



Evaluation of Antitoxoplasmic Potential of Selected Antimalarial Medicinal Plants from Togo: *Artemisia annua* L., *Jatropha curcas* L., *Moringa oleifera* Lam., and *Sarcocephalus latifolius* (Smith) Bruce

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Evaluation of Antitoxoplasmic Potential of Selected Antimalarial Medicinal Plants from Togo: *Artemisia annua* L., *Jatropha curcas* L., *Moringa oleifera* Lam., and *Sarcocephalus latifolius* (Smith) Bruce

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Authors' contributions

This work was carried out in collaboration among all authors. Author MD designed and executed the study, including ethnobotanical surveys and experiments in Lomé (supervised by Author ATB) and in vitro experiments in tours (directed by author FDG). Authors KA and MG managed Physiology-Pharmacology Laboratory, Physiopathology Bioactive Substances and Safety Research Unit of University of Lomé, providing the study framework. Author IDP headed the host laboratory at François Rabelais University of Tours and supported in vitro experiments. Author AMWA processed and analyzed field survey data, compiling and classifying plant species. Authors HD and BBT assisted with laboratory tests at François Rabelais University of Tours. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Toxoplasmosis, a prevalent zoonotic disease, poses significant health challenges, particularly in Togo with high prevalence. Limited public awareness and suboptimal treatments necessitate exploring novel therapeutic avenues. This study investigated Togolese medicinal plants, especially those traditionally used to cure malaria, as potential sources of antitoxoplasmic agents, leveraging ethnobotanical knowledge and scientific validation for accessible drug discovery.

Materials and Methods: Phytochemical screening quantified key groups: phenols, tannins, flavonoids, and polysaccharides in ethanolic extracts. In vitro biological activities were evaluated, including antioxidant capacity (AAPH & DPPH assays), cytotoxicity (UptiBlue assay), hemolytic potential, and antitoxoplasmic activity against *Toxoplasma gondii* in Human Foreskin Fibroblasts using the CPRG method. Cytokine secretion (TNF α , NO) from RAW264.7 macrophages was also assessed. Statistical analysis employed Kruskal–Wallis and Tukey's post hoc tests.

Results: Phytochemical analysis revealed ethanolic extracts, particularly from *Artemisia annua*, *Moringa oleifera*, and *Sarcocephalus latifolius*, to be rich in phenols and tannins. *Jatropha curcas* ethanolic extract showed high flavonoid content. In vitro assays demonstrated high antioxidant activity in ethanolic extracts, with *Artemisia annua* outperforming ascorbic acid in AAPH assay. Ethanolic extracts of *Artemisia annua*, *Jatropha curcas*, and *Sarcocephalus latifolius* exhibited significant antitoxoplasmic activity, *Artemisia annua* being the most potent.

Discussion: This study demonstrated a correlation between phytochemical profiles and biological activities. Ethanolic extracts, abundant in phenols and tannins, displayed enhanced antioxidant and antitoxoplasmic properties, particularly in *Artemisia annua*. The in vitro validation of antitoxoplasmic activity in antimalarial plants like *Vernonia amygdalina* and *Sarcocephalus latifolius* suggests pharmacological overlap. These findings highlight the synergistic value of ethnobotany and scientific methods in discovering bioactive compounds for parasitic diseases and oxidative stress, reinforcing the importance of traditional medicine and biodiversity.

Conclusion: This research successfully reveals the anti-toxoplasmic potential of Togolese medicinal plants, notably, *Artemisia annua*, *Sarcocephalus latifolius*, *Jatropha curcas*. The results support further phytochemical investigations, in vivo validation, and clinical trials to fully realize the therapeutic potential and advocate for integrative healthcare strategies addressing global health challenges like toxoplasmosis.

Keywords: *Toxoplasma gondii*; *Artemisia annua*; *Jatropha curcas*; *Moringa oleifera*; *Sarcocephalus latifolius*.

1. INTRODUCTION

Toxoplasmosis, an infection of remarkable global ubiquity, is caused by *Toxoplasma gondii*, a strictly intracellular parasitic protozoan (Robert-Gangneux et al., 2012). This widespread zoonosis presents a significant public health challenge, affecting a substantial portion of the human population and accounting for nearly one-third of the global population (Torgerson et al., 2013). The prevalence of toxoplasmosis exhibits

notable geographical heterogeneity, shaped by a constellation of interdependent factors, including socioeconomic determinants, region-specific environmental conditions, and cultural particularities (Webster et al., 2010; Jones et al., 2001).

In Togo specifically, while comprehensive epidemiological data are still being consolidated and refined, toxoplasmosis is recognized as an endemic infection. The study by Tété-Bénissan

et al. (Tété-Bénissan et al., 2018) underscores the significant public health challenge of toxoplasmosis in Togo, revealing a high overall anti-*Toxoplasma gondii* IgG seroprevalence of 59.7% in a large-scale prospective study of over 7000 participants (Tété-Bénissan et al., 2018). This prevalence, which is indicative of high parasite exposure, is within the upper range for sub-Saharan Africa (Dumètre and Dardé, 2003; Pangui et al., 2013; Angel et al., 2014) and comparable to that in neighboring countries (Millogo et al., 2000; Koffi et al., 2015). Importantly, seroprevalence in Togo has remained remarkably stable over the past four decades, with rates between 53% and 80% reported in studies dating back to the 1990s (Agbo et al., 1991; Balogou et al., 2007; Apetse et al., 2015; Tété-Bénissan et al., 2018), highlighting the persistent nature of *Toxoplasma gondii* exposure in the Togolese population. A lack of understanding regarding contamination sources impedes effective prevention strategies (Degbé et al., 2018a). *Toxoplasma gondii* is a complex parasite (Robert-Gagneux et al., 2012) with diverse transmission routes, including oocyst ingestion, consumption of tissue cysts in undercooked meat (Remington et al., 2011), and congenital transmission (Petersen, 2007). An epidemiological study in Lomé highlighted raw garden produce consumption (82.78%), untreated well water use (69.54%), and potentially contaminated agricultural practices as major risk factors, alongside less frequent undercooked meat consumption (7.28%) (Degbé et al., 2018a). Consistent with global data (Bastiaense et al., 2003; Villena et al., 2012; Tonouhewa et al., 2017), this study also emphasized domestic cats as significant parasite reservoirs, with high rates of feline parasitemia (61.59%) and oocyst excretion (17.22%).

While often asymptomatic, toxoplasmosis is severe in vulnerable groups such as pregnant women, leading to congenital toxoplasmosis with serious fetal complications (Gilbert et al., 2001), and immunocompromised individuals, potentially causing fatal cerebral toxoplasmosis (Luft et al., 1992). The clinical manifestations are varied (Hill et al., 2002), ranging from flu-like symptoms to severe neurological issues (Torgerson et al., 1998).

Currently, the conventional therapeutic arsenal for the treatment of toxoplasmosis relies primarily on the use of molecules such as pyrimethamine, sulfadiazine, and trimethoprim-sulfamethoxazole (Elsheikha et al., 2021). However, these

pharmacological treatments are not without notable drawbacks, particularly because of their potential side effects, their sometimes prohibitive cost, and the emergence of parasitic strains resistant to these molecules (Khan et al., 2022). These intrinsic limitations of conventional treatments strongly underscore the urgency of developing new therapeutic strategies that are more effective, better tolerated, and economically accessible (Yang et al., 2017). In this context, the exploration of bioactive substances from natural sources, more specifically from the plant kingdom, represents a promising avenue of investigation (Rates, 2001). The ethnobotanical approach, which consists of studying the complex and multifaceted relationships between human populations and plants, particularly the traditional uses of medicinal plants, is particularly relevant in the quest for new molecular entities with therapeutic potential (Heinrich et al., 2009). In numerous traditional health systems, particularly in sub-Saharan Africa and in Togo in particular, medicinal plants play a prominent role in the management of a wide range of ailments and constitute an invaluable source of empirical knowledge accumulated over generations (Koudouvo et al., 2003). Traditional healers and practitioners, repositories of ancestral knowledge often transmitted orally from generation to generation, possess in-depth expertise in the identification, preparation, and use of plants to treat a broad spectrum of symptoms and diseases (Anyinam, 1995). Their knowledge, derived from careful observation of plant effects and a holistic understanding of pathological processes, is likely to guide modern scientific research toward original and innovative therapeutic pathways.

Within the framework of the present study, we hypothesized that the proven taxonomic proximity between *Toxoplasma gondii* and *Plasmodium falciparum*, the causative agent of malaria, could translate into potential similarities in terms of pharmacological targets and mechanisms of action of bioactive molecules (Janovy et al., 2013). Malaria, a parasitic disease that is also highly prevalent in sub-Saharan Africa, particularly in Togo, has been the subject of extensive research on medicinal plants traditionally used for its management (Willcox et al., 2004). It is therefore plausible that certain plant species with significant antimalarial activity may also exhibit antitoxoplasmic activity because of the phylogenetic relationship between the two protozoa. *Aremisia annua*, *Jatropha curcas*, *Moringa oleifera* and *Sarcocephalus latifolius*,

which are medicinal plants commonly used for curing malaria in Togo, were selected to evaluate their antitoxoplasmic potential.

2. MATERIALS AND METHODS

2.1 Plant Collection and Identification

2.1.1 Collection process

The medicinal plants selected for study were collected in the field, and their use was observed. The collection sites were chosen on the basis of practitioner indications, prioritizing traditional harvesting locations and ensuring species availability. Botanical samples, including vegetative (leaves, stems, etc.) and reproductive (flowers, fruits) parts when available, were collected following good botanical practices.

2.1.2 Botanical identification methods

Plant identification was performed by experienced botanists using standard taxonomic methods at the University of Lomé's botany laboratory. A Togolese flora reference herbarium was consulted for morphological comparisons. Validated scientific names and local vernacular names (Ewe, Mina) were assigned, and a list of collected plants with these names was compiled. *Jatropha curcas* (leaf): TOGO15315; *Sarcocephalus latifolius* (root): TOGO15316; *Moringa oleifera* (leaf)= TOGO15317; *Artemisia annua* (leaf) TOGO15319.

2.2 Phytochemical Study

2.2.1 Preparation of plant extracts

The dried leaves or roots of the selected plants were divided into two batches of 500 g each. The first 500 g batch constituted the pulverized plant material, and the second 500 g batch was macerated for 72 hours in 3 L of ethanol to carry out alcoholic extraction. After filtration on Whatman n°1 paper, the filtrate obtained was concentrated on a rotavapor at 35°C in the Chemistry Laboratory of the Faculty of Science of Lomé to obtain dry extracts, which would later be lyophilized at the François Rabelais University of Tours.

2.2.2 Determination of total phenols and tannins

Total phenols were quantified using the Folin-Ciocalteu method, following tannin removal with PVP (polyvinylpyrrolidone) as described by Lawon-Evi and al (2011)

Total phenols were quantified using the Folin-Ciocalteu method, following tannin removal with PVP (polyvinylpyrrolidone). This determination involved two stages:

Stage A: 500 µL of the extract (stock solution at 1 mg/mL) were transferred into tubes containing 10 mg of PVP diluted in 500 µL of methanol. The resulting mixture was vortexed and incubated on ice for 30 minutes. After centrifugation, 200 µL of the supernatant were transferred to dry tubes for assay with the Folin-Ciocalteu reagent. A blank was prepared using 1 mL of methanol in place of the extract.

Stage B: To 200 µL of either the extract solution (stock solution at 1 mg/mL), or 200 µL of gallic acid standard solutions (200, 150, 100, 50, 25, and 0 µg/mL), or 200 µL of the solution obtained in Stage A (extract + PVP), 200 µL of 10% Folin-Ciocalteu reagent were added. After a 15-minute incubation at room temperature, 800 µL of sodium carbonate solution (700 mM) were added. The contents of the tubes were then transferred to a 96-well plate for absorbance reading. The optical density (OD) was measured at 630 nm.

The total phenol content is expressed as mg gallic acid equivalents (GAE) per gram of extract. The total tannin content was calculated using the following formula:

$$\text{Absorbance}_T = \text{AbExt} - \text{AbExt} + \text{PVP}$$

Where: AbT = Absorbance of tannins; AbExt= Absorbance of extract; AbsorbanceExt+PVP= Absorbance of extract + PVP.

The optical density (OD) was measured at 630 nm.

The total phenol content is expressed as mg gallic acid equivalents (GAE) per gram of extract. The total tannin content was calculated using the following formula:

2.2.3 Determination of total flavonoids

This assay is based on the ability of flavonoids to form aluminum chelates with aluminum chloride, as described previously (Kosalec et al., 2004).

Two milliliters of aluminum chloride (20 mg/mL) and 6 mL of sodium acetate (50 mg/mL) were added to 2 mL of extract (1 mg/mL) or the rutin standard. A blank was prepared using 2 mL of

ethanol instead of the sample. The contents of the tubes were transferred to a 96-well plate for absorbance reading. The OD was measured at 440 nm after 150 minutes of incubation.

2.2.4 Determination of polysaccharide contents

In a series of test tubes, the following were introduced: 200 µL of the samples to be assayed (extract, standard range, control); 200 µL of a 5% (w/v) aqueous phenol solution; and 1 mL of concentrated sulfuric acid. After homogenization, the mixture was heated in a water bath at 100°C for 5 minutes and then cooled in the dark for 30 minutes. The OD was measured at 480 nm (Dubois et al., 1956). All the samples were assayed in duplicate. A glucose standard range (50, 100, 150, and 200 µg/mL) and a water control were used under the same conditions.

2.3 Evaluation of the Antioxidant Activity of the Ethanolic Extract

2.3.1 Evaluation by the AAPH assay

The antioxidant activity of the plant extract was determined in sheep blood via the AAPH (2,2'-Azobis 2-Amidinopropane Dihydrochloride) assay described by Lawson-Evi et al. (2011).

Thermal decomposition of AAPH generates free radicals at a constant rate, which attack the red blood cell membrane. When endogenous antioxidants are depleted, the red blood cell membrane ruptures, and hemoglobin is released into the supernatant. The addition of molecules or extracts with antioxidant activity to the incubation medium delays hemolysis. The method was calibrated using known concentrations of ascorbic acid (AA) added to the incubation medium. A 200 mM AAPH solution was prepared, as well as serial dilutions of plant extracts and ascorbic acid at 62.5, 125, 250, and 500 µg/mL.

Sheep blood samples (ESA/University of Lomé and INRA/Tours) were used. The red blood cell pellet obtained was washed three times with 5 volumes of PBS (relative to the pellet volume). During the last rinse, centrifugation was performed at 3000 g for 10 minutes. All pellets were pooled and resuspended in 4 volumes of PBS before being brought into contact at 37°C with AAPH and the different concentrations of plant extract and ascorbic acid. Table III summarizes the treatments performed.

For each concentration, $N = 4$. For each sample, the percentage of inhibition was calculated using the following formula:

$$\% \text{ inhibition} = \frac{\text{Absorbance of AAPH} - \text{Absorbance of sample}}{\text{Absorbance of AAPH}} \times 100$$

2.3.2 Determination by the DPPH Assay

The antioxidant activity of the extract was evaluated by its radical scavenging capacity against DPPH (1,1-diphenyl-2-picrylhydrazyl) (Sigma, France), according to the method described by Kim et al., with slight modifications, primarily concerning the concentrations of ascorbic acid in the standard range. A 0.1 mM DPPH solution was prepared from a 27 mM stock solution, representing a 1:270 dilutions (100 µL of stock solution in 26.9 mL of methanol). A total of 125 µL of plant extract at concentrations of 250 µg/mL, 125 µg/mL, 62.5 µg/mL, and 31.25 µg/mL; ascorbic acid standard at concentrations of 250 µg/mL, 125 µg/mL, 62.5 µg/mL, 31.25 µg/mL, 15.625 µg/mL, 7.825 µg/mL, 3.9 µg/mL, and 1.925 µg/mL; and a methanol control were incubated with 125 µL of 0.1 mM DPPH solution for 30 minutes in the dark. The absorbance was read at 480 nm. The percentage of inhibition was calculated via the following formula:

$$\text{Inhibition \%} = \frac{Ac - As}{Ac} \times 100$$

Where, Ac is the absorbance of the control and As is the absorbance of the extract solution or the ascorbic acid standard range.

2.4 Evaluation of Hemolytic Potential

The hemolytic potential of the extract was evaluated according to the method described by Powell et al. (2000) with slight modifications. Fresh sheep blood (ESA/University of Lomé and INRA/Tours) collected with anticoagulant was centrifuged at $850 \times g$ with 10 mL of PBS and resuspended in the same buffer to achieve a 10% hematocrit. 40 µL of extract solution at concentrations of 5 mg/mL, 2.5 mg/mL, 1.25 mg/mL, and 0.650 mg/mL, 40 µL of Triton X-100 (0.1%, 0.05%, 0.025%, and 0.0125%) as a positive control, and PBS as a negative control were brought into contact with 360 µL of the red blood cell suspension. After homogenization, the tubes were incubated at 37°C for 35 minutes, placed on ice for 5 minutes, and subsequently centrifuged at $1310 g$. 100 µL of each

supernatant was diluted in 900 µL of PBS. After homogenization, 200 µL from each tube was transferred to a well of a 96-well plate, and the absorbance was read at 565 nm.

2.5 Determination of Cytotoxicity

HFF cells were cultured in 96-well plates at 2×10^4 cells per well in phenol red-free DMEM supplemented with 1% FBS. After 24 hours of culture at 37°C in a 5% CO₂ atmosphere, the plant extracts to be tested were added at different concentrations (from 1 to 100 mg/mL). Wells containing untreated cells were used as a reference. The cells were then incubated for 96 hours at 37°C in a 5% CO₂ atmosphere. At the end of the incubation period, 15 µL of UptiBlue® reagent (10% of the volume) was added. The plate was then incubated in the dark at 37°C under 5% CO₂ for 4 hours. The absence of a color change from blue to pink indicated cytotoxicity. The absorbance was measured at two different wavelengths for each well: 565 nm and 630 nm.

To calculate the difference in UptiBlue® reagent reduction between the control wells and the wells containing different plant extracts, the algorithm provided by the supplier (Uptima, France) was used.

2.6 Determination of *in vitro* Antitoxoplasmic Activity (Moine et al., 2015)

The determination of *in vitro* antitoxoplasmic activity was performed as described by Moine (Moine et al., 2015), with slight modifications concerning concentrations.

The parasite used was the RH-β-gal strain of *Toxoplasma gondii*. This strain is modified to express the bacterial *lacZ* gene, which encodes β-galactosidase, under the control of the promoter of the gene encoding SAG1, a major surface protein of the parasite. Tachyzoites were cultured on confluent human foreskin fibroblasts (HFFs) in DMEM supplemented with 5% FBS at 37°C in a 5% CO₂ atmosphere.

HFFs were cultured in 96-well plates at 2×10^4 cells per well in phenol red-free DMEM supplemented with 1% FBS. After 24 hours of culture at 37°C in a 5% CO₂ atmosphere, tachyzoites were added (100 parasites per well), as were the plant extracts tested at different concentrations (from 1; 10 to 100 µg/mL or 6.25;

12.5; 25 to 50 µg/mL for IC₅₀ determination of antitoxoplasmic activity). Wells containing untreated parasites were used as a reference. Treatment with 1 µM pyrimethamine served as a positive control. Wells containing cells alone served as a “blank” for the measurement of β-galactosidase activity. The cells were then incubated for 96 hours at 37°C in a 5% CO₂ atmosphere. At the end of the incubation period, the number of parasites was estimated by measuring β-galactosidase activity.

2.7 Cytokine assay of Macrophages (RAW264.7)

The cytokine assay of macrophages (RAW264.7) was performed as described by Dégbé (Dégbé et al. 2018). RAW264.7 macrophages were maintained in culture in DMEM + 5% FBS at 37°C in a 5% CO₂ atmosphere. To study the effects of the extracts, the macrophages were cultured in 96-well plates at 2×10^5 cells in 100 µL of DMEM alone. After 1 hour of adhesion, the extracts were added to 100 µL of DMEM to a final concentration of 10 µg/mL. The control cells were incubated in the same manner with an equivalent amount of DMSO alone.

After 24 hours of incubation, 50 µL of supernatant from each well was used for cytokine assays (TNFα, IL-5, and IL-12) via the sandwich ELISA (enzyme-linked immunosorbent assay) method with eBioscience kits (Affymetrix) or for NO quantification via the Griess method. To assay NO, a 0.1% aqueous solution of N-(1-naphthyl) ethylenediamine dihydrochloride (naphthylethylenediamine) and a 1% solution of sulfanilamide in 5% phosphoric acid (sulfanilamide) were used. A volume of 25 µL of cell supernatant or a NaNO₂ standard range (62.5–1000 µM) was added in triplicate to a 96-well plate, and 25 µL of naphthylethylenediamine/sulfanilamide (1:1) was added. The absorbance was then measured at 565 nm. The values obtained correspond to the nitrite ion concentration, reflecting the NO concentration in the samples.

2.8 Controls and Statistical Analyses

For each *in vitro* assay, negative (untreated parasites) and positive (pyrimethamine at 1 µM) controls were included. The assay results are expressed as a percentage of inhibition of parasite proliferation or invasion relative to the negative control. The inhibitory activity of each plant extract was evaluated at different

concentrations, making it possible to determine, if applicable, the 50% inhibitory concentration (IC₅₀), defined as the extract concentration that induces 50% inhibition of parasite proliferation. When a dose-dependent effect was observed, a regression line was established, and the equation of this line was used to calculate the IC₅₀. The data were statistically analyzed using GraphPad Prism 8 software. Comparisons between treated groups and control groups were performed using appropriate statistical tests. The Kruskal–Wallis test followed by Tukey's post hoc test was used for statistical analysis of the data. A *p* value < 0.05 was considered to indicate a significant difference between groups.

3. RESULTS AND DISCUSSION

3.1 Result

3.1.1 Phytochemical group dosages

3.1.1.1 Determination of total phenols and tannins

Fig. 1 shows the tannin content, revealing that ethanolic extracts from the leaves of *Moringa oleifera*, *Artemisia annua*, and *Sarcocephalus latifolius* presented the highest concentrations.

Where:

Aa: ethanolic extract of *Artemisia annua*
Jc: ethanolic extract of *Jatropha curcas*
Mo: ethanolic extract of *Moringa oleifera*
Sl: ethanolic extract of *Sarcocephalus latifolius*

The concentrations of total phenols (Fig. 2) followed a similar trend to those of the tannins. Notably, the ethanolic extracts from the leaves of *Moringa oleifera*, *Artemisia annua*, and *Sarcocephalus latifolius* presented the highest total phenol concentrations.

3.1.1.2 Determination of flavonoid contents

The results presented in Fig. 3 indicate that the highest flavonoid contents are found in the ethanolic extracts from the leaves of *Jatropha curcas*, *Moringa oleifera*, *Sarcocephalus latifolius*, and *Artemisia annua*, in descending order.

3.1.1.3 Determination of polysaccharide contents

Fig. 4 shows that all the plant extracts had high polysaccharide concentrations (>250 µg/mL glucose equivalent), with the exception of the *Artemisia annua* extracts.

3.1.2 In vitro evaluation of the antioxidant activity of extracts

3.1.2.1 AAPH Assay

The ethanolic extract of *Artemisia annua* presented greater antioxidant activity than the reference drug did (51.9 µg/mL versus 120 µg/mL).

3.1.2.2 DPPH Assay

In the DPPH assay, the ethanolic extracts also presented a relatively high antioxidant capacity. Specifically, ethanolic extracts from *Artemisia annua* and *Jatropha curcas* presented significant antioxidant activity. The antioxidant capacity of the different extracts was dose dependent.

3.1.3 Cytotoxicity of the plant extracts

The most toxic extracts had lower CC50 values. Thus, extracts from *Jatropha curcas* leaves and *Sarcocephalus latifolius* roots are the most cytotoxic.

3.1.4 Hemolytic potential of the plant extracts

The plant extracts studied do not induce strong hemolysis. The rate of hemolysis induced is related to the saponin content, with *Moringa oleifera* extracts resulting in the highest rate of hemolysis.

3.1.5 In vitro antitoxoplasmic activity of extracts

The reference drug used for evaluating antitoxoplasmic activity was pyrimethamine (pyr) at a concentration of 1 µM. The positive control consisted of wells containing uninfected host cells (cells alone), and the negative control consisted of infected, untreated cells (Toxo).

Ethanolic extracts from *Artemisia annua*, *Jatropha curcas* and *Sarcocephalus latifolius* roots inhibited the development of *Toxoplasma gondii* tachyzoites.

-Determination of the IC₅₀ values of extracts with in vitro toxoplasmodicidal activity

The antitoxoplasmic potency was highest in the ethanolic extracts of *Artemisia annua*, *Jatropha curcas*, and *Sarcocephalus latifolius* roots, in decreasing order of potency.

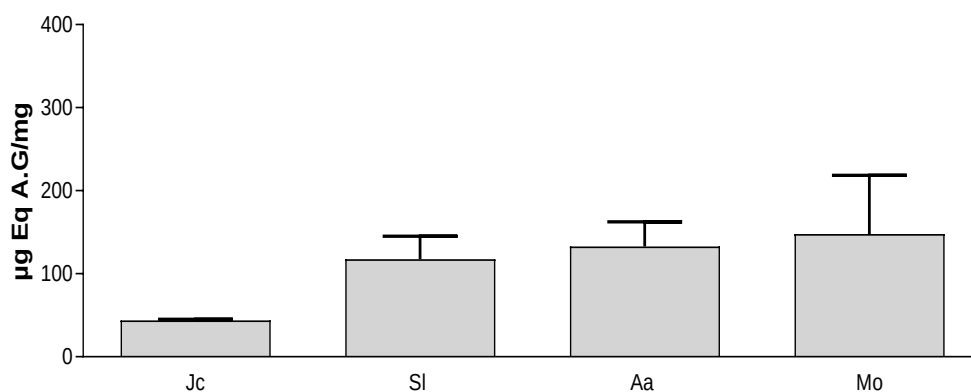


Fig. 1. Concentration of tannins in plant extracts

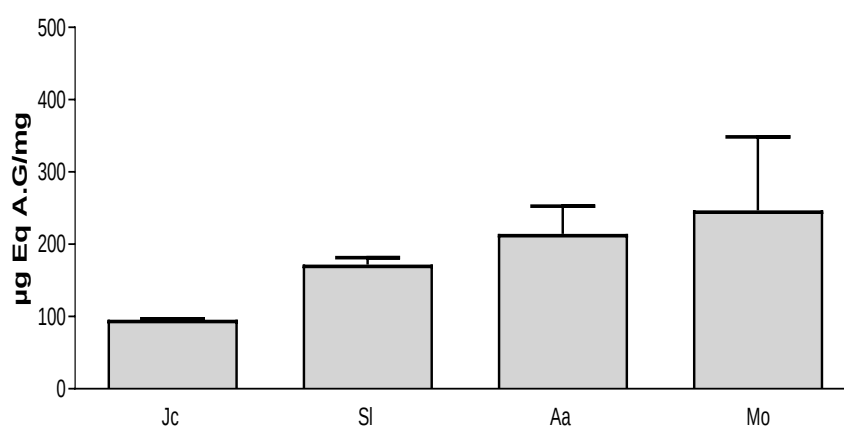


Fig. 2. Concentration of total phenols in plant extracts

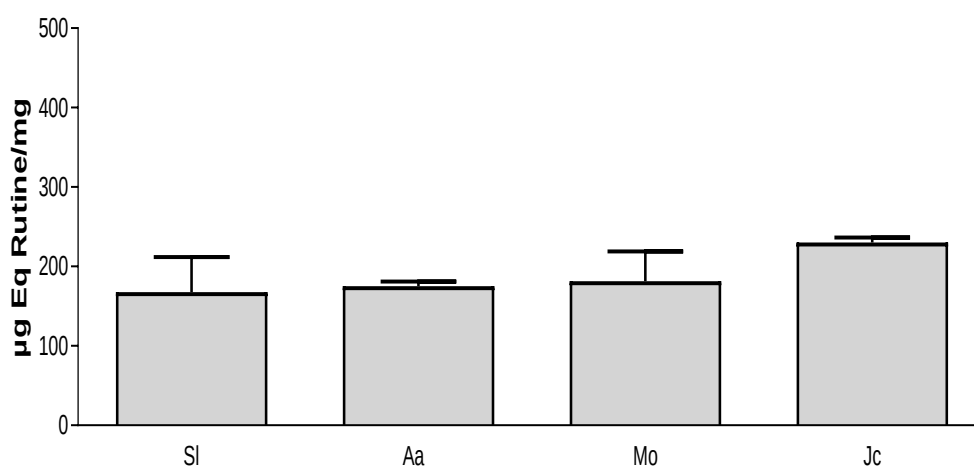


Fig. 3. Concentration of flavonoids in plant extracts

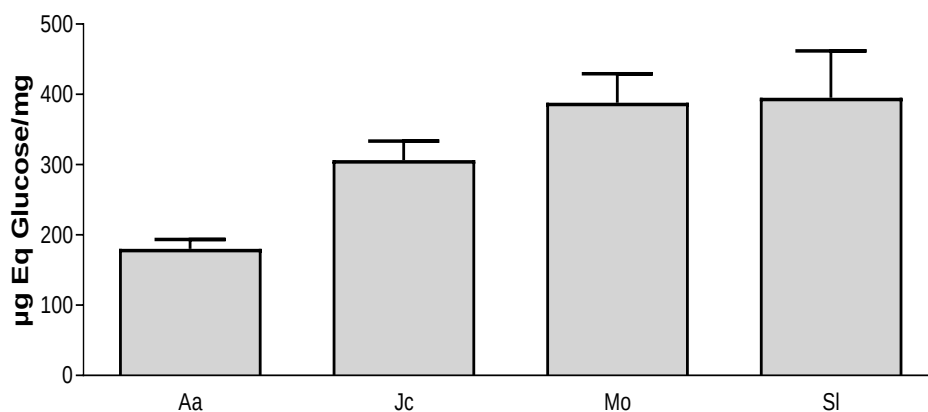


Fig. 4. Concentration of polysaccharides in plant extracts.

Table 1. IC₅₀ values demonstrating the antioxidant activity of plant extracts using the AAPH assay

	<i>Artemisia annua</i>	<i>Jatropha curcas</i>	<i>Moringa oleifera</i>	<i>Sarcocephalus latifolius</i>
Alcoholic Extract	51.9	377	222	415

IC₅₀ Ascorbic Acid = 120 µg/mL

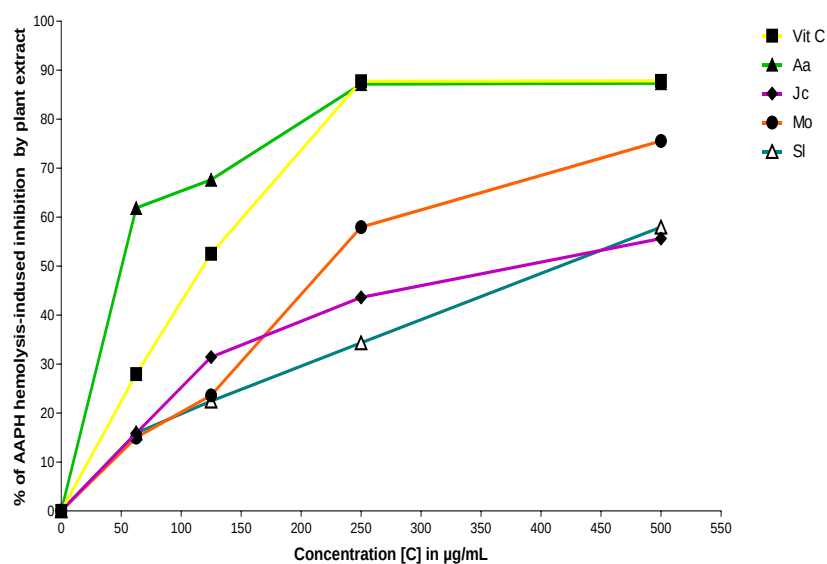


Fig. 5. Evaluation of the antioxidant capacity of plants using the AAPH assay

Table 2. IC₅₀ values demonstrating the antioxidant activity of plant extracts using the DPPH assay

	<i>Artemisia annua</i>	<i>Jatropha curcas</i>	<i>Moringa oleifera</i>	<i>Sarcocephalus latifolius</i>
Alcoholic Extract	39.5	124	113	155

IC₅₀ Ascorbic Acid = 20.3 µg/mL

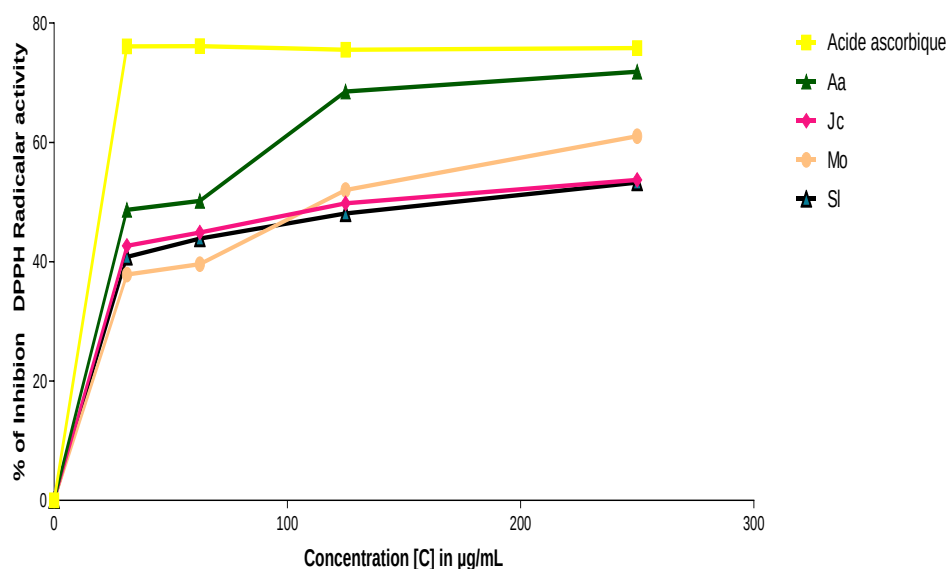


Fig. 6. Evaluation of the antioxidant capacity of plants using the DPPH assay

Table 3. Cytotoxic Concentrations (CC50) of different plant extracts

	<i>Artemisia annua</i>	<i>Jatropha curcas</i>	<i>Moringa oleifera</i>	<i>Sarcocephalus latifolius</i>
Alcoholic Extract	158.48	30.19	169.82	114.81

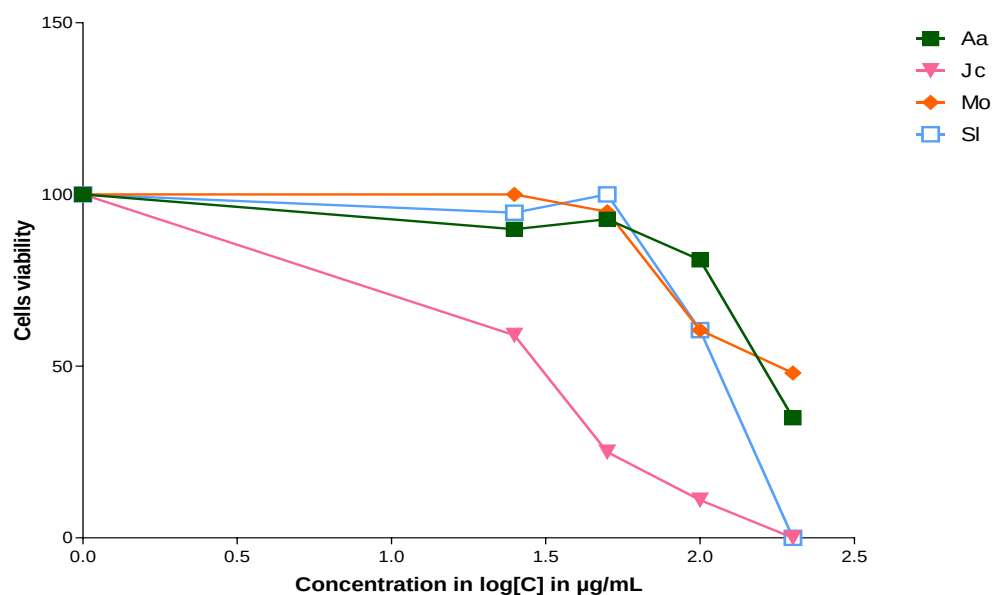


Fig. 7. Evaluation of plant cytotoxicity using the UptiBlue assay

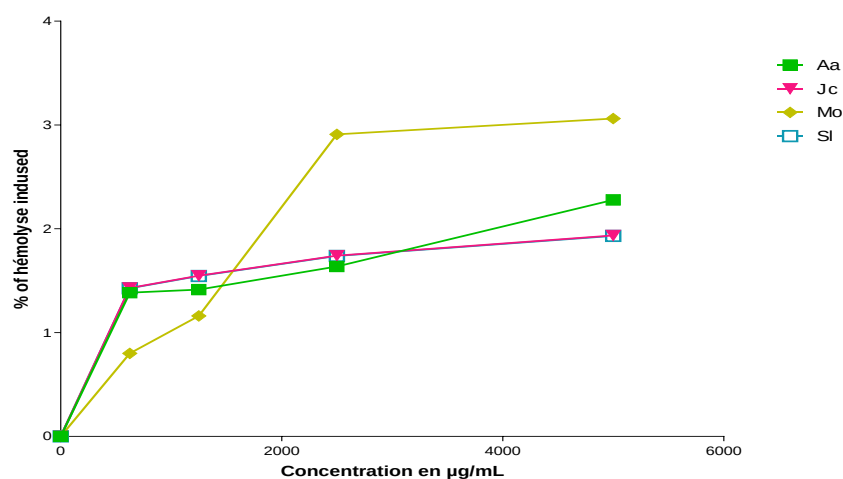


Fig. 8. Evaluation of the hemolytic potential of plants.

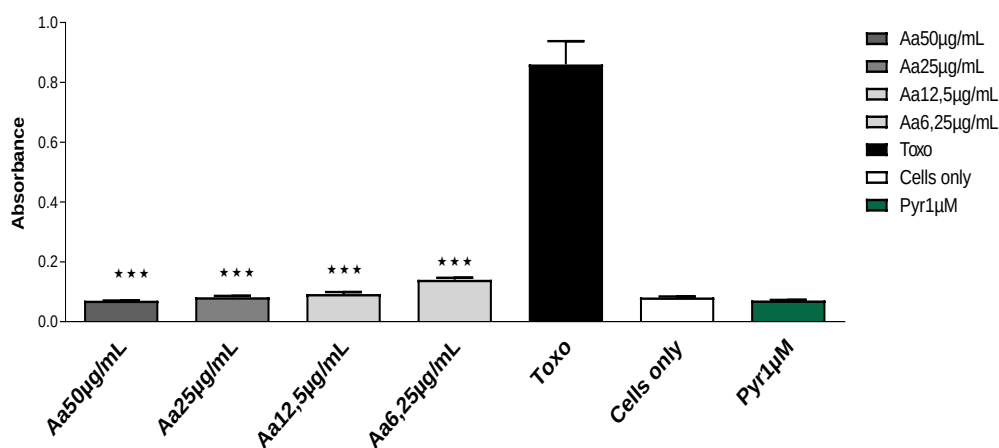


Fig. 9a. Determination of the antitoxoplasmic activity of ethanolic extracts from *Artemisia annua*

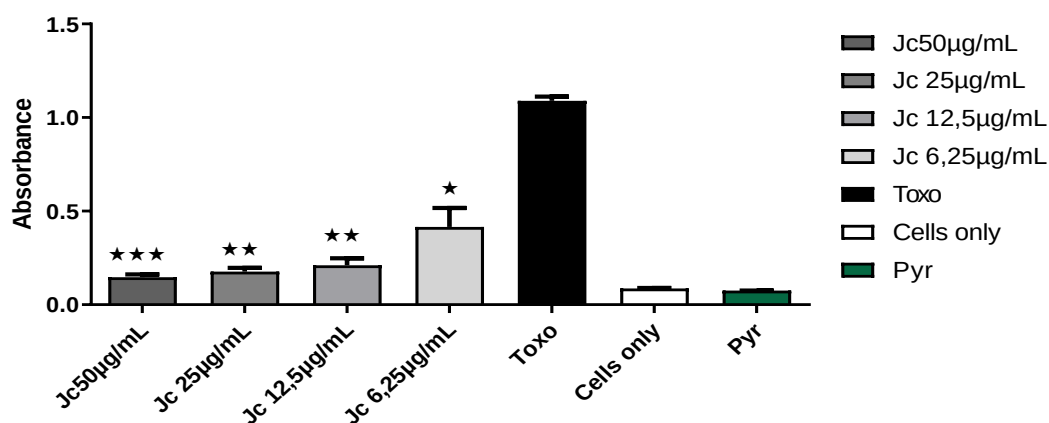


Fig. 9b. Determination of the antitoxoplasmic activity of ethanolic extract of *Jatropha curcas* leaves

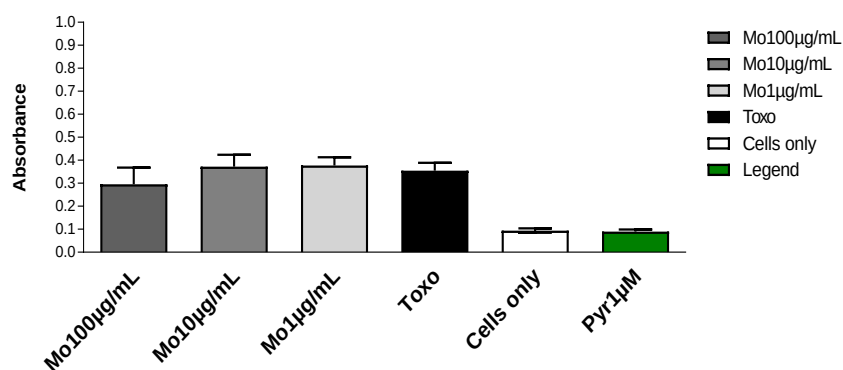


Fig. 9c. Determination of the antitoxoplasmic activity of ethanolic extracts from *Moringa oleifera*

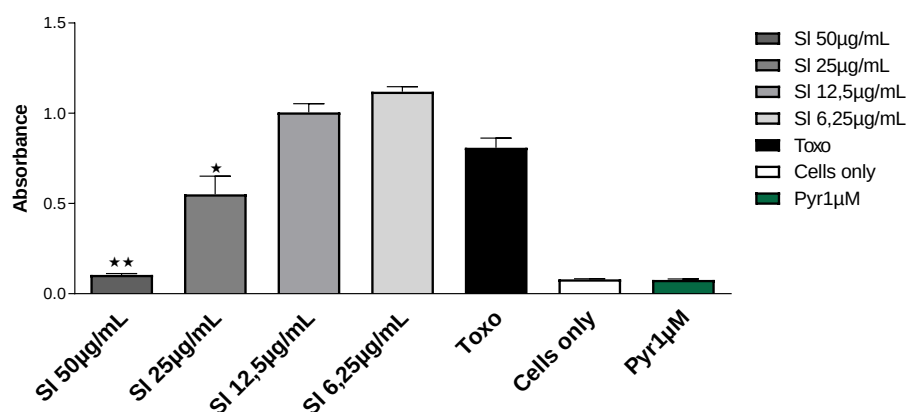


Fig. 9d. Antitoxoplasmic activity of alcoholic extract of *Sarcocephalus latifolius* roots

Table 4. IC50 values of different plant extracts

	<i>Artemisia annua</i>	<i>Jatropha curcas</i>	<i>Moringa oleifera</i>	<i>Sarcocephalus latifolius</i>
Alcoholic Extract	3.38	7.21	-	29.2

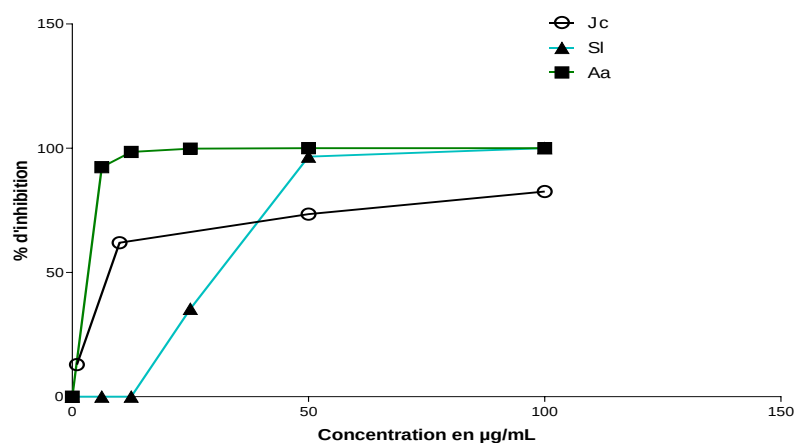


Fig. 10. Inhibition of *Toxoplasma gondii* tachyzoites

3.1.6 Détermination of selectivity index of plants extracts

The selectivity Index is a crucial parameter in drug development or the evaluation of bioactive compounds as plant extracts. We used this selectivity Index (SI) formula:

$$SI = \frac{CC_{50}}{IC_{50}}$$

Where: CC50 (Cytotoxic Concentration 50): This is the concentration of the plant extract that is toxic to 50% of the host cells (HFF cells).

IC50 (Inhibitory Concentration 50): This is the concentration of the plant extract that inhibits

50% of the targeted activity (tachyzoite of *Toxoplasma gondii*).

These results present the anti-*Toxoplasma gondii* activity (IC50) and host cell (HFF) cytotoxicity (CC50) ethanolic plant extracts. Notably, *Artemisia annua* showed the most potent activity (IC50 = 3.38 mg/mL) and the highest selectivity index (SI = 46.89), suggesting strong efficacy against the parasite with relatively low host cell toxicity. In contrast, *Jatropha curcas* and *Sarcocephalus latifolius* displayed lower potency and selectivity (SI = 4.19 and 3.93, respectively), while *Moringa oleifera* did not exhibit detectable anti-parasitic activity under these conditions.

Table 5. IC50 values of selectivity index of plant extracts

	<i>Artemisia annua</i>	<i>Jatropha curcas</i>	<i>Moringa oleifera</i>	<i>Sarcocephalus latifolius</i>
IC50 (mg/mL)	3.38	7.21	-	29.2
CC50 (mg/mL)	158.48	30.19	169.82	114.81
Selectivity index	46.89	4.19	-	3.93

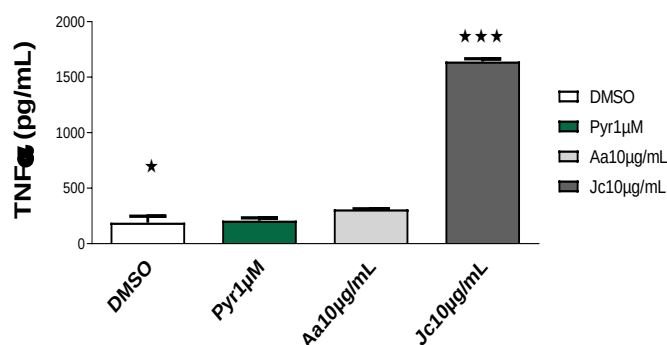


Fig. 11a. TNFα secretion by Raw 267.7 macrophages stimulated with plant extracts

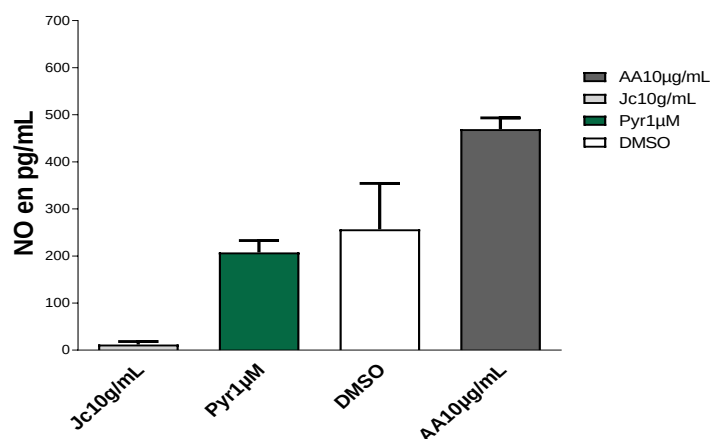


Fig. 11b. NO secretion by Raw 267.7 macrophages stimulated with plant extracts

3.1.7 Effects of extracts on cytokine secretion by macrophages stimulated with plant extracts

Fig. 11a. TNFalpha and NO secretion by Raw 267.7 macrophages stimulated with plant extracts.

Compared with the control (DMSO), the ethanol extracts of *Artemisia annua* and *Jatropha curcas* significantly increased TNFalpha secretion by macrophages (Fig. 11a).

3.2 Discussion

The aim of this study was to evaluate the in vitro antitoxoplasmic potential of selected medicinal plants from Togo, which are traditionally used for their antimalarial properties.

The phytochemical screening of ethanolic extracts from selected plants revealed a rich array of phytochemical groups known for their therapeutic potential, including tannins, flavonoids, polyphenols, and polysaccharides. These compounds are frequently utilized in pharmaceutical formulations that target antimalarial, antibacterial, and antifungal infections. Consistently, alcoholic extracts presented significantly higher concentrations ($p < 0.05$) of these key chemical groups, which aligns with previous studies that emphasized the efficacy of ethanol as a polar solvent for extracting diverse phytochemicals (Omoriege et al., 2010). Notably, *Artemisia annua* leaf extracts presented the highest levels of tannins and total phenols, which is consistent with prior reports documenting the presence of these compounds, along with flavonoids and polysaccharides, in various *Artemisia annua* extracts (Shahid, 2012). In terms of flavonoids, ethanolic extracts of *Jatropha curcas* stood out at the highest concentrations, corroborating existing research that has identified various polyphenolic glycosides, such as vanillic acid, gallic acid, rutin, naringin, and pyrogallol, within *Jatropha curcas* extracts (Namuli et al., 2011; Abd-Alla et al., 2009). These findings underscore the varied phytochemical profiles of the investigated plants and the solvent-dependent extraction efficiency of these bioactive compounds.

The biological activities assessed in this study, including antioxidant, cytotoxic, and antitoxoplasmic properties, appear to be intricately linked to the identified phytochemical profiles. The observed antioxidant capacity,

evaluated through both AAPH and DPPH assays, demonstrated that the ethanolic extracts generally exhibited superior activity. This can be directly correlated with the higher concentrations of total phenols and tannins in ethanolic extracts, as these compounds are well-established free radical scavengers. In the AAPH assay, which measures protection against free radical-induced erythrocyte hemolysis, and the DPPH assay, which assesses the reduction of DPPH radicals, the extracts demonstrated dose-dependent inhibition and reduction, respectively. This aligns with the established mechanism of phenolic compounds acting as antioxidants by directly interacting with reactive oxygen species (Martin-Nizard et al., 2003). Notably, the ethanolic extracts of *Artemisia annua*, with their high tannin and total phenol contents, presented the lowest IC₅₀ values and thus the highest antioxidant capacities, confirming the findings of previous studies (Heim et al., 2002). Interestingly, our results also seem to align with observations from Liu et al. (2008), who reported a negative correlation between flavonoid concentration and antioxidant capacity. For example, the ethanolic extract of *Jatropha curcas*, despite having the highest flavonoid concentration, did not exhibit the highest antioxidant capacity, suggesting that, in these extracts, phenols and tannins might be the dominant contributors to antioxidant activity.

The cytotoxicity evaluation, which used the UptiBlue assay, which measures cellular metabolic activity, revealed dose-dependent toxicity for all the extracts. This finding is further supported by the increased hemolytic potential observed for alcoholic extracts, particularly *Moringa oleifera*. Saponosides are recognized for their cytotoxic properties, inducing cell membrane lysis and necrosis (Vincken et al., 2007; Speroni et al., 2005), which underlies their cytotoxic activity and potential applications in cancer treatment. Furthermore, a correlation between flavonoid content and cytotoxicity was also suggested, as ethanolic extracts from *Jatropha curcas* and *Sarcocephalus latifolius* leaves, which are rich in flavonoids, also demonstrated significant cytotoxicity, echoing findings from Liu et al. (2005).

The investigation of antitoxoplasmic activity via the CPRG method revealed that ethanolic extracts of *Artemisia annua*, *Jatropha curcas*, and *Sarcocephalus latifolius* roots effectively inhibited *Toxoplasma gondii* tachyzoites in vitro. The ethanolic extract of *Artemisia annua* demonstrated antitoxoplasmic activity,

corroborating earlier findings on the antitoxoplasmic potential of *Artemisia annua* infusions (Taísa Carrijo de Oliveira et al., 2009). This activity may be linked to the high phenolic content of *Artemisia annua*, as these compounds are known to reduce oxidative stress and contribute to coccidian elimination (Singh, 2001). The significant antitoxoplasmic activity of *Artemisia annua* extracts, particularly the ethanolic extract with the lowest IC₅₀, suggests a potential mechanism of action similar to artemisinin's antiplasmodial activity (De Ridder et al., 2008). While the *Jatropha curcas* ethanolic extract also displayed notable antitoxoplasmic activity, its increased cytotoxicity necessitates cautious consideration because of its relatively low selectivity index. Interestingly, while *Moringa oleifera* is known for its antiplasmodial activity (Osei-Djarbeng et al., 2015; Olasehinde et al., 2012; Garima et al., 2011), its ethanolic extract did not exhibit inhibitory effects on *Toxoplasma gondii*, indicating differential sensitivity between these parasites and *Moringa oleifera* extracts. Overall, the observed antitoxoplasmic activities across various plant extracts, particularly those rich in phenolics, reinforce the potential of plant-derived compounds in combating parasitic infections, as demonstrated by previous studies on plants such as *Nigella sativa*, *Psidium guajava*, and *Tinospora crispa* (Osei-Djarbeng et al., 2015; Hanan et al., 2011; Wei et al., 2012).

In conclusion, this study established a clear relationship between the phytochemical profiles of the investigated plant extracts and their biological activities. Ethanolic extracts, which are generally richer in phenols and tannins, exhibited high antioxidant and antitoxoplasmic activities. The *Artemisia annua* ethanolic extract has emerged as particularly promising because of its potent antioxidant and antitoxoplasmic activities, coupled with its favorable phytochemical profile. *Jatropha curcas* also presents significant bioactivity, but its cytotoxicity warrants further investigation and careful consideration for potential applications. These findings support further research into the isolation and characterization of bioactive compounds from these plants, particularly focusing on *Artemisia annua* and *Jatropha curcas*, and exploring their potential for therapeutic development against oxidative stress-related diseases and parasitic infections such as toxoplasmosis.

Finally, the study of the plants extract effect on cytokine secretion by RAW264.7 macrophages

reveals a complex immunomodulatory activity. The ethanolic extract of *Jatropha curcas* and of *Artemisia annua* induced a significant increase in the secretion of TNF- α , a key pro-inflammatory cytokine in the immune response against *Toxoplasma gondii*. This stimulation of TNF- α production could be beneficial in the context of the infection by contributing to the activation of host defense mechanisms against the parasite. However, it is important to note that the extract of *Jatropha curcas* also induced a decrease in the secretion of nitric oxide (NO) which is an important mediator of macrophagic activity and the destruction of intracellular parasites and plays a crucial role in polarizing the Th1 immune response, which is essential for controlling toxoplasmic infection. Ethanolic extract of *Artemisia annua* increase both TNFalpha and NO production, that suggest it's proinflammatory activity.

Previous studies (Dégbé et al., 2018b) have shown significant *in vitro* anti-toxoplasmic activity in extracts of selected plants, notably *Tectona grandis* and *Vernonia amygdalina*. *In vitro* tests revealed varying antitoxoplasmic activities in *Tectona grandis* and *Vernonia amygdalina* extracts. *Tectona grandis* bark ethanolic extract (Tg-BE) showed promising activity (CI₅₀ of 15.3 mg/mL, SI 9.9), indicating notable anti-toxoplasmic effects with moderate selectivity. *Vernonia amygdalin* leaf ethanolic extract (Va-LE) exhibited superior activity (CI₅₀ of 5.6 mg/mL, SI 50.7). These *in vitro* results confirm the anti-toxoplasmic properties of *Tectona grandis*, particularly its bark extract, and of *Vernonia amygdalina*, notably its leaf extract (Degbe et al., 2018b).

This research may lead to improved, more effective, better tolerated, and affordable drugs, enhancing toxoplasmosis management, particularly in high-prevalence developing countries.

4. CONCLUSION

This investigation systematically evaluated the phytochemical composition and biological activities of selected Togolese plants that are traditionally used against malaria, with a focus on their potential against *Toxoplasma gondii*. Our findings revealed a strong correlation between the phytochemical profiles, particularly the abundance of polyphenols and tannins in ethanolic extracts, and the observed biological effects. Ethanolic extracts generally exhibited

superior antioxidant capacity, as assessed via AAPH and DPPH assays, which correlated positively with higher total phenol and tannin contents, notably in *Artemisia annua*. Conversely, hydroethanolic extracts tended to display greater cytotoxicity, potentially linked to higher concentrations of saponosides, although significant cytotoxicity was also observed in flavonoid-rich ethanolic extracts such as *Jatropha curcas*.

Crucially, ethanolic extracts of *Artemisia annua*, *Jatropha curcas*, and *Sarcocephalus latifolius* demonstrated significant *in vitro* inhibitory activity against *T. gondii* tachyzoites. *Artemisia annua*, which is rich in phenolics, has emerged as a particularly promising candidate that displays potent anti-toxoplasmic effects alongside strong antioxidant activity, corroborating previous reports and suggesting a favorable therapeutic profile. While *Jatropha curcas* also showed notable activity, its associated cytotoxicity warrants caution and necessitates further investigation into its selectivity index. The lack of anti-toxoplasmic activity of *Moringa oleifera* extracts, despite their known antiplasmodial properties, highlights their parasite-specific sensitivity.

These results lend support to the initial hypothesis of potential cross-activity, where plants effective against *Plasmodium* may also target *Toxoplasma*, as evidenced by the anti-toxoplasmic activity found in known antimalarial species (*A. annua*, *J. curcas*, *S. latifolius*, and previously reported *Vernonia amygdalina*). This underscores the value of exploring ethnobotanical leads for broad-spectrum antiparasitic agents.

In summary, this study validates the antitoxoplasmic potential of specific Togolese medicinal plants, identifying *Artemisia annua* and, with caveats regarding toxicity, *Jatropha curcas* and *Sarcocephalus latifolius* as priority species for further research. Future work should focus on the isolation and structural elucidation of the bioactive compounds responsible for the anti-toxoplasmic effects, detailed mechanistic studies, and *in vivo* assessments of efficacy and safety. These efforts hold significant promise for developing novel, potentially more accessible therapeutic strategies against toxoplasmosis, leveraging the rich biodiversity and traditional knowledge of Togo.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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