26*

**p<0.05; *p<0.001 compared with healthy control

In vitro hemolysis assay

To determine the hemotoxic potential of the compounds, an *in vitro* erythrocyte lysis assay was performed at three concentrations (0.1, 1 and 10 μg/mL). It should be noted that all the compounds tested alone produce a hemolysis percentage of less than 50%, indicating that all the compounds produce a slight erythrocyte lysis. The results in Table V show that the AE shows a hemolysis percentage of 4.87% at a concentration of 10 μg/mL, which is lower than the hemolytic activity of CQ (30.29%), reflecting that the AE tested is not hemotoxic. The results of 0.1 and 1 μg/mL are not expressed in Table V.

Table V.
Hemolysis percentage of the CQ and AE from the leaves of the *Plecthantus amboinicus*

Treatments	Hemolysis Percentage (%) E.E.M
Control	100 ± 0.01
CQ (10 µg/mL)	30.29 ± 0.23**
AE (10 µg/mL)	4.87± 0.14**

**p<0.05 compared with healthy control

Conclusions

When comparing the effects of chloroquine (CQ) and the aqueous extract (AE) from *Plectranthus amboinicus* leaves, the results suggest that AE, at the tested concentrations reduces the percentage of parasitemia in *Plasmodium berghei*-infected mice, though it does not achieve a complete cure, unlike the group treated with 25 mg/kg CQ. However, the prolonged survival of mice (10–16 days) indicates that AE could serve as an effective adjuvant to conventional antimalarial treatments. Additionally, AE appears to normalize CAT levels altered by malaria infection over the 5-day treatment period. Moreover, AE tended to restore AST, ALT, and GGT levels toward those of the uninfected control group. Importantly, AE demonstrated no hepatotoxic or hemotoxic effects, as evidenced by liver transaminase levels and the absence of erythrocytic lysis. Finally, the experimental design of this study allowed for a risk-benefit assessment of both chloroquine and the aqueous extract of *Plectranthus amboinicus*.

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