



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Research Article

April 2018 Vol.:12, Issue:1


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Anti-Plasmodial and Toxicological Effects of Methanolic Bark Extract of *Chrysophyllum albidum* in Albino Mice



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



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Submission: 20 March 2018
Accepted: 27 March 2018
Published: 30 April 2018

Keywords: Anti-plasmodial, toxicological, *Chrysophyllum albidum*, Albino rats.

ABSTRACT

The study was designed to determine the anti-plasmodial and toxicological effects of methanolic bark extract of *Chrysophyllum albidum*. The anti-plasmodial, haematological, serum biochemical effects of *Chrysophyllum albidum* methanolic extract was evaluated using swiss albino mice. The LD₅₀ of the methanolic bark extract was estimated to be 750mg/kg body weight. *C. albidum* methanolic bark extract (125-375mg/kg/day) showed significant (P<0.05) schizontocidal activities both in a 4 day (early) infection and in an established (7 days) infection. The effect of oral administration of the leaf extract of *Chrysophyllum albidum* on biochemical and haematological parameters did not show any significant effect (P < 0.05) on the plasma concentration of total bilirubin, albumin, total protein, alkaline phosphatase (ALP) as well as the haemoglobin (Hb), red blood cell (RBC), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and mean corpuscular volume (MCV) (and also do not show any significant effect (P < 0.05) on packed cell volume (PCV). The concentration of the platelet was significantly decreased (P > 0.05) at 125mg/kg body cells (WBC) was significantly reduced (P < 0.05). The doses significantly reduced (P <0.05) plasma levels of AST, ALT and creatinine. *C. albidum* contains anti-plasmodial substances which help to reduce parasitaemia and the results of the biochemical and hematological parameters show that the extract is non-toxic. Further studies need to be done to identify and characterize the active principles/substances in the extract.



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INTRODUCTION

Malaria remains one of the major killer diseases of the world. It causes illness by the ability of the causative parasite to invade the red blood cells (Beteck *et al.*, 2014) and the liver where they multiply. In extreme infections, up to 80% of the red blood cells can be parasitized and destroyed (Katzung *et al.*, 2012). This massive cell destruction is known to lead to severe anaemia and clogging of the blood circulation of vital organs particularly the brain and eventually death.

Antimalarials are agents used to inhibit the development of plasmodium (the causative parasite of malaria) and they are administered so they can completely destroy these parasites. There are quite a wide range of antimalarials available. They may be classified according to the different stages of the parasites they affect or according to their chemical nature and function (Tripathi, 2009). All efforts made so far to eradicate malaria using these agents and very highly effective residual insecticides against mosquito have failed (Rang *et al.*, 2008). This is basically due to the increasing resistance of mosquito to insecticides and the parasites to the drugs. One of the major challenges of the medical world remains the eradication of malaria due to many reasons among which is resistance to antiplasmodial agents. The need to achieve a more radical cure of the malaria scourage remains with us considering the continuous development of resistance to known and existing antimalarials being reported in different parts of the world. Currently, the World Health Organization guidelines for the treatment of malaria include the combination of one antimalarial and one antibiotic provided that there is evidence of their efficacy and safety (WHO, 2010). Combined therapy which will help in tackling this challenge has therefore been recommended and efforts are one to find appropriate combinations to be used. Combination therapy with antimalarial drug is the simultaneous use schizontocidal drugs with independent mode of action and different biochemical targets in the parasites. These can either be fixed where the drugs to be combined are co-formulated in the same tablet or capsule or non-fixed, where they are co-administered in separate tablets or capsules. Drug combinations are used to exploit the synergistic and additive potentials of each drug as well as helping to improve efficacy while retarding the development of resistance to individual components (Andrade *et al.*, 2007). One optimistic source for new affordable treatment against malaria lies in the use of traditional herbal remedies. Despite the recent successes in rational drug design and synthetic chemistry techniques by pharmaceutical companies, natural products and particularly medicinal plants

have remained an important source of new drugs (Kaushik *et al.*, 2013, Lombardino and Lowe 2004). A definite virtue with medicinal plants is the rich ethnopharmacological history of traditional knowledge and usage associated with them. It is already providing a significant degree of protection to people at large against malaria. However, if the gist of traditional knowledge can be validated by scientific experiments, affordable and dependable cures can be found against the drug resistant dreaded forms of malaria further, such exploratory endeavours can pave the path for identifying novel pharmacophores against malaria, which can be chemically synthesized and fine tuned as drugs of the future.

As a result of limited availability or affordability of pharmaceutical medicines in many tropical African region has led majority remedies (WHO, 2002, Zirihi *et al.*, 2005). *Chrysophyllum albidum* (Linn), also known as African star apple belongs to the family sapotaceae. It is widely distributed in the low land rain forest zones and frequently found in villages (Madubuike and Ogbonnaya, 2003). Across Nigeria, it is known by several local names and is generally regarded as a plant with diverse ethnomedicinal uses (Amusa *et al.*, 2003). In southwestern Nigeria, the fruit is called "agbalumo" and popularly referred to as "Udara" in south-eastern Nigeria. It is a plant which has been used in traditional medicine in Nigeria to treat health problem, phytochemical profile shows it contains many biologically active substances that include alkaloids, tannin, saponin etc (Okoli and Okere, 2010). Its rich sources of natural antioxidants have been established to promote health by acting against oxidative stress related diseases such as diabetics, cancer and coronary heart disease (Bunts and Bucar, 2002). The bark is used for the treatment of yellow fever and malaria while the leaf is used as an emollient and for the treatment of skin eruption, stomach ache and diarrhea (Adisa, 2000). Eleagnine, an alkaloid isolated from *C. albidum* seed. Cotyledon has been reported to have anti-nociceptive, anti-inflammatory and anti-oxidant activities (Idowu *et al.*, 2006). This research, therefore, is aimed at providing information on the possible anti-malaria and toxic effects of the Ethanolic bark extract of *C. albidum* against plasmodium *berghei* infection of swiss abino mice.

MATERIALS AND METHODS

Plant Materials, Collection and Identification

The fresh bark of *Chrysophyllum albidum* was collected from its natural habitat at Agbozu Uzuakoli, Bende Local Government Area of Abia State, South-Eastern Nigeria. It was

collected between the months of June and July 2016 (raining season). The plant was identified at the taxonomic unit of the department of plant science and Biotechnology, Michael Okpara University of Agriculture Umudike by Mr. Nduche, M. U. who is an authority in this area. The plant materials were dusted and dried at room temperature (37 - 40°C) for 3 weeks and the grounded to powder using a dry electric mill. (Moulineux, U.K).

Preparation of Extract

Exactly 2.5kg of the powdered bark of *C. albidum* was exhaustively dissolved in 2.5L of 90% methanol for 72hrs. The mixture was filtered with whatman's filter paper (No.1) and the filtrate evaporated to a paste on a thermostatic controlled water bath at 60°C. The yield, a solid residue obtained was referred to as the extract. The evaporation produced 28g of the extract. All preparations were stored at 4°C until use.

Animals

One hundred and two (102) Swiss albino mice were used in this experiment. They were obtained from Dr. Fred Ugwuoke of the animal house, Department of Veterinary Anatomy University of Nigeria, Nsukka. They were maintained under standard conditions (12hrs light and 12 hrs dark) and have access to mice chow and clean water.

Acute Toxicity Test: Determination of LD₅₀

The acute toxicity of *C. albidum* Bark extract was estimated using 42 albino mice. The mice were divided into 7 groups consisting of 6 mice per group. Each group of mice was injected intraperitoneally with different doses 250-5000 mg/kg of the extract after having fasted them overnight. The number of deaths in each group within 24hrs was recorded and various clinical signs exhibited by the mice were noted. The LD₅₀ was calculated according to Lorke (1983).

Parasites

Chloroquine sensitive *Plasmodium Berghei Berghei* was obtained from Dr. Aina of the Nigerian Institute of Medical Research, Yaba Lagos State.

Experimental Design

Extract Administration of drugs and extract were administered orally using orogastric tube.

Evaluation of Schizontocidal Activity in Early Infection (4- day test):

The schizontocidal activity of the methanolic bark extract of *C. albidum* was evaluated using the method described by knight and Peters (1980). Thirty swiss albino mice were used in this experiment. The animals were divided into five groups of 6 mice each. Shortly after inoculation of each mice with 1×10^6 *P. Berghei Berghei* they were administered with 250 and 375 mg/kg/b.W/day dose of the *C. albidum* extract. Chloroquine 10mg/kg/day (both dissolved in normal saline) and an equivalent volume of distilled water (negative control) for 4 consecutive days (days 0 to 3) percentage parasitaemia was determined using standard laboratory procedures described by Knight and Peters (1980). The groups are as indicated below:

Group 1: Uninfected and untreated (normal animals)

Group 2: Infected and untreated (Negative Control)

Group 3: Infected and treated immediately with 250 mg/kg/B.W/day *C. albidum*

Group 4. Infected and treated immediately with 375mg/kg/B.W/ day *C. albidum*

Group 5: infected and treated with 10mg/kg/b.W/day chloroquine (positive control)

Evaluation of Schizontocidal Activity in Established Infection (Curative of Rane Test)

The evaluation of the curative potential of the extract was done using the methods described Ryley and Peters (1970). Thirty swiss albino mice were used in the experiment. Seventy two hours after parasite inoculation of each mouse with 1×10^6 *P. berghei berghei*. The animals were divided into five groups of 6 mice each. These mice were treated with 125, 250 and 375 mg/kg/day doses of the *C. albidum* Ethanolic extract. Chloroquine 10mg/kg/day (both dissolved in normal saline) and an equivalent volume of distilled water (negative control) for 4 consecutive days. The drug or extract was given once daily to the appropriate group at 9.00 am. The levels of parasitaemia were determined using standard laboratory procedure (knight and Peters 1980). The groups are as underlisted.

Group 6: Infected and untreated

Group 7: Infected and treated on day 5 with 125 mg/kg/b.W/ day *C. albidum* for 3 consecutive days.

Group 8: Infected and treated on day 5 with 250 mg/kg/b.W/ day *C. albidum* for 3 consecutive days.

Group 9: Infected and treated on day 5 with 375 mg/kg/b.W/ day *C. albidum* for 3 consecutive days.

Group 10: Infected and treated on day 5 with 10 mg/kg/b.w/ chloroquine for 3 consecutive days.

Hematological and Biochemical Determination

Each mouse was sedated by ether Suffocation and pooled blood from mice in each group. Was collected by cardiac puncture into heparinized tubes for hematological studies-red blood cell (RBC) counts. Haemoglobin (Hb) concentration, Total White Blood Cell (WBC) counts and Platelets counts according to method described by Dacie and Lewis (1991). Red blood cell indices such as Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin Concentration (MCHC) were calculated (Jain, 1996). Pooled blood samples from animals in each of the groups were also collected into plain vacutainer tubes to obtain sera for biochemical analysis; total protein, total bilirubin, creatinine, total cholesterol, albumin and serum activities of Alanine Transaminase (ALT) and Aspartate Transaminase (AST).

Determination of Serum Alanine Aminotransferase (ALT) Activity

The method employed was the colourimetric method described by Reitman and Frankel (1957).

Determination of Serum Aspartate Aminotransferase (AST) Activity

The method employed was the colourimetric method described by Reitman and Frankel (1957).

Determination of Serum total protein

Serum total protein was determined by the method described by Henry *et al.*, (1974). This method is based on the principle that the carboxyl and the amino end of peptide bond of proteins react with cupric ions in moderate alkaline medium to form violet colour whose intensity is proportional to the concentration of protein present in the sample.

Procedure:

Clean test tubes were labeled samples, standard and blank followed by the addition of 0.05ml of serum, protein standard and distilled water respectively. Two and a half milliliter (2.5ml) of Biuret reagent was added into the test tubes and was incubated at room temperature for 20mins. The absorbance was read with spectrophotometer at 540nm.

Determination of Serum Albumin

Albumin concentration of the serum was determined using commercial diagnostic kit (Fortres, United Kingdom). The method used was Bromocresol Green (BCG) as was described by Dumas *et al.*, (1971).

Determination of Serum Creatinine

Colorimetric method as was described by Taursky (1956) was used for creatinine determination.

Phytochemical Screening

Determination of Saponins

This was done by the double solvent extraction gravimetric method (Harbone, 1973).

Determination of Flavonoids

Flavonoid was determined using the method described by Harborne (1993).

Determination of Tannins

This was determined by folin Denis colometric method.

Determination of Alkaloids

The alkaline precipitation gravimetric method (Harbone, 1993) was used.

Evaluation of Schizontocidal Activity in Established Infection (Curative or Rane Test)

From day 5 to 7 in the established infection, a daily increase in the parasitaemia level of the infected untreated (negative) control group was recorded. However a daily reduction in the parasitaemia levels was observed in the methanolic bark extract-treated groups and in the

group treated with chloroquine on day 7, the average percentage reduction in parasitaemia for the groups were 86.05% 68.42 and 79.34% for 175, 250 and 375 mg/kg/b.w of the methanolic extract and chloroquine (10mg/kg/b.w) gave 100%.

RESULTS

Result of Schizontocidal Activity of the methanol extract

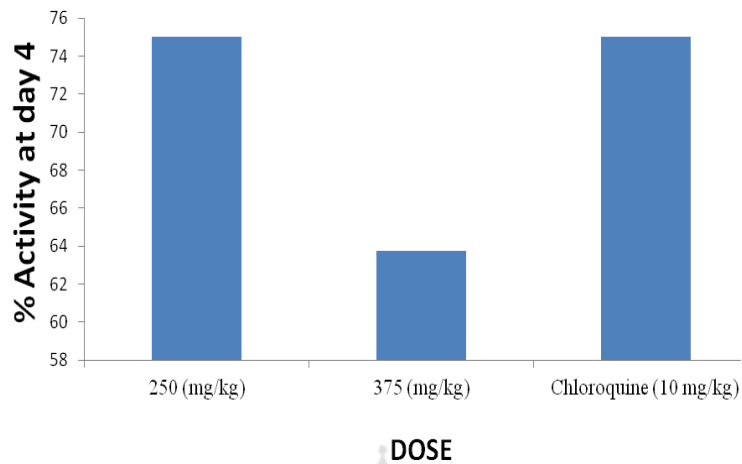


Figure I: Schizontocidal Activity of the methanol extract

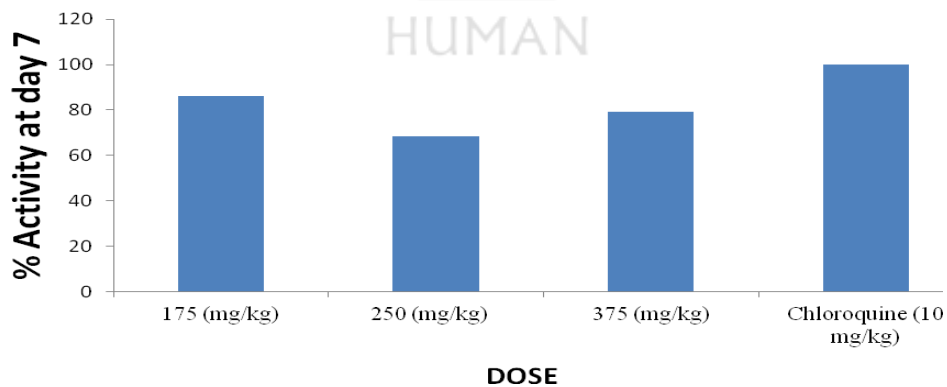


Figure II: Schizontocidal Activity of the methanol extract

Table 1: Result of Hematological Analysis

Parameter	UNITR	PUT	PT375	PT250	PT125
Hb Conc. (g/dl)	13.00±0.32 ^e	10.40±0.14 ^e	11.60±0.35 ^e	11.20±0.09 ^e	11.00±0.25 ^e
PCV (%)	41.00±1.15 ^c	33.00±0.58 ^c	39.00±1.15 ^c	38.00±1.15 ^c	35.00±0.58 ^c
WBC (x10 ¹² /μl)	9.40±0.11 ^f	7.40±0.19 ^f	2.80±0.46 ^f	4.50±0.10 ^f	5.00±0.33 ^f
RBC (x10 ¹² /L)	4.30±0.25 ^g	3.50±0.23 ^g	4.10±0.32 ^f	4.00±0.50 ^f	3.70±0.23 ^f
MCHC (g/dl)	31.54±0.16 ^d	31.50±0.56 ^c	29.40±0.44 ^d	29.40±0.28 ^d	31.40±0.14 ^d
Platelet (x10 ⁹ /L)	189.00±0.58 ^a	170.00±1.15 ^a	198.00±0.58 ^a	201.00±1.73 ^a	170.00±1.73 ^a
MCH (Pg)	30.20±0.39 ^d	29.70±0.24 ^d	28.30±0.47 ^d	28.00±0.12 ^d	29.70±0.17 ^d
MCV (fl)	95.30±0.42 ^b	94.30±0.42 ^b	95.10±0.28 ^b	95.00±0.22 ^b	94.60±0.27 ^b

Results = Mean±SEM. Means with same letter in same column are not significantly different.

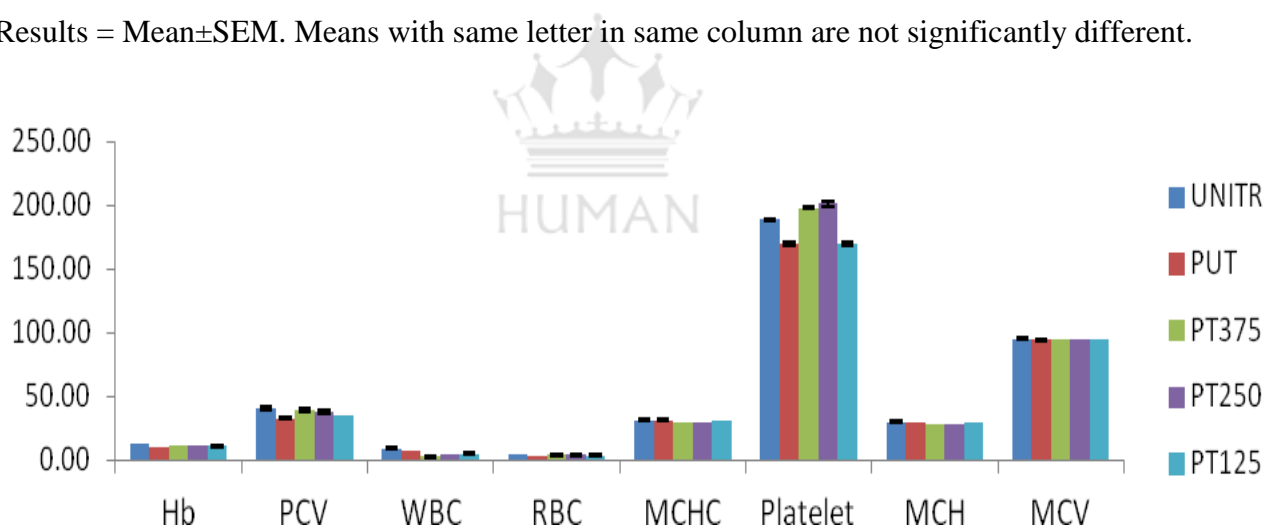


Figure III: Result of Hematological Analysis

Table 2: Result of Biochemical Analysis

Parameters	UNITR	PUT	PT375Ca	PT250Ca	PT125Ca	PTCQ
Creatinine (mg/dl)	1.11±0.13 ^g	1.42±0.25 ^g	0.94±0.09 ^f	0.91±0.25 ^f	0.99±0.18 ^f	0.60±0.06 ^f
AST (ul)	89.00±0.59 ^a	78.90±0.32 ^a	69.70±0.28 ^a	67.90±0.10 ^a	64.80±0.47 ^a	68.30±0.54 ^a
ALT (ul)	26.30±0.25 ^b	25.30±0.42 ^b	24.00±0.27 ^b	24.70±0.22 ^b	22.20±0.31 ^b	20.50±0.11 ^b
Bilirubin (mg/dl)	2.30±0.06 ^f	2.43±0.24 ^f	1.47±0.03 ^f	1.60±0.23 ^f	1.60±0.06 ^f	1.50±0.23 ^f
Total protein (mg/dl)	12.60±0.28 ^d	11.10±0.12 ^d	12.70±0.20 ^d	12.51±0.64 ^d	11.50±0.47 ^d	11.20±0.22 ^d
ALP (ul)	15.20±0.11 ^c	15.60±0.46 ^c	15.20±0.21 ^c	14.10±0.47 ^c	19.50±0.28 ^c	16.40±0.54 ^c
Albumin (mg/dl)	4.90±0.27 ^e	4.60±0.23 ^e	6.18±0.51 ^e	5.11±0.33 ^e	5.45±0.24 ^e	4.10±0.32 ^e

Results = Mean±SEM. Means with same letter in same column are not significantly different.

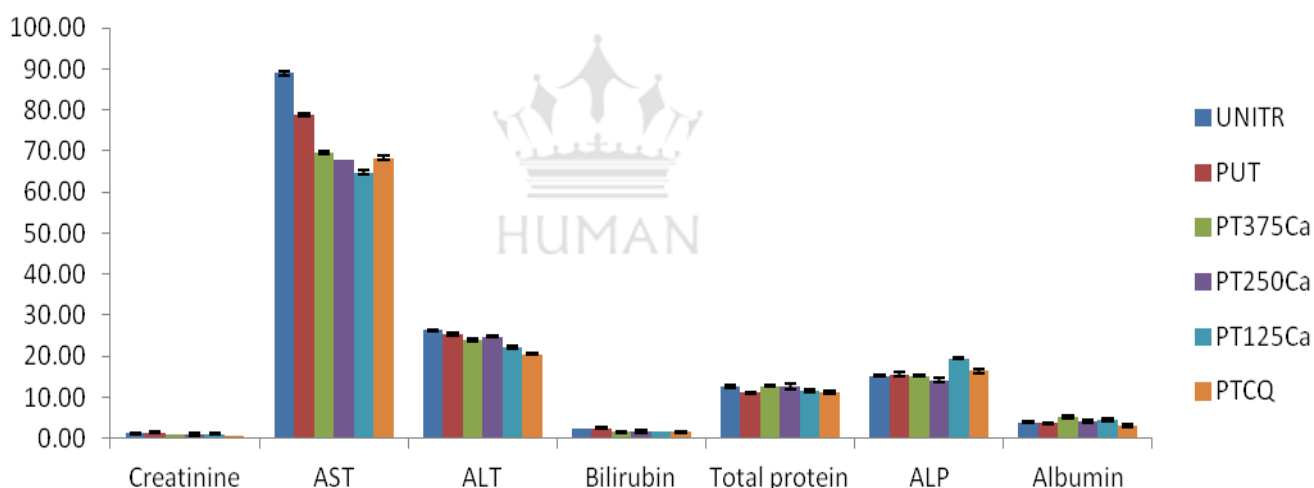


Figure IV: Result of Biochemical Analysis

Table 3: RESULT OF PHYTOCHEMICAL ANALYSIS

Phytochemical	Mean
Alkaloids (mg/dl)	0.08±0.00
Flavonoids (mg/dl)	0.40±0.00
Saponins (mg/dl)	0.10±0.00
Tanins (mg/dl)	0.80±0.00

No deaths occurred in the period of treatment, no change in locomotor activity was observed. The methanolic extract of *C. albidum* did not have any significant effect on RBC, Hb, MCHC, MCH, PCV and MCV while WBC was significantly reduced ($P < 0.05$) in the group treated with 125mg/kg body weight. The platelet was significantly reduced ($P > 0.05$). The extract did not have exact any significant effect ($P < 0.05$) on alkaline phosphatase (ALP), total bilirubin, albumin and total protein. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine were significantly decreased ($P < 0.05$).

DISCUSSION

Results from investigation suggest that the Ethanolic extract of the bark of *C. albidum* has anti-plasmodial activities and is non-toxic to mice when administered even at 375mg/kg/day. It, however, appears to be more effective at a dose of 175mg/kg/day. The lifespan of the mice infected with *P. berghei berghei* had earlier been carried out by Anigbogu and Fagbure (1997). This revealed that the lifespan of mice inoculated with *P. berghei berghei* is between the 7 to 10 days post-inoculation. This is in line with the drug treatment employed both in the suppressive and established or Rane test in this study. This time frame was used in order to prevent the death of animals before the end of drug treatment regime during the experiment.

Philipson and Wright (1981) as well as Christensena dn Kharazami (2001) reported that plant whose phytochemical compounds include alkaloids, and saponins may have antimalarial activities. These reports are similar to those obtained in this study as ethanolic bark extract of *C. albidum* contains alkaloids, saponins, cardenolides and tannins. These phytochemical compounds were also similar to those reportedly found in the leaves and stems of *C. albidum* by Smolenski *et al.*, (1975) and Delande *et al* (1979).

Saponins have been found to have anti protozoan activities (Wallace *et al.*, 1994; Newbold *et al.*, 1997). This properties has been exploited in the treatment of protozoal infections in other animals. Triterpenoid and steroid saponins have been found to be detrimental to several infectious protozoans one of which is *P. falciparum* (Traore *et al.*, 2000). This report supports what was observed in this experiment both in the suppressive and established infections. The mechanism of action by which saponins work might be through their toxicity to protozoans which may be widespread and non-specific. It might also be as a result of their detergent effect on the cell membranes (George) (Francis *et al.*, 2002).

C. albidum has also been found to contain alkaloids and these have been associated with

medicinal uses for centuries, though other possible roles have not been examined. One of the most common biological properties of alkaloids in their toxicity against cells of foreign organism like bacteria, viruses and protozoans to which malaria parasite belong. These activities have been widely studied for their potential use in the elimination and reduction of human cancer cell lines (Nobori *et al.*, 1994). Alkaloids also possess anti-inflammatory, anti-asthmatic and anti-anaphylactic properties with consequences (Staerk *et al.*, 2002). The various biochemical and haematological parameters investigated are useful indices of evaluating the toxicity of plant extract in animals (Yakubu *et al.*, 2008). Assessment of haematological parameters cannot only be used to determine the extent of deleterious effect of extracts on the blood of an animal but it can also be used to explain blood relating functions of a plant extract on its products (Yakubu *et al.*, 2007). Analysis of blood parameters is relevant in risk evaluation as changes in the haematological system have higher predictive value for human toxicity when the data are translated from animal studies (Olson *et al.*, 2000). The non-significant effect of the extract on the RBC may be an indication that the balance between the rate of production (erythropoiesis) and destruction of the blood corpuscles was not altered. MCHC and MCH relate to individual red blood cells while Hb, RBC and PCV are associated with total population of Red Blood Cells. Therefore, the absence of significant effect of the extract on RBC, Hb, PCV, MCH and MCHC could mean that neither the incorporation of haemoglobin into red blood cells nor the morphology and osmotic fragility of the red blood cells was altered (Adebayo *et al.*, 2005). There was an increase in platelet count in the group administered with 375 and 250mg/kg/b.w and a reduction in the platelet count for the group administered with 125mg/kg/b.w indicating thrombocytopenia. Platelet aggregation plays a pivotal role in the physiopathology of thrombotic diseases.

Moreover, platelet activity may play a major role in the development as well as in the stability of atherosclerotic plaques and as a consequence, antiplatelet agents have been used clinically in patients at risk of myocardial infarction (Albers 1995; George 2000). Flavonoids have shown to act at the blood platelet level by preventing platelet activity-related thrombosis (Harnafi and Amrani, 2007). *C. albidum* has been reported to contain flavonoids as one of its active compounds (Akaneme, 2008). The significant reductions observed in the activity of AST and ALT indicates that the extract of *C. albidum* was not harmful to the liver. ALT is a cytoplasmic enzyme found in very high concentration in the liver and increase of this enzyme indicates hepatocellular damage, while AST is less specific than ALT as an indicator of liver

function (Aliyu *et al.*, 2006).

The serum creatinine level was decreased significantly suggesting that the bark extract was not toxic to the kidney. Creatinine is the major catabolic products of the muscle and is excreted in the kidneys. Creatinine levels are useful as indicators of renal failure (Aliyu *et al.*, 2006).

The significant reduction in parasitic load in infected mice treated with methanolic extract of *C. albidum* prevented rapid destruction of parasitized red blood cells and development of mild and insignificant anaemia, especially in the group administered with 125mg/kg/b.w. It is note worth, however, that all the infected mice treated or untreated developed leucocytosis and this is in line with the studies of (Adewoye *et al.*, 2010). The leucocytosis may be an indication of enhanced granulopoiesis and lymphocytosis as cellular and humoral responses respectively to the protozoan infection (Jubb *et al.*, 1996). This is corroborated by enhanced serum albumin levels. Histopathological studies were not carried out in this research because an extensive work has been done on it by E.O Adewoye using the same extract and on a malaria studies using swiss albino mice.

CONCLUSION

From these results, we conclude that the methanolic bark of *Chrysophyllum albidum* extract have antiplasmodial activity against chloroquine-sensitive *P. Berghei Berghei* parasites. The extract may not cause adverse effect on the biochemical and haematological indices of toxicity. These results lend support to claims of herbalists that decoctions of *C. albidum* bark are useful medicines in the treatment of malaria. These notwithstanding, further studies needs to be carried out in humans to demonstrate the extract effectiveness, and the mechanisms of action of this extract, since humans are currently using it to treat malaria and other disease. This could be followed by pilot clinical trials for therapeutic dose range finding. The plant extracts of *C. albidum* could be useful alternatives to antimalarial drug or useful in combination therapy since they are cheaper. This research demonstrates that *Chrysophyllum albidum* extract has anti-platelet properties and might be employed in the treatment of myocardial infarction and could help in prevention of high parasitaemia and development of less oxidative stress.

RECOMMENDATION

Further studies needs to be carried out in humans to demonstrate the extract effectiveness and determine appropriate dosage regimens. The mechanism (s) of action of this extract is yet to be ascertained and also there is a need to establish the antiplatelet property of the extract, and to identify and characterize the active principles/substances in the extract.

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