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Effect of *Aqueous Extract of Gymnanthemum Amygdalinum* Bark's on Experimental Cerebral Malaria

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Abstract

Malaria remains a major public health problem in the intertropical zone. Due to the growing problem of *Plasmodium*'s resistance to conventional antimalarials, which is largely responsible for the appearance of severe forms of the disease, there is an urgent need to discover new molecules. Most of these drugs are synthesized from plants or modelled on the structures of their compounds. *Gymnanthenum amygdalinum* (Asteraceae) have been reported to have antimalarial effects in traditional medicine. The objective of this work was to investigate the antiplasmodial and preventive activities of *G. amygdalinum* on *Plasmodium berghei*-induced cerebral malaria in mice. Mice were infested intraperitoneally with 200 µl of blood containing 10^7 infected red blood cells with delicate monitoring of signs of cerebral malaria. On the sixth day post-infestation, the different treatments extracts from the barks of *G. amygdalinum* were administered to the various groups of mice except the control mice. The results showed that *G. amygdalinum* had antiplasmodial and preventive properties on chronic *P. berghei* infection. All doses of *G. amygdalinum* showed significant suppressive activity ($P < 0.001$) compared with negative control. Mortality rates obtained two days after treatment were 77.56, 58.18, 53.46 and 38.22% respectively at doses 187, 93.50, 46.75 and 18.7 mg/Kg.

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Introduction

Cerebral malaria is one of the most important complications of *Plasmodium falciparum* Welch, 1897 infection. It is a disease whose pathophysiology is not well documented; however, a number of host-parasite and epidemiological factors have been proven to play a role or influence its pathogenesis (Idro *et al*., 2005; Lackner *et al*., 2006; McKenzi *et al*., 2008). Although no experimental model can fully reproduce all aspects of the disease, mouse models have been instrumental in the study of the pathophysiology. The most commonly used model is the infestation of mice susceptible to *Plasmodium berghei* Vinkel and Lips, 1948, strain Anka (Colette *et al*., 2004), which shares many similarities with human cerebral malaria (Hunt *et al*., 2003). Infested

mice develop a lethal neurological syndrome 6 to 12 days after infection (Rest, 1982; Grau *et al*., 1986; Neill *et al*., 1992). In humans, despite the deplorable consequences caused by this encephalopathy, little work has been done to help prevent its advent.

In order to contribute in this direction and with the aim of valorising the species of medicinal plants which have been the subject of little scientific work, the antiplasmodial activities of the decoction of the bark of *Gymnanthemum amygdalinum* (Del.) and their effects on the prevention of cerebral malaria in white mice *Mus musculus* Linnaeus, 1758 were evaluated.

Materials and Methods

Plant material

Plant material consisted of the barks of *G. amygdalinum* harvested from September to October 2017 in Dang (Adamawa Region, Cameroon), then dried under the shade, away from sunlight and reduces to powder using a mortar and a pestle.

To prepare the decoction, 10g of powder were introduced into a beaker containing 50ml of distilled water, then the solution was placed on a heating plate at 100°C for 20 minutes. The mixture was then filtered using filter paper (Whatman, FG/C). The filtrate obtained was subjected to evaporation in the oven (PROTAIS, France) maintained at 60°C for 24 hours. The obtained paste served as an extract for the rest of the experiment.

Animal material

It consisted of the white mice *Mus musculus* and *P. berghei*. The healthy albino white mice of both sexes, aged about two months, weighing between 20 and 22g, were obtained from the National Veterinary Laboratory (LANAVET) of Garoua. *Plasmodium berghei* strain used for experimental infestations came from partner in Montpellier.

Preparation of parasites and mice

The parasites were stabilized and stored in EDTA tubes before being stored in a refrigerator at -4°C (Helmby and Brian de Souza, 2008). Each tube was defrosted at 37°C in a water bath, then the parasites were immediately inoculated intraperitoneally to the donor mice. Thick smears were made every day to check the state of the infestation.

Infestation and treatment

On the day of the test, the donor mice previously infested with *P. berghei* trophozoites were introduced into a hermetically sealed jar, in which care was taken to place a cotton impregnated with diethyl ether. A few minutes later, the sleeping mice were removed from the jar, then their blood was taken using a Pasteur pipette through the jugular vein and introduced into a heparin tube. The parasite blood collected was diluted with physiological sodium chloride solution taking into account the parasitemia of the blood collected. The mice were infested intraperitoneally (IP) on the same day according to the method of Fidock *et al*. (2004) with 0.2 ml of previously prepared solution containing each on average 10^7 parasitized erythrocytes (Peters *et al*., 1948).

Treatment

Six batches of five mice each were formed (Table I). Each group, except for the control groups, received by gavage the different doses of plant decoction for 3 days from the sixth day post-infestation.

Assessment of Score indicators

To evaluate the effect of the test plant extract on infested mice, parasitaemia, temperature and body weight were measured every two days.

Parasitaemia

Thick smears were made from day 3 post infestation. These blood smears were stained with a solution of Giemsa diluted to 10% and then examined under an optical microscope at the 100X objective. The parasitaemia was determined by counting the number of parasites read in 10 microscopic fields. The parasite density (Pd: number of trophozoites /µl blood) was calculated using the following formula (WHO, 1982):

$$Pd = \frac{\text{Total number of parasites counted}}{\text{Number of fields}} \times 50$$

Temperature and Weight of animals

The mice temperature was measured before and after infestation of the mice by introduction of an electronic thermometer into the rectum of the animal.

The weight of the animals was evaluated at regular intervals of two days using an electronic kitchen scale.

Evaluation of the signs of cerebral malaria

The mice were observed three times a day and the diagnosis was made based on neurological signs (ataxia, disorientation, paraplegia and coma) from day 5 to day 12 post-infestations. Thus, the progression of cerebral malaria was controlled according to the presentation of ruffled coat, ataxia, hemiplegia, convulsions, coma and reduction in body temperature (Harms *et al*., 2008). This study was conducted with a predefined human endpoint: animals were deemed "terminal" when they recorded a body temperature below 32°C. Body temperature was measured three times a day non-invasively with a thermometer (Testo 845, Germany) and confirmed with a rectal probe (DM852 Ellab DK). When the temperature was below 32 °C, mice were considered to have cerebral malaria (Dadachova *et al*., 2006)**.** The clinical signs which have been evaluated to assess the severity of the disease are given in Table II.

Behavioural assessment

In order to provide a behavioural and functional profile of the mice every 24 hours, from day 3 to day 12 post-infection, the primary protocol of SHIRPA (SmithKline, Harwell, Imperial College, Royal Hospital, Phenotype Assessment) was used as described by Lackner *et al*. (2006)**.**

The Percentage of Suppression (Ps) was calculated in the preventive tests using the following formula:

$$Ps = \frac{(Pn - Pt)*100}{Pn}$$

with Pn: parasitaemia of negative control; Pt: parasitaemia of the treated group

The lethal dose 50 (LD50) was calculated using the linear regression line equation expressed as follows: Y = aX + b

with X = (5-b)/a, value of the decimal logarithm of the doses with, as hypothesis, Y = 5.

Mortality rates of *P. berghei* trophozoites were expressed using the probit table. The values of mortality probits were expressed as a function of the decimal logarithms of the doses of the various extracts. The mortality rates of trophozoites induced by the various extracts were compared using the ANOVA test. The influence of the factors was analysed using the ANOVA test (multiple factors). The materiality threshold was set at 5%.

Data analysis

The mortality rate of the parasite (T) was determined using the following formula (Tona *et al*., 2001):

$$T = \chi = \frac{(A-B)*100}{A},$$

With A and B, the parasite densities before and after the treatment respectively (the same animal being considered as control before treatment).

Analysis of variance (ANOVA) was performed to assess the difference between the positive control and the treated group followed by Tukey's post-hoc test using GraphPad Prism 8.1 software. P values ≤ 0.05 were considered statistically significant.

Results and Discussion

Effect of *Gymnanthemum amygdalinum* decoction on parasite density

The results of figure 1 reveal an increase in parasite density before the administration of the post-infestation treatments (day 3 - day 6). Mean values ranged from 170 ± 3.53 to 190 ± 11.18 trophozoites/µl of blood in day 6.

This figure also shows that, independently of the doses administered, the decoction of *G. amygdalinum* resulted in a significant reduction [F (4. 16) = 365. 2; P < 0.0001] of the parasite density at Day 2 post-treatment with respect to Day 6 post-infection of mice with *P. berghei*, proof of the effectiveness of this plant in combating in a timely manner the parasitaemia threshold likely to cause cervical malaria in mice. On day 10 post-infestation (Day 4 post-treatment), no increase in parasite densities was observed in the different groups treated with the decoction of *G. amygdalinum* where the values were markedly lower than those obtained on Day 2 post-treatment unlike the negative control where the parasitaemia had increased from 252 ± 9.08 to 263 ± 9.74 trophozoites/µl of blood. However, a significant decrease was noted between the groups treated at the different doses of the decoction and the negative control group [F (4. 16) = 1679; P < 0.0001]. On Day 12 post-infection, the final development stage of experimental cervical malaria, the mean parasite density of the

negative control group was 283 ± 17.58 trophozoites/µl of blood. A significant difference was observed compared to those treated at 187, 96.5, 46.75 and 18.7 mg/kg doses of *G. amygdalinum* where parasitaemia was respectively 16 ± 2.23, 18 ± 5.7, 23 ± 2.73 and 31 ± 4.18 trophozoites/µl of blood, which resulted in a significant and dose-dependent reduction in parasites compared with negative control.

Effect of *Gymnanthemum amygdalinum* on parasite mortality rate

Figure 2 reveals that on the second day of the treatment, all the doses of *G. amygdalinum* resulted in parasitic mortality rates of more than 50% except for the smallest dose (18.7 mg/kg) which induced a mortality rate of 38.22%.

On the fourth day post-treatment, decoction-induced parasitic mortality was greater than 60%. On the other hand, the mortality rates on the sixth day post-treatment passed the 80% milestone leading to a dose-dependent mortality of the parasite at periods conducive to the appearance of cervical malaria.

Effect of *Gymnanthemum. amygdalinum* on temperature

The analysis of temperature (Figure 3) indicates that before administration of the treatments, all the mice exhibited a drop in the temperature characteristic of a *P. berghei* infection. The temperature on day 0 was significantly higher than that taken on Day 6 post-infection, the initial day of *G. amygdalinum* treatments in all groups.

From days 8 to 12 post-infection, corresponding respectively to Days 2 to 6 post-treatment, all doses administered except the 187 mg/kg dose of *G. amygdalinum* at day 8 post-infection prevented the drastic reduction in temperature compared to negative control (INCT), a significant difference was noted on day 12 post-infestation [F (5. 20) = 9.549; P < 0.0001].

Effect of *Gymnanthemum amygdalinum* on weight gain percentage

Before administration of treatments (day 0-day 6 post-infestation, Figure 4), no significant difference [(FJ0 (5.20) = 2.458; P = 0.0684; FJ6 (5.20) = 2.458; P = 0.0684)] was observed in the weight gain percentage (Figure 4).

After treatment, all doses of *G. amygdalinum* increased body weight compared to negative control (INCT). However, a significant increase in weight at doses 187 and 46.75 mg/kg was observed compared to negative control on the 12th day post-infestation[(F (5.20) = 3.466; P = 0.0204].

Influence of factors Days/Doses of *Gymnanthemum amygdalinum*

The parasite density decreased as a function of time and of doses of *G. amygdalinum* administered (Table III). In view of the F-ratio values, the dose administered influenced more than the treatment time.

This table shows that the dose administered and the day of treatment on decoction of *G. amygdalinum* influenced the mortality rate (P < 0.001) of the parasites, the treatment time being a key factor in therapeutic research. Such results with crude extracts are of paramount importance in the management of critical malaria cases because of their effectiveness from the first days of treatment.

For the decoction of *G. amygdalinum*, the linear regression equation line obtained from probit of mortality rates was: Y = 0.0738x + 6.6838 (Figure 5). The LD50 value after calculations was 1.35 mg/kg.

Effect of *Gymnanthemum amygdalinum* on clinical signs

Before the treatment of infested mice, all the experimental groups had a SHIRPA score less than or equal to 9, although significant fluctuations (P < 0.001) were observed on days 5 and 6 post-infection in the groups tested (Figure 6).

From day 8 to 12 post-infestation, a significant increase in SHIRPA score was noted in the negative control group and that treated with dose 18.7 mg/kg of *G. amygdalinum* (20.13) at Day12 post-infestation compared to the healthy control. However, administration of the 187, 96.5 and 46.75 mg/kg doses of *G. amygdalinum* a significantly (P < 0.001) reduced these scores to 0.2 and 7.0 respectively (Figure 6).

This study explores the antiplasmodial activities of *G. amygdalinum* bark on *P. berghei* infection in mice. To account for a possible preclinical effect of drugs and the possible involvement of the immune system in the eradication of an infection, studies on the antimalarial

properties of substances generally use *in vivo* models (Hilou *et al*., 2006). Although primate models provide a better prediction of the evaluation of antimalarial efficacy in humans, the rodent model is used as a first step to test the efficacy of most compounds (Fidock *et al*., 2004). The mouse model was also validated for the identification of several conventional antimalarials such as chloroquine, halofantrine, mefloquine, artemisinin and its derivatives (Ryley and Peters, 1970; Fidock *et al*., 2004). *Plasmodium berghei* is an appropriate parasite, commonly used because of its greater susceptibility to develop cerebral malaria comparable to that caused by *P. falciparum* in humans (Fidock *et al*., 2004).

All doses of *G. amygdalinum* showed highly significant suppressive activity ($P < 0.001$) compared with negative control. This could be explained by the possible synergistic effects that could have existed between the various components of the crude extract. Treatments with *G. amygdalinum* doses showed a highly significant decrease ($P < 0.001$) in parasitaemia compared with the negative control. Achievement of morality rates of 77.56%, 58.18%, 53.46%, 38.22% respectively at doses 187, 93.5, 46, 75 and 18.7 mg/kg two days after administration of the decoction of *G. amygdalinum* suggests a reduction in parasitaemia after the first dose. The low mortality observed at the lowest dose (18.7 mg/kg) could be due to the fact that at these doses, the extract had not accumulated sufficiently to cause considerable suppression of the parasite. From day 12 post-infestation, animals treated with *G. amygdalinum* resulted in parasite mortality rates between 82.83% and 90.63%. This confirms that the plant material used has effective antiplasmodial activity in the later stages of infection. In contrast, there was an increase in the level of parasitaemia in the control group; this shows that just as in humans, *Plasmodium* will multiply in mice until it is intercepted by an effective antimalarial.

Table.1 *Distribution and treatment of experimental groups*

Groups	Treatments	Doses (mg/kg)
INCT (negative control)	*Plasmodium berghei* + Distilled water	10
Group 1	*Plasmodium berghei* + *Gymnanthemum amygdalinum*	18.7 (Ga18.7)
Group 2	*Plasmodium berghei* + *Gymnanthemum amygdalinum*	46.75 (Ga 46.75)
Group 3	*Plasmodium berghei* + *Gymnanthemum amygdalinum*	93.5 (Ga 93.5)
Group 4	*Plasmodium berghei* + *Gymnanthemum amygdalinum*	187 (Ga 187)
UC (not-infested)	Normal Control + Distilled water	10

INCT= Infested Control Treated with Distilled water; UC=Uninfested Control

Table.2 *Scoring for the definition and severity of experimental cerebral malaria disease according to clinical signs*

Appearence	**Normal** **Slight change** **Average change** **Deep change**	**0** **1** **2** **3**
Behaviour	Normal Jerky March Partial paralysis, Immobile Convulsion, Coma *	0 1 2 3
Weight	Normal Less than 10% Body weight loss 10% -15% * body weight loss Greater than 15% body weight loss *	0 1 2 3
Body Temperature	Normal (36-37°C) 34-35°C 32-33°C* Low< 32°C	0 1 2 3

Score ≥ 10: Mice with clinical signs of cervical malaria, *: severity of disease

Table.3 *Interactions between days and doses of* Gymnanthemum amygdalinum *treatments*

Source	Sum of squares	ddl	Square mean	F-ratio	P value
Dose	8593.44	3	2864.48	47.13	<0.0001
Day	269141.0	3	89713.6	1476.01	<0.0001
Interaction Day/ dose	6975.31	9	775.035	12.75	<0.0001
Residual	3890.0	64	60.7813		
Total	288600.0	79			

Determination of the lethal dose 50 (LD50) of the decoction of *Gymnanthemum amygdalinum*

Figure.1 Variation in parasite density before and after treatment with *G. amygdalinum*.

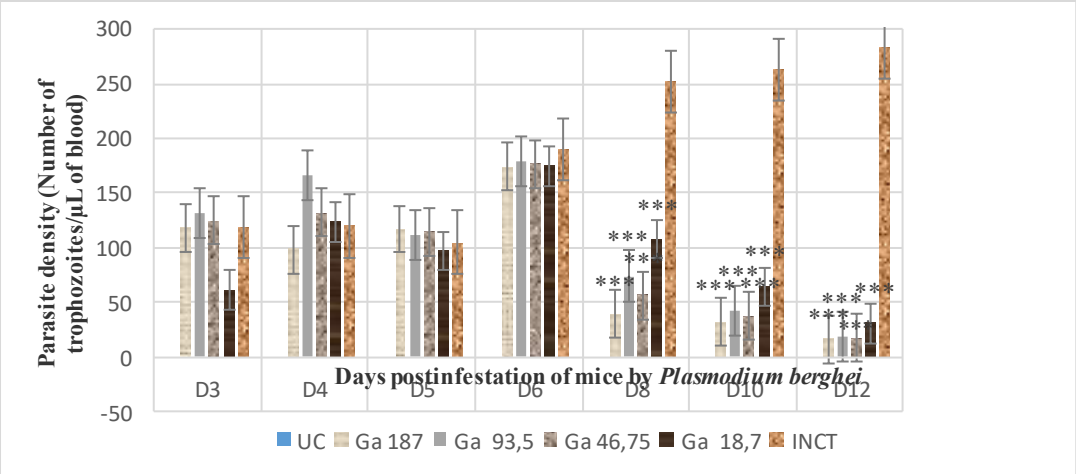


Figure.2 *Effect of* Gymnanthemum amygdalinum *decoction on trophozoite mortality.*

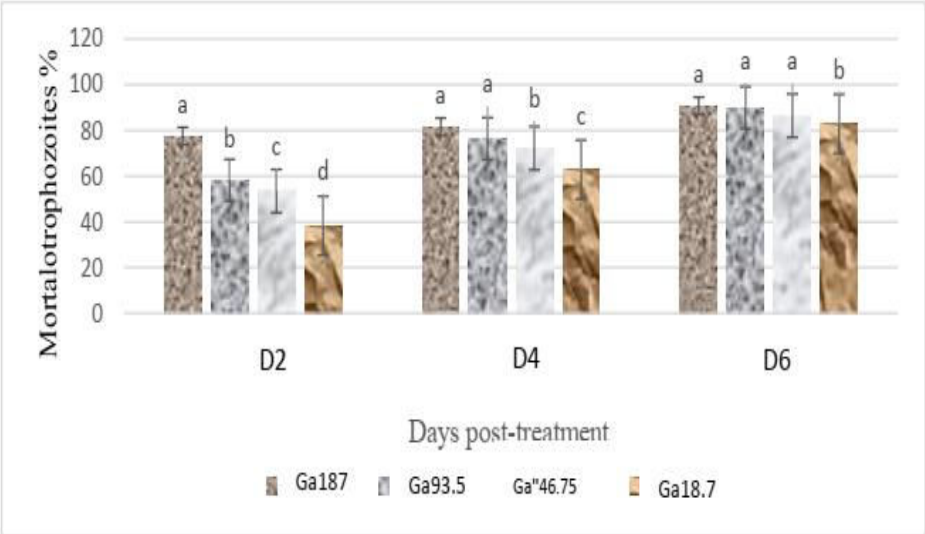


Figure.3 *Effects of* Gymnanthemum amygdalinum *on the rectal temperature of mice infested with* Plasmodium berghei.

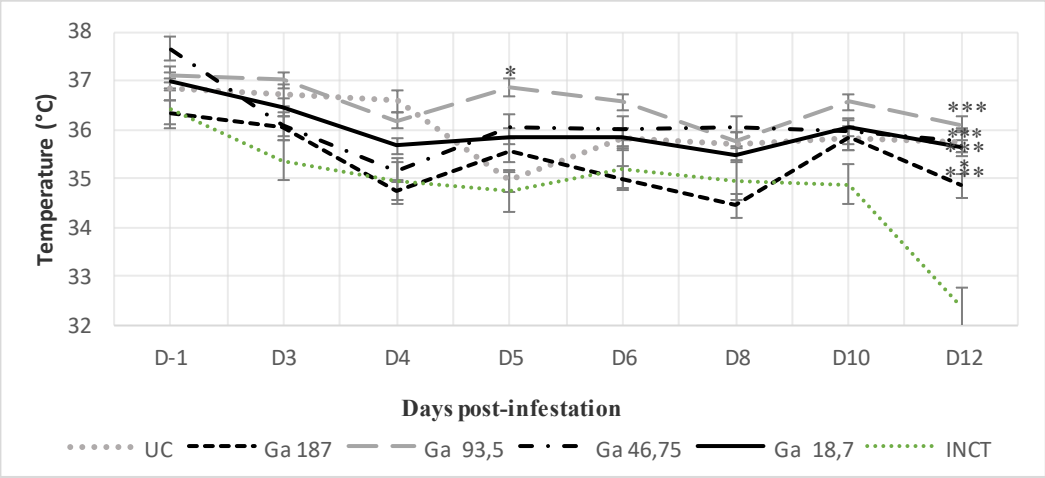


Figure.4 *Effect of* Gymnanthemum amygdalinum *on the percentage of weight gain in mice infested with* Plasmodium berghei.

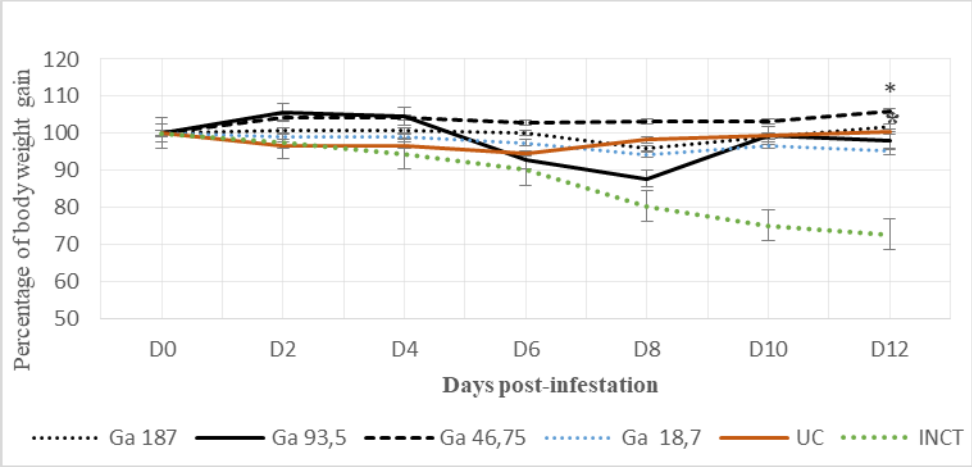


Figure.5 *Regression line of the mortality (in probit) of* Plasmodium berghei *as a function of the decimal logarithm of the doses of the decoction of* Gymnanthenum amygdalinum.

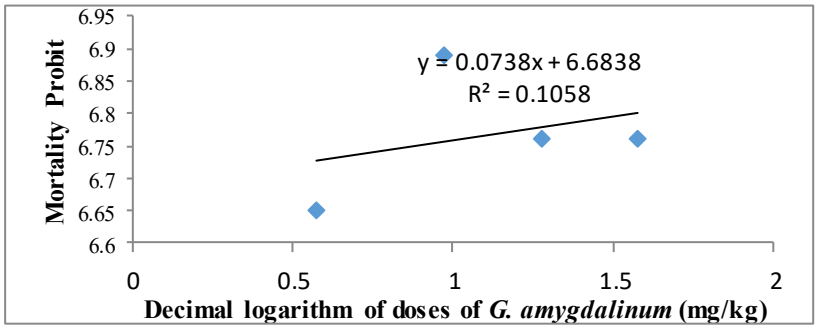
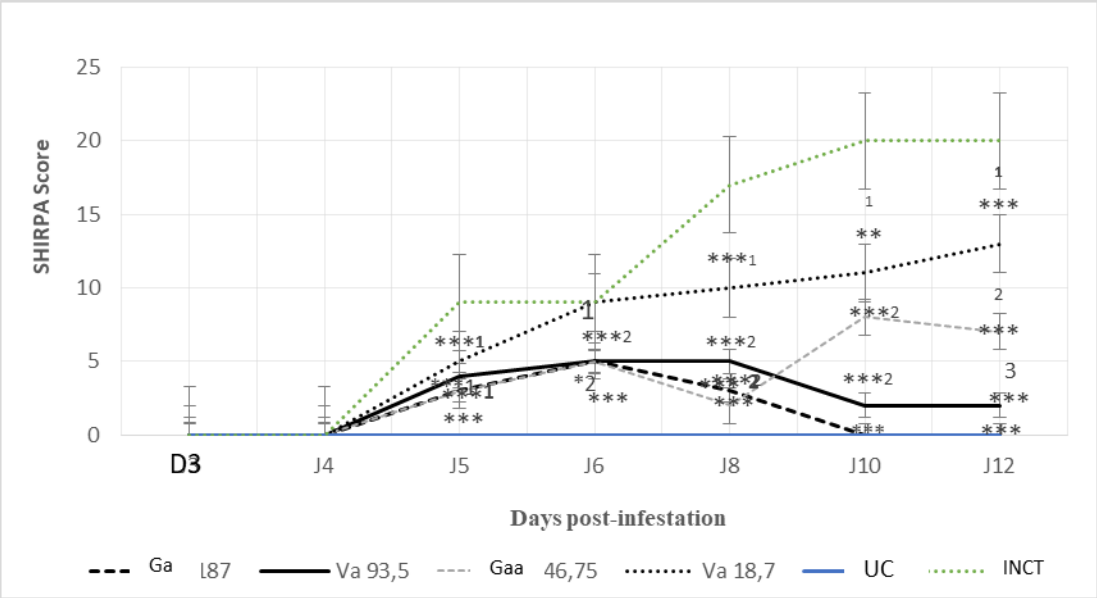


Figure.6 *SHIRPA clinical score during the antiplasmodial activities of* Gymnanthemum amygdalinum *administered on day 6 post-infection. Ga:* Gymnanthemum amygdalinum,



A suppressive test using the mouse model provides a preclinical indication of the potential bioactivity of the test sample (Peter and Anatoli, 1998; Fidock *et al*., 2004). Antiplasmodial activity can be classified as moderate, good and very good if an extract has a percentage of suppression equal to or greater than 50% at doses 500, 250 and 100 mg/kg body weight respectively (Obey *et al*., 2018). In this study, the level of decoction suppression was greater than 80% at day12 post-infestation, the terminal stage of infection. Based on the above classification, these plants are considered to have good prophylactic activity. This claim has been highlighted by studies that have reported antimalarial activity of certain plants such as *Terminalia chebula*, *T. bellerica* (Pinmai *et al*., 2010) and *T. macroptera* (Haidara *et al*., 2018). In addition, the parasite suppression presented by *G. amygdalinum* was comparable to the results of previous studies conducted on the methanolic extract of *Artemisia abyssinica* (Adugna *et al*., 2014), *Croton macrostachyus* (Mekonnen, 2015) and *Strychnos mitis* (Fentahun *et al*., 2017). However, the chemosuppression of the aqueous extract was lower than that of a study conducted on the aqueous extract of *Strychnos mitis* (Fentahun *et al*., 2017)**.**

Temperature reduction and weight loss are common manifestations of malaria infection in rodents, which develop due to the intensity of infection (Yun, 2010; Mengiste *et al*., 2012). A decrease in metabolic activity in infested mice occurs before death and is accompanied by a drastic decrease in internal temperature (Bantie *et al*., 2014). Unlike malaria in humans, infested mice experience a decrease in body temperature as a result of brain haemorrhage and a decrease in metabolic rate before death (Bantie *et al*., 2014). Thus, antimalarials obtained from plants should prevent this decrease in infested mice (Bantie *et al*., 2014; Fentahun *et al*., 2017; Hintsa *et al*., 2019). According to the literature, the normal temperature of the mice varies between 36.5°C and 38°C. Although the treated and untreated mice developed a certain hypothermia in the suppressive and prophylactic tests, the hypothermia was however less pronounced in the groups treated with the decoction compared to the negative control. Although below standard temperatures, all doses of *G. amygdalinum* administered except the 187 mg/kg dose at day 8 post-infestation prevented this drastic reduction in body temperature compared to negative control (INCT). The difference was not significant [F (5.20) = 9.549; P < 0.0001] than at day 12 post-infestation. These observations have been reported and confirmed by several studies on different strains of *Plasmodium* (Tarkang *et al*., 2014; Nardos *et al*., 2017). In suppressive and prophylactic tests, all doses of *G. amygdalinum* showed an increase in body weight compared to negative control (INCT). However, only the 187 and 46.75 mg/kg doses of *G. amygdalinum* resulted in a significant increase in weight compared with negative control [(F (5.20) = 3.466; P = 0.0204] on the

12th day post-infestation (Figure 4). Weight reduction in untreated mice may be due to reduced food intake, dysfunctional metabolism, and malaria-associated hypoglycaemia (Basir *et al*., 2012). This activity may contribute to improved parasite clearance in mice treated with decoction (Mengiste *et al*., 2012; Nureye *et al*., 2018). The effect of *G. amygdalinum* on temperature and body weight in infested mice could be attributed to the significant suppression of parasitaemia and the consequent attenuation of the overall pathological effects of infection (Nureye *et al*., 2018).

The SHIRPA Protocol evaluates mouse behaviour to reflect the real-time function of the central nervous system (Rogers *et al*., 1997; Lackner *et al*., 2006). It can be used to objectively evaluate the pathological process in mice and provides a tool to evaluate new adjuvantive therapies. During the observation period, mice in the negative control group gradually showed signs of instability in walking, ataxia and disappearance of the atrial reflex, convulsions, symptoms of coma and death. A significant increase ($P < 0.001$) in SHIRPA score was observed consistent with neurological symptoms observed in mice with cerebral malaria (Lackner *et al*., 2006). Mice treated at all doses of decoction significantly reduced this score on days 8, 10, 12 post-infestation when compared to negative control. Based on neurological and behavioural assessment specific to cerebral malaria, decoction of *G. amygdalinum* was confirmed to prevent significant deterioration ($P < 0.001$) of neurological functions. It has been shown through the models put forward in this work, the decoction of *G. amygdalinum* prevented significant deterioration of neurological functions with the exception of animals treated at dose 18.7 mg/kg of *G. amygdalinum* which had a SHIRPA score of more than 10 and whose value was equal to the negative control on the 12th day post-infestation, evidence of brain damage although it resulted in significant suppression ($P < 0.001$) of parasitaemia as compared to the negative control.

In conclusion, the different doses of *G. amygdalinum* administered to the mice prevented the development of severe malaria. The antiplasmodial activities of *G. amygdalinum* in the prevention and suppression of the parasite while inhibiting the pathology induced when the fatal outcome was evident were described in this study. This plant proved effective on the cardinal signs of cerebral malaria that are the reduction in weight and temperature as well as the increase in SHIRPA score observed in the negative control group.

Conflicts of Interest

The authors do not have any possible conflicts of interest

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