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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2021.571.578

Research Article
In vivo Antimalarial, Antioxidant Activities and Safety of *Carapa procera* DC. (Meliaceae)

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Abstract

Background and Objectives: *Carapa procera* is a popular herb used by traditional healers in the western part of Burkina Faso. In a previous study, *Carapa procera* showed interesting antiplasmodial activity *in vitro* against *P. falciparum*. The present study aimed to evaluate its *in vivo* potential against malaria parasites and its safety in mice. **Materials and Methods:** The antimalarial activity of the ethanolic extract was evaluated on *Plasmodium berghei* Anka in the Naval Medical Research Institute (NMRI) mice using the Peters 4-day suppressive test. The acute toxicity was performed according to the Lorke method and sub-acute toxicity following the Seewaboon method. The polyphenols and flavonoids were determined by colorimetric methods. The antioxidant activity of the extract was evaluated *in vitro* by Ferric Reducing Antioxidant Power (FRAPP) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) methods. **Results:** *Carapa procera* had a good antiplasmodial activity at a dose of 250 mg kg^{-1} b.wt. Phytochemical screening revealed the presence of polyphenols and flavonoids in the extracts. Soxhlet ethanolic extracts had the highest content in polyphenols and flavonoids. The antioxidant activity of Soxhlet ethanolic extracts was better than macerated extract by DPPH method and FRAP method. Besides, no mortality in mice was recorded with the soxhlet ethanolic extract. No toxic signs were observed in animals in the sub-acute toxicity test. **Conclusion:** *Carapa procera* soxhlet ethanolic stem bark extract had a good *in vivo* antimalarial activity against *Plasmodium berghei* infection in mice and the extract was relatively safe when administered orally in mice.

Key words: *Carapa procera*, malaria, toxicity, *P. berghei*, *in vivo*, polyphenols, antioxidant

Citation: Koama, K.B., R.S. Yerbanga, N.T.R. Meda, N. Ouedraogo, O. Da, J.B. Ouedraogo, M.T. Coulibaly and G.A. Ouedraogo, 2021. *In vivo* antimalarial, antioxidant activities and safety of *Carapa procera* DC. (Meliaceae). Pak. J. Biol. Sci., 24: 571-578.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Malaria remains the greatest burden of morbidity and mortality in the world. In 2018, 228 million cases with 40,5000 deaths were reported in the world[1]. About 94% of these deaths occur in sub-Saharan Africa. In South Asia and Africa, malaria continues to affect pregnant women and children mostly and around 80% of deaths occur in pregnant women and children under 5 years[1]. In Burkina Faso, around 12 million malaria cases were reported causing 4,144 deaths in 2017[2].

Currently, recommended treatments by World Health Organization (WHO) are based on Artemisinin-based Combination Therapies (ACTs), however their costs seem to be expensive for populations in endemic countries[3,4]. *Plasmodium* resistance to antimalarial drugs is also challenging the access to effective treatment of the disease[5,6]. Besides, mosquito resistance to insecticide is increasing, limiting the effectiveness of vector control programs[7]. In a remote region, malaria has been treated with medicinal plants. Patients often first consult traditional herbalists and healers before visiting the nearest clinic or hospital[4]. Numerous antimalarial recipes are available worldwide and some have been scientifically validated from the most historic, *Cinchona officinalis* (Rubiaceae) to the most recent, *Artemisia annua* (asteraceae), *Cryptolepis sanguinolenta* (Periplocaceae) and many others[8]. The treatment of malaria remains a challenge and finding new therapeutic agents from plants can be a solution.

In the western region of Burkina Faso, *Carapa procera* DC. (Meliaceae) is widely used to treat malaria. *Carapa procera* is a small forest timber tree up to 30 m tall, which is found in South America in Surinam, French Guiana and the State of Amazonas in Brazil, as well as in western and central Africa[9,10]. The nut of the plant is used to treat skin diseases and also used as repellent and insecticide[11]. A Ring D-Seco-Tetranortriterpenoid isolated from seeds of *Carapa procera* was active against Breast Cancer Cell Lines[12]. Crude ethanolic extract of *Carapa procera* has shown *in vitro* activity against *Plasmodium falciparum,* chloroquine-sensitive 3D7 strain[13]; elsewhere, the crude stem bark displayed *in vitro* anti-sickling activity[14].

Until now, no *in vivo* antimalarial study has been performed on the plant. The objective of this study was to evaluate the antimalarial activity, antioxidant activity and toxicity of *Carapa procera* stem bark in mice.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Parasitology, Pharmacology Laboratory, Bobo-Dioulasso from January, 2018-December, 2020. Bobo-Dioulasso is located in the Western region of Burkina Faso at around 360 km from Ouagadougou, the capital city of the country.

Plant material collection: The stem bark of *C. procera* was collected from Tin surroundings, in the Western region of Burkina Faso. *Carapa procera* was identified by Dipama Pascal at Bobo-Dioulasso Research Institute for Health Sciences and voucher specimen Cp 2018 was deposited in the unit of pharmacognosy at Bobo-Dioulasso Research Institute for Health Sciences. The stem barks were thoroughly rinsed with water, reduced to small pieces, air-dried at room temperature for about two weeks and powdered with a mechanical grinder.

Extraction: Two organic extracts (macerated ethanolic and soxhlet ethanolic extracts) were prepared.

Macerated ethanolic: About 100 g of dried powdered stem barks were macerated with 1 L of ethanol at room temperature for about 24 hrs with stirring.

Soxhlet extraction: A total of 20 g of powdered stem barks in 200 mL of ethanol were extracted by a soxhlet extractor (Behr Labor Technik™ behrotest™ R 104 S, Germany) for 4 hrs. The experiment was repeated five-time to extract a total of 100 g of stem bark powder). Then, the supernatant of the mixture was filtered through a Whatman filter paper (Whatman™ Chalfont, Buckinghamshire, UK).

Extracts were evaporated to dryness with an R-200 rotary evaporator (BUCHI Labortechnik AG, United Kingdom) at constant temperature (60°C) and pressure below 1 bar.

Determination of total polyphenols and flavonoids content

Total phenolic: The total phenolic content of extracts was determined according to the Folin-Ciocalteu method[15]. To 0.5 mL of extract was added 2.5 mL of diluted Folin-Ciocalteu (MP Biomedicals, USA) reagent 0.2 N. The mixture was allowed to stand at room temperature for 5 mn and 2 mL of 20% (w/v) carbonate (Na_2CO_3, 75 g L^{-1}) was added. The absorbance was then measured at 760 nm with a spectrophotometer (Thermo Scientific™ GENESYS™ 30 Visible Spectrophotometer, EU) against a blank and compared to a gallic acid curve

($Y = 1.7298x+0.0278$; $R^2 = 0.9921$). A standard calibration curve was plotted using gallic acid (Sigma-Aldrich, Germany) 0-200 mg L^{-1}. Total phenolic content was determined as gallic acid equivalents (mg EAG/100 mg extract). Each sample was analyzed in triplicate.

Total flavonoids: The total flavonoids content was estimated according to the Dowd method as adapted by Arvouet-Grand *et al.*[16]. The measurement is based on the formation of an aluminium complex with maximum absorption at 415 nm. A total of 0.625 mL of extract solution (0.1 mg mL^{-1}) was mixed with a solution of 0.625 mL of aluminium trichloride (Honeywell Fluka™) in methanol (2%). The absorption was measured after 10 mn against a blank. Quercetin (Sigma-Aldrich, Germany) was used as a reference compound to produce the standard curve (Y = 1.259 e-02 *x; $r^2 = 0.9990$) and absorbance was measured at 415 nm. The results were expressed as mg of quercetin equivalents (QE)/100 mg extract. Each sample was analyzed in triplicate.

Iron (III) to iron (III) reduction activity (FRAP): The total antioxidant capacity of each extract was determined using the iron (III) reduction method[17]. The diluted aqueous solution of each extract (1 mL), at a concentration of 100 µg mL^{-1}, was mixed with phosphate buffer (0.2 M, pH 6.6, 2.5 mL) and 1% aqueous potassium hexacyanoferrate [$K_3Fe(CN)_6$] (SLR, Fisher Chemical) solution (2.5 mL). After 20 min incubation at 50°C, trichloroacetic acid (10%, 2.5 mL) was added and the mixture was centrifuged at 3000 rpm for 10 min. Then, the upper layer solution (2.5 mL) was mixed with water (2.5 mL) and aqueous $FeCl_3$ (0.1%) solution (0.5 mL). The absorbance was read at 700 nm and ascorbic acid (Sigma-Aldrich, Germany) was used to produce the calibration curve. The iron (III) reducing activity was expressed in mmol ascorbic acid equivalents/g of extract. Each sample was analyzed in triplicate.

DPPH radical method: The ability of the extract to scavenge 2,2-diphenyl-1-picrylhydrazyl radical (Fischer Scientific) was evaluated as described previously[18,19]. A total of 1.5 mL of extract was mixed with 3 mL of DPPH (0,02 mg mL^{-1}) and incubated for 15 min in the dark. Methanol was used as the blank. The absorbances were read at 517 nm and antioxidant content was determined using a standard curve of ascorbic acid (0-10 µg mL^{-1}). The results were expressed as mg of Ascorbic Acid Equivalent Antioxidant Content (AEAC) per gram of extract. Each sample was analyzed in triplicate.

Parasites and experimental animals: Female NMRI albino mice aged 8-12 weeks and weighing 25±2 g from the International Centre for Research and Development on Livestock in Sub-humid Areas in Bobo-Dioulasso were used. The animals were housed in the same environmental conditions (temperature 25°C, 12 hrs photoperiod) and fed with standard food provided by International Centre for Research and Development on Livestock in Sub-humid Areas in Bobo-Dioulasso, Burkina-Faso. ANKA *P. berghei* strain originally obtained from Malaria Research Reagent Resource Center (MR4) was maintained by serial passage of blood from infected to uninfected mice. Experiments were conducted under the international guidelines for animal care.

Ethical considerations: This study protocol was approved by the national ethic review board of "Comite d'Ethique pour la recherche en sante" (ref:2015-5-056/CERS). The animals were used following Directive 86/609/EEC and compliance with animal welfare assurance guidelines for foreign institutions (OLAW A5926-01). All animals have been provided by the lab of animal production in the International Centre for Research and Development on Livestock in Sub-humid Areas in Bobo-Dioulasso, Burkina-Faso), reference centre in West and Central Africa.

***In vivo* antiplasmodial activity test:** Three doses (100, 250 and 500 mg kg^{-1} b.wt.) of each extract were used to treat animals. The extracts were dissolved in distilled water. The experiments were performed in mice according to Peters' 4-day suppressive test[20]. Mice were randomly divided into 6 mice per group. On day 0, the mice were inoculated with 10^7 parasitized red blood cells by intraperitoneal route. Two hours after infection, the animals received orally (PO), 200 µL of each dose of extract once a day from day 0-3. The control group received only the solution used to dissolve the extracts. On day 4 thin blood smears were made with blood drawn from the tail of mice; fixed with methanol when dried and stained with Giemsa 10%. The slides were read with an optical microscope, under a 100X oil immersion objective. Each experiment was repeated three times. The mean parasitemia of each group of mice was then calculated.

The percentage inhibition of parasitemia was calculated according to the formula previously described by Fidock *et al.*[21].

Acute toxicity test: The acute toxicity (LD_{50}) of the active ethanol extract was evaluated using the Lorke method[22]. NMRI mice, aged 8-12 weeks weighing 25±2 g were used.

The animals were divided into six groups of six mice (three female and three male) and received the following extract doses: 1500, 2250, 3375 and 5062.5 mg kg^{-1} b.wt. The extracts previously dissolved were administered orally as a single dose. The control group received the distilled water used to dissolve the extracts; after treatment, animals were monitored for 14 days; they were weighed first at the beginning and on days 7 and 14. Mortality, as well as behavioural and physical changes, were also recorded.

Sub-acute toxicity test: The sub-acute toxicity test with Soxhlet ethanolic extract was evaluated using the seewaboon method[23]. Wistar rats, 8-12 weeks old and weighing 200±10 g were used. Animals were divided into three groups of six rats (three groups of males and three groups of females) and received orally 125 and 250 mg kg^{-1} b.wt. once a day for 14 days; the control group received the solution used to dissolve the extract, under the same experimental conditions. The rats were followed for 28 days. Body weight, signs of toxicity and mortality were recorded. The day after the test, all rats were fasted and anaesthetized. Blood was collected for evaluation of biological parameters. Serum was tested for Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), urea and creatinine (Crea) using an automated analyzer (ARCHITECT). Heart, lung, liver, kidney and spleen samples were collected from all rats for visual detection of macroscopic lesions.

Statistical analysis: Microsoft Excel 2016 were used for data analysis and R software (version 3.6.0 2019).

Values are presented as mean±standard deviation. Statistical significance was determined at the p = 0.05 level and performed by One-way analysis of variance (ANOVA) followed by Dunnett's post-test.

RESULTS

Total phenolics and flavonoids: The content of polyphenols in the Soxhlet extract was estimated at 43.20±0.0.06 mg EAG/100 mg and 38.76±0.34 mg EAG/100 mg for the macerated extract. The Soxhlet extract (43.20±0.06 mg EAG/100 mg) was found to have a relatively higher content of polyphenols compared to the macerated extract (38.76±0.34 mg EAG/100 mg), p<0.001 (Table 1).

Flavonoid's content was estimated at 1.47±0.04 mg EQ/100 mg for the soxhlet extract and 1.22±0.1 mg EQ/100 mg for the macerated extract. Soxhlet extract (1.47±0.04 mg EQ/100 mg) had higher level of flavonoids than macerated extract (1.22±0.1 mg EQ/100 mg) (p = 0.01 (Table 1).

Table 1: Total phenolics and flavonoids contents of *C. procera*

Extracts	Total phenolics (mg EAG/ 100 mg of extract)	Total flavonoids (mg EQ/ 100 mg of extract)
CP-S	43.20±0.06	1.47±0.04
CP-M	38.76±0.34	1.22±0.1

CP-S: *Carapa procera* soxhlet ethanolic extract, CP-M: *Carapa procera* macerated ethanolic extract

Table 2: Antioxidant capacity of *C. procera*

Extracts	FRAP (mg AEAC g^{-1} of extract)	DPPH (mg AEAC g^{-1} of extract)
CP-S	518.20±2.42	15.99±0.04
CP-M	372.27±3.64	15.57±0.01
Quercetin	5991.48±75.56	646.85±1.48
Trolox	2211.24±36.17	765.99±7.70

FRAP: Ferric reducing antioxidant power, DPPH: 2,2-diphenyl-1-picrylhydrazyl, CP-S: *Carapa procera* soxhlet ethanolic extract, CP-M: *Carapa procera* macerated ethanolic extract

Total antioxidant capacity

Radical DPPH: The antioxidant capacity by the DPPH method was around 15.99±0.04 mg AEAC g^{-1} for the ethanol soxhlet extract and around 15.57±0.01 mg AEAC g^{-1} for the macerated ethanol extract. The antioxidant power of ethanol soxhlet extract was higher than macerated extract (p<0.001) (Table 2).

Iron reducing power (FRAP): The Iron reduction power was estimated to 518.20±2.42 AEAC g^{-1} for the ethanol soxhlet extract and to 372.27±3.64 AEAC g^{-1} for the macerated ethanol extract. The ethanol soxhlet extract had a higher antioxidant capacity by FRAP method than the macerated ethanol extract (p<0.001) (Table 2).

Antiplasmodial activity: *Carapa procera* had *in vivo* antiplasmodial activities on *Plasmodium berghei*. The Soxhlet ethanol extract exhibited 46.3, 56.7 and 11.6% inhibition of the parasites respectively at 100, 250 and 500 mg kg^{-1} b.wt. while macerated ethanol extract gave 23.6, 23.1 and 6.0% inhibition respectively at 100, 250 and 500 mg kg^{-1} b.wt. The Soxhlet ethanol extract of *C. procera* displayed a dose-dependent effect on the parasites at 100 and 250 mg kg^{-1} b.wt.; but the inhibition rate decreased at 500 mg kg^{-1} b.wt. For the macerated ethanol extract, the inhibition was weak and was not dose-dependent (Table 3).

Acute toxicity: Oral administration of the Soxhlet ethanol extract in mice showed that *C. procera* was relatively safe. No death among animals was recorded. At the highest dose (5062.5 mg kg^{-1} b.wt.), slight 30 min depression was observed. No significant difference was noted on relative body weight (p>0.1) (Table 4).

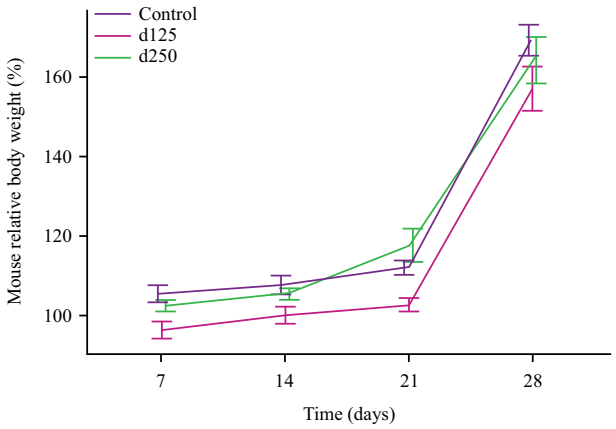

Fig. 1: Relative body weight between treated and control rats during the sub-acute toxicity testing with the Soxhlet ethanolic extract
d125: Dose 125 mg kg^{-1}, d250: Dose 250 mg kg^{-1}

Table 3: Parasitaemia reduction by stem bark extracts of *Carapa procera* in mice

Extracts	Doses (mg kg^{-1})	Parasitemia (±SD)	Reduction (%)	IC 95%
CP-S	Control	32.8±4.3	-	
	100	17.6±10.3	46.3	9.0
	250	14.2±13.1	56.7	11.5
	500	29.0±3.0	11.6	2.7
CP-M	Control	29.3±5.2	-	
	100	21.5±7.8	23.6	6.8
	250	22.5±3.9	23.1	3.4
	500	28.2±4.4	6.0	3.8

CP-S: *Carapa procera* soxhlet ethanolic extract, CP-M: *Carapa procera* macerated ethanolic extract

Table 4: Relative body weight between exposed and non-exposed mice during the acute toxicity testing with the Soxhlet ethanolic extract

	Mice		Days	
Doses (mg kg^{-1})	Number	Death	D7	D14
Control	6	0	106.62±5.96	110.6±7.3
1500	6	0	103.99±6.68	104.95±8.1
2250	6	0	105.78±11.06	114.43±15.03
3375	6	0	107.74±3.01	111.37±3.85
5062.5	6	0	104.92±5.18	112.46±4.64

Table 5: Relative organs weights between exposed and unexposed animals to the Soxhlet ethanolic extract in sub-acute toxicity test

	Doses (mg kg^{-1})		
Organ	Control group	125	250
Heart	0.36±0.12	0.38±0.14	0.36±0.12
Liver	2.83±0.76	2.71±0.89	2.71±0.91
Kidney	0.88±0.27	0.76±0.3	0.91±0.34
Lungs	0.66±0.18	0.58±0.3	0.62±0.18
Spleen	0.25±0.06	0.22±0.09	0.22±0.04

Subacute toxicity

Body and organ weight: No evidence of toxicity was observed in rats after administration of the Soxhlet ethanol extract of *C. procera* at 125 and 250 mg kg^{-1} b.wt. Only, weight loss in the first week was noted, but after that, the weight of animals in all groups increased, p>0.2 (Fig. 1). No difference in organ relative weight was observed between treated rats and control rats at a dose of 125 and 250 mg kg^{-1} b.wt. (p>0.8) (Table 5). Macroscopic observation of liver, heart, lung, kidney and spleen samples from treated animals did not show significant changes when compared to those of the control group.

Table 6: Biochemical parameters between exposed and unexposed rats to Soxhlet ethanolic extract of *Carapa procera*

	Doses (mg kg^{-1})					
Biochemical parameters	Control group	125	p-value (Ctl^{-1}25)	250	p-value (Ctl-250)	p-value (125-250)
ALT (U L^{-1})	63.16±21.36	59.00±21.14	0.93	54.14±13.33	0.73	0.91
AST (U L^{-1})	148.66±28.97	129.43±25.17	0.96	127.53±17.78	0.34	0.52
Creatinine (Umol L^{-1})	42.18±9.79	35.42±6.86	1	38.56±6.37	0.73	0.77
Urea (mmol L^{-1})	6.25±1.73	5.64±0.87	0.68	6.06±0.41	0.96	0.84

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Ctl: Control group

Biochemical parameters: ALT and AST levels were lower in the treated groups at 125 and 250 mg kg^{-1} b.wt. when compared to the control group but the difference was not significant ($p>0.05$). No difference was found between the treated group at dose 125 and 250 mg kg^{-1} b.wt. at the levels of ALT and AST.

About urea and creatinine parameters, no significant difference was noted between treated and control groups and also between the two-groups treated ($p>0.05$) (Table 6).

DISCUSSION

This study reported on the antimalarial activity of *Carapa procera* in mice. The results showed that macerated ethanolic extract of *Carapa procera* displayed a moderate activity at 100 and 250 mg kg^{-1} b.wt. according to the antiplasmodial activity scale established previously[24,25]. The antiplasmodial activity of Soxhlet ethanolic extract was optimum at 250 mg kg^{-1} b.wt. However, a decrease of this activity at a higher dose (500 mg kg^{-1} b.wt.) was observed. The decrease of the activity at the highest dose (500 mg kg^{-1} b.wt.) could be explained by the saturation of the plasma protein binding sites and also the possibility of toxicity at the highest doses[26]. The *in vitro* antiplasmodial activity of *Carapa procera* on 3D7 *Plasmodium falciparum* strain was previously demonstrated by Sarpong *et al*.[14].

Phytochemical screening showed that *Carapa procera* contained polyphenols and flavonoids. The amount depended on the type of extraction (Table 1).

The temperature and solvent polarity were known to influence the extraction of secondary metabolites in plants[27-29]. Phenols and flavonoids are reported to have antiplasmodial activities[30]. And maybe contributed to the good antiplasmodial activity of *Carapa procera* with the synergetic activity of compounds[31-33]. The antioxidant capability investigation showed that *Carapa procera* had an antioxidant activity that is linked to the content in phenols and flavonoids (Table 2). Antioxidant activity of *Carapa procera* may play an important role in plants good antiplasmodial activity by inhibiting the polymerization of heme, fatal for the intra-erythrocyte parasite[21,34].

The acute toxicity was performed in the mice model. The results showed that the Soxhlet ethanolic extract of stem bark of *Carapa procera*, was relatively safe by the oral route. Indeed, no significant body weight loss and no physical changes in mice were observed. Slight changes may be more related to stress from infection than to extract. Hepatic damage was attested by the level of released cytosolic transaminases ALT and AST in blood circulation. Subacute test of the Soxhlet ethanolic extract showed a decrease in AST and ALT levels in exposed rats but the difference was not significant, suggesting that the extract had no toxicity on liver[35-37].

Besides, creatinine and urea level was lower in treated rats compared to the control group but not significative. These results suggested that *Carapa procera* may not have a toxicity effect on kidney[38]. The results of the sub-acute toxicity tests revealed a more therapeutic potential for the plant.

These findings support the use of *Carapa procera* in the treatment of malaria by traditional healers in the western part of Burkina Faso.

CONCLUSION

In this study, the Soxhlet ethanolic extract of *C. procera* had a good *in vivo* antimalarial activity against *Plasmodium berghei* infection in mice. More interestingly an antioxidant activity of this plant was also observed. The acute and subacute toxicity tests revealed that *Carapa procera* extract was relatively safe when administered orally in mice. Therefore, these findings support the use of *Carapa procera* in the treatment of malaria by traditional healers in the western part of Burkina Faso.

SIGNIFICANCE STATEMENT

This study discovers that the soxhlet ethanolic extract of *Carapa procera* had good *in vivo* antiplasmodial activity in mice against *Plasmodium berghei*. It also displayed that the same extract was safe by the oral route. These findings support the use of *Carapa procera* in the

treatment of malaria in the western part of Burkina Faso. *Carapa procera* could be considered as a potential source of the drug against malaria for further investigations.

ACKNOWLEDGMENTS

The authors are grateful to Bobo-Dioulasso Research Institute for Health Sciences and Nazi Boni University of Bobo-Dioulasso for permanent support.

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