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(RESEARCH ARTICLE)



## Anti-plasmodial, analgesic and anti-inflammatory activities of crude and alkaloidal fraction of *Terminalia glaucescens* stem bark

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### Abstract

*Terminalia glaucescens* (*T. glaucescens*) stem bark is used in ethno-medicine for the management of malaria and other diseases in Northern Nigeria. In this study, antiplasmodial, analgesic and anti-inflammatory activities of crude and alkaloidal extracts of *T. glaucescens* stem bark were evaluated against *Plasmodium berghei* in mice. Six (6) groups of 3 mice each were inoculated with *Plasmodium berghei* infected blood. Groups I to V were treated orally with 250 and 500 mg/kg bw crude methanol extract of *T. glaucescens* stem bark, 100 mg/kgbw of alkaloidal fraction, 100 mg/kg body weight *Artemisia* herbal and 5 mg/kg bw chloroquine, once daily for five days. Analgesic and anti-inflammatory activities of the crude extract were evaluated at doses of 400 and 800 mg/kg bw. Results shows that chloroquine reduced the parasitaemia level the most (89.20 %) this was followed by *Artemisia* herbal standard (72.80 %) and alkaloidal extract recorded 72.07 % parasitaemia reduction. The extract caused an increase in packed cell volume and body weight of the animal. The analgesic and anti-inflammatory effects of crude extract of *T. glaucescens* stem bark (800 mg/kg body weight) were 56.86 and 78.79 % respectively compared to the acetyl salicylic acid standard drug (75.68 and 95.96 %) respectively. From the study *Terminalia glaucescens* stem bark extract was found to possess antimalarial, analgesic and anti-inflammatory properties, which however was lower than that of the standards used. This however, provides a scientific basis to the folkloric claim of the plant in the management of pain and similar ailments.

**Keywords:** Malaria; Analgesic; Anti-Inflammatory; Alkaloid; *Terminalia glaucescens*

### 1. Introduction

Malaria is intractable globally and it remains one of the most deadly parasitic diseases in the tropics and subtropics. It was estimated that 214 million cases of malaria occurred worldwide in 2015, and an estimated 438,000 deaths [1]. African region has a disproportionately high share of the global malaria burden. Most of the death was in the Africa regions, followed by South Eastern region and Eastern Mediterranean region [2]. Thirty percent of these deaths occur in Nigeria and Democratic Republic of Congo. In areas with high transmission of malaria, children under 5 years are particularly susceptible to infection, illness and death; more than two thirds (70 %) of all malaria deaths occur in this age group [3]. However, malaria remains a major killer of children under five years old, taking the life of a child every two minutes [4]. In Nigeria malaria is endemic and approximately 97 % of the population of about 173 million are at risk, and about 300, 000 deaths reported annually [2].

Human malaria is caused by blood parasites, *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium vivax* and *Plasmodium knowlesi*. The plasmodium parasite is transmitted by female *Anopheles* mosquito to man and animals [5]. Mosquitoes control strategy to prevent widespread of the disease is made difficult due to

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insecticide resistance. No effective vaccine for malaria prevention is in use to date. Also, treatment of the *plasmodium* infection with drugs have been compromised by widespread resistance [6].

Investigations of inflammation and pains are gaining research popularity owing to the etiologic role they play in various human diseases [7]. Dexamethasone opioids, morphine and aspirin and other drugs have been established for the management of pain and inflammation, however, these drugs have recorded limited success due to unintended effects such as gastric lesions caused by non-steroidal anti-inflammatory drugs [8], [9]. New relatively effective, safe and affordable anti-malarial agents are therefore needed.

Medicinal plants play a key role in the control of malaria, especially where access to modern health services is limited [10]. Tropical rainforest plants are fertile sources of potential candidates for the development of new alternative anti-malarial drugs. In many rural areas in Africa, anti-malarial traditional medicine is even preferred to pharmaceutical drugs, suggesting that herbal preparations can serve as alternative antimalaria agents [11].

Alkaloids have a well-known pharmacological activity comprising antimalarial (e.g. quinine), analgesic (e.g. morphine), anticancer (e.g. homoharringtonine), antiasthma (e.g. ephedrine), cholinomimetic (e.g. galantamine), antibacterial (e.g. chelerythrine), vasodilatory (e.g. vincamine), and antihyperglycemic activities (e.g. piperine). Many have found use in traditional or modern medicine, or as starting points for drug discovery [12-13].

*Terminalia glaucescens* is a plant indigenous to Africa and belongs to the family Combretaceae. In Cameroon, it is traditionally used in the treatment of diabetes [14]. It is also one of the widely used plants employed as chewing stick in Nigeria thus various studies have been carried out on its antimicrobial activity against oral pathogens [15]. Information regarding antiplasmodial activity of total alkaloidal extract from this plant on *Plasmodium berghei* is lacking. This study was therefore aimed at investigating the *in vivo* antimalarial activity of total alkaloids extract from *Terminalia glaucescens* stem bark.

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## 2. Material and methods

### 2.1. Plant sample

Fresh stem bark of *Terminalia glaucescens* was collected from Minna Niger State, Nigeria. It was identified and authenticated by a Botanist in the Department of Biological Science, Federal University of Technology, Minna, Niger State, Nigeria.

### 2.2. Experimental animals

Healthy albino mice of average weight 25-30 g and rats of average weight 150-180 g were purchased from Animal House Unit of Biochemistry Department Federal University of Technology, Minna, Nigeria. The rodents were kept in clean plastic cages and maintained under standard laboratory conditions (temperature;  $27 \pm 2$  °C; 70 % relative humidity; 12 h daylight/night cycle) and had free access to commercial feed pellets and water. Experiments were conducted in strict compliance with internationally accepted principles for laboratory animal use and care as contained in the Canadian Council on Animal Care Guidelines and Protocol Review [16].

### 2.3. Malaria parasites

*Plasmodium berghei* NK65 chloroquine-sensitive strain was obtained from National Institute of Pharmaceutical Research and Development (NIPRD) Abuja, Nigeria and maintained in the laboratory by serial passage in mice.

### 2.4. Plant sample preparation and crude extraction procedure

The fresh stem bark of *Terminalia glaucescens* were washed with clean-water (distilled water), dried under shade at 37 °C and finally grounded using a grinder mill. Extraction of plant materials was performed by weighing 50 g of the powdered plant and extracted in the cold at room temperature for 72 hours using 500 ml of methanol. The extract was filtered with Whatman filter paper (No. 1) and solvent removed in a regulated water bath (60 °C). Brown coloured pastes were obtained, weighed and stored in a refrigerator at 4 °C until required.

### 2.5. Extraction of alkaloids

*T. glaucescens* stem bark (50 g) powder was moistened with 200 ml of 95 % ethanol, alkalified with 200 ml of ammonia solution and macerated for 24 hrs followed by extraction with ethanol. The ethanol extract was filtered,

concentrated and treated with 1.0 N hydrochloric acid. The filtrate was further alkalinified with ammonia solution and the alkaloid was obtained by fractionation in separating funnel using chloroform [13]. The residue was weighed and percentage yield was calculated using the formula below:

$$\% \text{ yield} = \frac{\text{Weight of the alkaloidal residue}}{\text{Weight of ground } T. \textit{glaucescens} \text{ stem bark}} \times 100$$

## 2.6. Acute toxicity

Acute toxicity of the extract was determined in 2 phases according to Lorke's [17]. In Phase 1, a total of 9 mice were grouped into 3 of two (3) mice each and were given a single dose of 10, 100 and 1000 mg/kg bw of the alkaloid respectively. The absence of death after 24 hours of extract administration led to the initiation of Phase II which was set up with another 3 groups of 3 mice each and were given a single dose of 1600, 2900 and 5000 mg/kg bw of the extract respectively.

## 2.7. Antiplasmodial studies

### 2.7.1. Inoculation of animals with *Plasmodium berghei*

*Plasmodium berghei* parasitized erythrocytes (1 ml) were obtained from a donor-infected mouse through the jugular vein into an EDTA-sample bottle and diluted with physiological saline (5 ml). Five groups of 3 mice each were inoculated intraperitoneally with infected blood suspension (0.2 ml), and were observed for 72 hours, after which thin blood smears were prepared from tail of each mouse onto slides. The slides were allowed to dry, fixed with methanol and stained with giemsa solution for 30 minutes and examined microscopically with 100x magnification to check for the parasites [18].

### 2.7.2. Malaria curative test

Evaluation of the curative potential of the plants extract was carried out according to the method described by Ryley and Peters [19]. Groups I to V animals orally received 250 mg/kg body weight, 500 mg/kg body weight of *T. Glaucescens* extract, 100 mg/kg body weight of alkaloidal extract of *T. glaucescens*, 5 mg/kg body weight of chloroquine and 100 mg/kg body weight of *Artemisia annua* respectively. Group VI received 20 ml/kg body weight of normal saline. Administration was once daily for five days. The percentage inhibition of parasites was calculated for each dose level by comparing the parasitaemia in infected and untreated controls with those of treated groups.

### 2.7.3. Determination of mean survival time

Mortality was monitored daily and the number of days from the time of inoculation of the parasite up to time of death or no death was recorded for each mouse in the treatment and control groups.

### 2.7.4. Determination of packed cell volume (PCV)

This was carried out to monitor the level of the red blood cells in the course of the experiment. The method employed was as described by Dacie and Lewis, [20].

### 2.7.5. Determination of change in body weight

A sensitive digital weighing balance (ATOM A-110) was used to weigh each mouse in all the groups before infection (day 0), during infection and after treatment.

## 2.8. Determination of anti-inflammatory activity

The anti-inflammatory activity of the extract was tested using egg albumin induced paw oedema in rats [21]. A digital plethsmometer was used to measure the volume of paw oedema at 20 minutes interval for 120 minutes after the fresh egg albumin administration.

## 2.9. Analgesic assay

Analgesic activity was assessed by the method of Koster *et al.* [22]. The number of writhes (wave of contraction of abdominal musculature followed by extension of the hind limbs) of each mouse was recorded over ten minutes period.

## 2.10. Statistical analysis

Values were analyzed using statistical package for social sciences (SPSS) version 16 and presented as means and standard error of the mean. Comparisons between different groups were carried out by one way analysis of variance (ANOVA) followed by Duncan's Multiple Range Test (DMRT). The level of significance was set at  $p < 0.05$  [23].

### 3. Results

#### 3.1. Acute toxicity

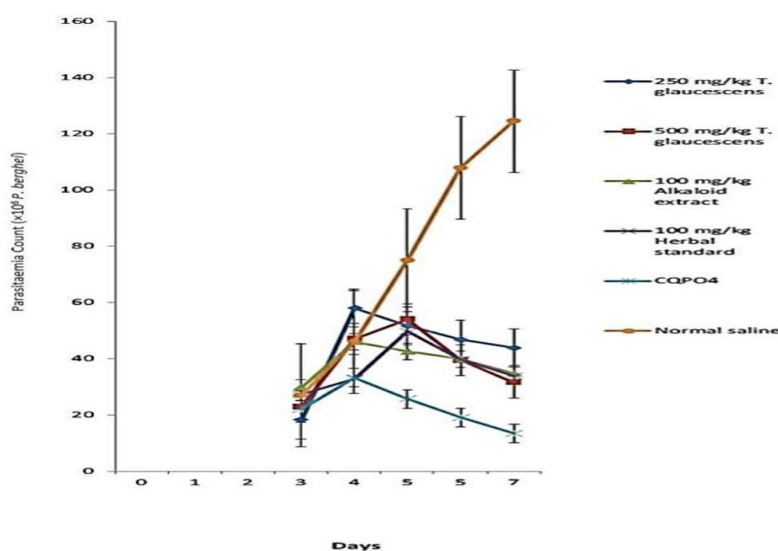
In the acute toxicity study, no death was recorded in the animals receiving methanol extract of *Terminalia glaucescens* up to a dose of 5000 mg/kg body weight. Furthermore, the animals did not show any changes in general behaviour and other physiological activities like giddiness, sniffing, aggressiveness, tachypnoea, or convulsion. From the toxicity studies (Table 1), the lethal dose ( $LD_{50}$ ) of the plant extract was estimated to be greater than 5000 mg /kg body weight in rats, suggesting the extract is safe to be used.

**Table 1** Acute oral toxicity effect of crude methanol extract of *Terminalia glaucescens* stem bark in wista albino rats

Group	Dosage (mg/kg bw)	No of animals	Mortality
Phase I			
1	10	3	0/3
2	100	3	0/3
3	1000	3	0/3
Phase II			
1	1600	3	0/3
2	2900	3	0/3
3	5000	3	0/3

#### 3.2. Anti-plasmodial activity

Figure 1 shows the antiplasmodial activity of the crude and alkaloidal extract of *Terminalia glaucescens* stem bark. The result showed a progressive decrease in parasitaemia count for mice treated with crude methanol extract, alkaloidal extract of *T. glaucescens* stem bark, herbal standard (*Artemisia anua*) and chloroquine while the negative control showed a progressive increase in parasitaemia count. The *plasmodium* infected mice in the positive control group (5 mg/kg body weight chloroquine phosphate (CQPO<sub>4</sub>)) had the highest reduction in the parasite count.



**Figure 1** Effects of crude and alkaloidal extracts of *T. glaucescens* on parasitaemia count in *Plasmodium berghei* infected mice

### 3.3. Percentage parasite inhibition and mean survival time

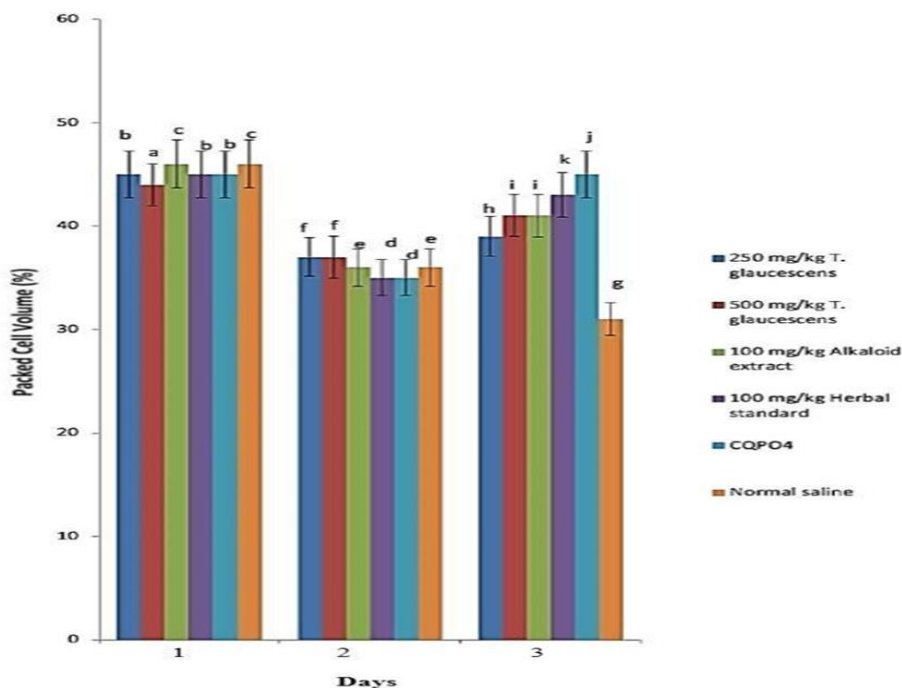
The percentage parasite inhibition (89.20 %) and mean survival period (45.71 days) for the chloroquine treated plasmodium infected mice were the highest (Table 2). The percentage parasite inhibition of 64.76, 74.66, 72.0 and 74.66 (%), and mean survival periods of 24.67, 24.50, 27.67 and 29.46 days were obtained for methanolic extract of *T. glaucescens* at doses of 250 and 500 mg/kg, alkaloidal extract (100 mg/kg body weight) and herbal standard (*Artemisia anua*) respectively. The groups administered normal saline survived for 13.69 days (Table 2).

**Table 2** Percentage Parasite Inhibition and Mean Survival time of Crude extract of *T. glaucescens* stem bark in *Plasmodium berghei* infected mice

Treatment	Dose (mg/k bw)	% Parasite inhibition	Mean survival time (day/s)
Crude extract of <i>T. glaucescens</i>	250	64.76	24.67,
Crude extract of <i>T. glaucescens</i>	500	74.66	24.50,
Chloroquine phosphate (CQPO <sub>4</sub> )	5	89.20	27.67
Alkaloid	100	72.0	29.46
<i>Artemisia anua</i> )	100	74.66	13.69

### 3.4. Packed cell volume

The packed cell volume of the mice before inoculation, 3<sup>rd</sup>, and 7<sup>th</sup> day for both crude and alkaloidal extract of *T. glaucescens* are shown in Figure 2. All the animals indicated a decrease in packed cell volume on the third day (after infection). However, after treatment of infected mice with the crude and alkaloidal extracts of *T. glaucescens*, *aternia* herbal standard as well as chloroquine (standard drug) exhibited a dose dependent increase in PCV while there was a decrease in the PCV significantly ( $p < 0.05$ ) for the negative control compared to the positive control and extracts treated animals.

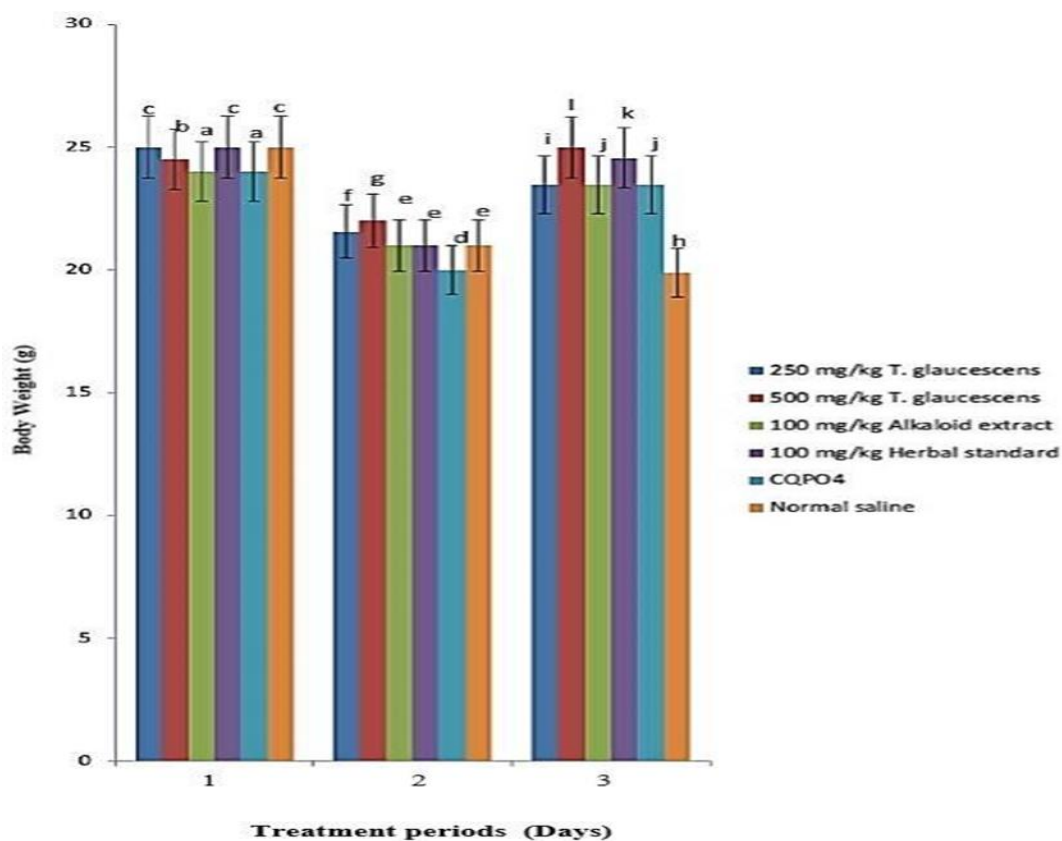


**Figure 2** Effects of crude and alkaloidal extracts of *T. glaucescens* stem bark on packed cell volume in *Plasmodium berghei* infected mice

Values are Mean  $\pm$  SEM of triplicate determinations. Values with different alphabets are significantly ( $p < 0.05$ ) different

### 3.5. Body weight

The average weight of the groups before inoculation (Day 0), 3<sup>rd</sup>, and 7<sup>th</sup> day for both crude and alkaloidal extract of *T. glaucescens* are shown in Figure 3. A significant decrease in weight was recorded for all the mice by day 3 after infection. Infected mice treated with crude and alkaloidal extracts of *T. glaucescens* showed an increase in weight from day 3 through day 7 while the negative control animals decreased in weight significantly ( $p < 0.05$ ) compared to the positive control and animals treated with the extracts of *T. glaucescens* stem bark (Figure 3).



**Figure 3** Effects of crude and alkaloidal extracts of *T. glaucescens* stem bark on bodyweight in *Plasmodium berghei* infected mice

Values are Mean  $\pm$  SEM of triplicate determinations. Values with different alphabets are significantly ( $p < 0.05$ ) different

### 3.6. Anti-inflammatory activity

Anti-inflammatory effects of crude extracts of *T. glaucescens* stem bark on paw oedema in rats are presented in Table 3. The crude extract of *T. glaucescens* stem bark exhibited a lower anti-inflammatory effect (62.63 % and 78.79 % for 400 and 800 mg/kg body weight respectively) compared to the acetyl salicylic acid standard drug (95.96 %).

**Table 3** Anti-inflammatory effects of crude extracts of *T. glaucescens* stem bark on paw oedema in albino rats

Treatment	Dose (mg/kg)	20	40	60	80	100	% Inhibition
<i>T. glaucescens</i>	400	0.75 $\pm$ 0.3	0.78 $\pm$ 2.4	0.56 $\pm$ 4.1	0.41 $\pm$ 3.3	0.37 $\pm$ 4.1	62.63
<i>T. glaucescens</i>	800	0.48 $\pm$ 1.6	0.49 $\pm$ 3.2	0.41 $\pm$ 2.0	0.29 $\pm$ 1.1	0.21 $\pm$ 0.3	78.79
Acetyl salicylic acid	150	0.18 $\pm$ 2.8	0.14 $\pm$ 3.0	0.11 $\pm$ 2.5	0.09 $\pm$ 2.2	0.04 $\pm$ 1.4	95.96
Normal saline	20 ml	0.87 $\pm$ 2.5	0.76 $\pm$ 2.2	0.78 $\pm$ 1.7	0.88 $\pm$ 3.2	0.99 $\pm$ 3.7	-

### 3.7. Analgesic activity

The Analgesic activity of crude extract of *T. glaucescens* stem bark in albino rats is shown in Table 4. The crude extract of *T. glaucescens* stem bark exhibited a lower analgesic effect (36.58 and 56.86 (%) for 400 and 800 mg/kg body weight respectively) compared to the acetyl salicylic acid standard drug (75.68 %).

**Table 4** Analgesic effects of crude extracts of *T. glaucescens* stem bark in albino rats

Treatment	Dose (mg/kg bw)	Mean Abdominal Constriction	% Inhibition
<i>T. glaucescens</i>	400	24.67 ± 2.34 <sup>c</sup>	36.58
<i>T. glaucescens</i>	800	16.78 ± 2.34 <sup>b</sup>	56.86
Acetyl Salicylic acid	150	9.46 ± 1.45 <sup>a</sup>	75.68
Normal saline	20 ml	38.90 ± 4.57 <sup>d</sup>	-

Values are mean ± SEM of 5 determinations. Values along the same column with different superscripts are significantly different. (p < 0.05)

## 4. Discussion

The antiplasmodial activity demonstrated by the crude extract of *T. glaucescens* stem bark may be due to the presence of phytochemicals in the plant which have been reported to have antimalarial properties. This is further substantiated by the antiplasmodial activity of the alkaloidal extract of *T. glaucescens* stem bark which agrees with the findings of Kabiru *et al.* [24], who reported that antiplasmodial activities of several medicinal plants have been attributed to the presence of some of the phytochemicals like saponins, alkaloids and flavonoid identified in the crude extracts of several plants. Alkaloids are among the most effective and medicinally significant plant secondary metabolite [13]. Pure alkaloids and their derivatives are used as basic therapeutic agents such as morphine is used as an analgesic, quinine as antiplasmodial, colchicines is used for gout treatment, reserpine is a tranquilizer, vincristine and vinblastine have antitumor effects [25]. Research studies have shown that isolated alkaloid, 9-methoxycanthin-6-one displayed higher antimalarial activity against *Plasmodium falciparum* Gombak A isolate, when compared with chloroquine [26]. In addition, potent antimalarial agents, raphidecurperoxin and polysyphorin, were isolated from the Vietnamese medicinal plants, *Rhaphidophora decursiva* [27]. The extracts of *Nigella sativa* (black seed), contained different classes of alkaloids that were believed to block protein synthesis in *Plasmodium falciparum* [28].

The higher antiplasmodial activity of the crude extract compared to the alkaloid extract (Figure 1), may be due to the synergistic effect of other phytochemicals in the crude extract. The dose dependent reduction in parasitaemia count of the crude plant extract is in consonance to the earlier report by George *et al.* [29], who documented that plants extract caused a dose dependent reduction in parasitaemia. The lower antiplasmodial activity of the plant extract compared to the standard drug (chloroquine), implies that the active ingredient in the chloroquine is in a purer state than the alkaloid extract, these supports the findings of George *et al.* [29], who reported that chloroquine had a higher antiplasmodial effect than crude plant extracts.

The fluctuations of packed cell volume (Fig 2), may be as a result of destruction of the red blood cell by the parasites, these findings are in agreement with the work of Kabiru *et al.* [24], who reported that initial fall in packed cell volume of infected mice was reversed after five days of treatment with the extracts. A reversal of the weight loss observed in the animals (Figure 3) suggest the fact that changes in general behavior, effect on body weight and mortality, which are critical for the evaluation of adverse effects of a compound on test animals, were not evident on the test animals is good evidence for the absence of toxicity. Thus, since this plant is believed to have several traditional medicinal uses, including malaria treatment by different traditional healers, the experimental determination of lack of acute toxicity would justify the use of the plant extracts for malaria treatment at primary health care level. This finding agrees with previous studies reported, that plant extracts have the potential to prevent loss in body weight of *Plasmodium berghei* infected rodents [18]. The absence of any significant differences in the body weight and PCV parameters provides a support for the safety (non-toxic) of *T. Glaucescens*.

The results show that the *T. glaucescens* extracts may contain substances which protects against the actions of histamine, serotonin and enzymes produced in the first phase of the oedema [30]. The second phase of the oedema is sensitive to most clinically active anti-inflammatory drugs. The ability of the extract to almost completely inhibit oedema (78.79 %) indicate that it contains bioactive components which are active against the liberation of

prostaglandins and other inflammatory agents usually released in the second phase of oedema. According to Mossa *et al.* [31], agents that inhibit paw oedema significantly must have anti-inflammatory agents which act by inhibiting the mediators of acute inflammation.

Acetic acid-induced writhing in mice is a model of visceral pain which is highly sensitive and useful for screening analgesic drugs. Crude extract of *T. glaucescens* stem bark caused significant antinociception against chemical induced pain in mice. Acetic acid-induced writhing model represents pain sensation by triggering localized inflammatory response. Such pain stimulus leads to the release of free arachidonic acid from tissue phospholipid by the action of phospholipase A2 and other acyl hydrolases [32]. The prostaglandins, mainly prostacyclin and prostaglandin-E have been reported to be responsible for pain sensation by exciting the A-fibres. Activities in the A  $\delta$ -fibres cause a sensation of sharp well localized pain. Any agent that lowers the number of writhing will demonstrate analgesia preferably by inhibition of prostaglandin synthesis, a peripheral mechanism of pain inhibition [33].

The alkaloid and other constituents including flavonoids, tannins and saponins in *T. glaucescens* stem bark may be responsible for the analgesic activity of the extract. Alkaloids are reported to play important role in analgesic activity primarily by targeting prostaglandins [34-35]. So it can be assumed that their Cyclooxygenase (COX) inhibitory activity and antioxidant activity may reduce the production of free arachidonic acid from phospholipid or may inhibit the enzyme system, which is responsible for the synthesis of prostaglandins and ultimately relieve pain-sensation [35]. However, the contribution of anti-inflammatory and analgesic activity of the test extract towards antimalarial outcome cannot be ruled out [25]. Consequently, it is assumed that the antimalarial effect of *T. glaucescens* stem bark extract is attributed as well to its analgesic and anti-inflammatory effect.

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## 5. Conclusion

In conclusion, it can be claimed that crude and alkaloid extracts of *T. glaucescens* stem bark possesses significant anti-plasmodial activities. The crude extract also exhibited significant analgesic and anti-inflammatory activities which provides a scientific basis to the folkloric claim of the plant in the management of pain and similar ailments. However, a lot remains to find out the exact mechanism of action of the.

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## Compliance with ethical standards

### *Acknowledgments*

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### *Disclosure of conflict of interest*

This work is a collaboration of all the authors. All authors read and approved the final manuscript. The authors declared no conflict of interest exist.

### *Statement of ethical approval*

The principles governing the use of laboratory animals as laid out by the Federal University of Technology, Minna Committee on Ethics for Medical and Scientific Research and also existing internationally accepted principles for laboratory animal use and care as contained in the Canadian Council on Animal Care Guidelines and Protocol Review were duly observed.

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