Phytochemical Screening, Antioxidant and Antiplasmodial Activities of methanol and n-hexane extracts from Stem Bark of *Tectona grandis* (Lamiaceae)

*Kenneth.U.Nwaeze[1], Gloria.O.Ayoola[1], Chimezie.A.Anyakora[1], Blessing Oparah[1], Daphnie Chiedu[1], Francis.O.Shode[2], Bharti Odhav[2], Peter Smith[3]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Lagos, Nigeria.

[2] Department of Biotechnology & Food Technology, Faculty of Applied Sciences, Durban University of Technology, Steve Biko Campus, South Africa.

[3] Division of Pharmacology, School of Medicine, University of Cape Town, South Africa.

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ABSTRACT

Tectona grandis belongs to the family Lamiaceae commonly known as Teak and it is majorly found in India, Myanmar, Laos and Thailand. It is now one of the most important species of tropical plantation forestry. The whole plant is medicinally important with negligible cytotoxicity accounting to its wide traditional use in the treatment of certain diseases. The aim of this study is to determine the phytochemical constituents, *in vitro* antioxidant and antiplasmodial activities of methanol and n-hexane extracts from *Tectona grandis* stem bark . Both extracts were obtained by maceration method using standard procedures. The antioxidant activity was determined by 2, 2-diphenylpicryl-1- hydrazyl (DPPH) free radical scavenging activity and Reducing Power (RP) assays. The phytochemical screening revealed the presence of phenolics, saponins, alkaloids, terpenes, tannins, and protein in methanol extract only while n-hexane extract contained flavonoids and steroids.The *in vitro* antioxidant assay gave percentage inhibition from 38.44± 0. 38 - 63.67± 0.29 % activity for methanol extract, 19.42±0.47 – 54.32± 0.33% for n-hexane extract, 40.22± 0.21-84.09± 0.41% for ascorbic acid and 42.35±0.19 -85.31±0.09% for gallic acid standards with IC_{50} of 120µg/ml, 190µg/ml, 98µg/ml and 70µg/ml respectively.The antiplasmodial activity for both the methanol and n-hexane extracts gave IC_{50} = 2.54± 0.44µg/ml (good) and 36.14± 0.37µg/ml (moderate) when compared to chloroquine (0.03± 0.01) and artesunate (<0.02± ND) standards respectively against *P.falciparum* chloroquine sensitive (FN54) strain. These results reveal the antiplasmodial potential of *T. grandis*. The plant is also a source of promising secondary metabolites having great antioxidant activity that could be useful medicinally.

Keywords: *Tectona grandis*, Phytochemical, Antioxidant, Antiplasmodial, *Plasmodium falciparum*.

INTRODUCTION

The plant *Tectona grandis,* commonly known as Teak, teakwood, heartwood or Indian teak (English), Bimbol ti (Ghana), Igi tiki (Nigeria) belongs to the family lamiaceae. It is now one of the most important species of tropical plantation forestry. The whole plant is medicinally important with negligible cytotoxicity accounting to its wide traditional use in the treatment of certain diseases. Several reports have revealed that the plant is used in the treatment of urinary discharge, bronchitis, cold and headache, scabies and as a laxative, sedative, diuretic, antidiabetic, analgesic and anti-inflammatory agent (Singh *et al,* 1996). The various phytochemical constituents isolated from *Tectona grandis* include juglone, which has been reported to have anti-microbial activity (Gupta *et al*., 2004), betulin aldehyde shows anti-tumor activity (Pathak *et al.,* 1998), lapachol shows anti-ulcerogenic activity (Goel *et al.,* 1987). Several classes of phytochemicals like alkaloids, glycosides, saponins, steroids, terpenes, flavonoids, proteins and carbohydrates have been reported in *Tectona grandis* (Asif, 2011). Secondary metabolites such as tectoquinone, 5-hydroxylapachol, tectol, betulinic acid, betulinic aldehyde, squalene, lapachol were isolated from the plant (Gupta, *et al*, 2004). Acetovanillone, E-isofuraldehyde , Evofolin, syringaresinol, medioresinol, balaphonin, lariciresinol, zhebeiresinol, 1-hydroxypinoresinol together with two new compounds Tectoneolin A and B were isolated from the leaves of *Tectona grandis* (Rodney *et al.,* 2012). 9, 10 dimethoxy-2 methyl-anthra-1,4-quinone, 5-hydroxylapachol along with tectomaquinone, methylquinizarin, lapachol dehydro-α-lapachone were isolated from the heartwood of *Tectona grandis* (Singh, *et al.,* 1989). Teak wood contains napthaquinone (lapachol, deoxylapachol, 5-hydroxylapacol), napthoquinone derivatives (α-dehydrolapachone, β-dehydrolapachone, tectol, dehydrotectol), anthraquinones (tectoquinone, 1-hydroxy-2-methylanthraquinone, 2-methyl quinizarin, pachybasin), and also obtusifolin, betulinic acid,

***Correspondence author: Email**: nkennethuzoma@gmail.com **Tel**: +234-08023329259.

trichione, β-sitosterol and squalene. Roots are rich in lapachol, tectol, tectoquinone, β-sitosterol and diterpenes, tectograndinol (Goswami, *et al*., 2009).Antioxidants are compounds widely used to counter the free radicals mediated oxidative stress in the cells. They can be derived from natural and chemical sources but research has shown that natural sources are far safer to use due to lower toxicity and side effects, hence production of antioxidant compounds from natural sources such as plants and algae is in great demand (Pant *et al*, 2011). DPPH assay has been extensively used for screening antioxidant activity because it can accommodate many samples in a short period and is sensitive enough to detect active principles at low concentration. When DPPH radicals encounter a proton donating substance such as an antioxidant, it would be scavenged and the substance is reduced. Thus .the DPPH radicals were widely used to investigate the scavenging activity of some natural compounds (Satyanarayana *et al*., 2010). Apart from DPPH free radical scavenging activity, the reducing power (RP) is another method to assay for antioxidants widely used among others.Free radicals are implicated in more than 80 diseases. In treatment of these diseases, antioxidant therapy has gained an utmost importance. Current research is now directed towards finding naturally occurring antioxidants from plants hence, the investigation of *Tectona grandis* stem bark antioxidant activity (Nayeem *et al*, 2010a). Malaria is one of the first seven most deadly infectious diseases in history, influencing the health of mankind with ravaging effects in the world and can result to death within 24hr of attack (White *et al*. 2013). The World Health Organization (WHO) recent report has revealed that 91 countries and areas are under malaria transmission with 216million cases more than the previous year resulting to about 445,000 death (72% are mostly children under 5years)(WHO,2017).

However, Africa as a continent is highly endowed in floral biodiversity and her plant materials are very rich in natural products with intriguing pharmacophoric compounds with great biological activities (Boyom *et al*,2009; Dolabela *et al*, 2008; Hostettmann *et al*,2000; Komlaga *et al*,2016;Nayeem *et al*,2010b; Traore-Keita *et al*,2000). It is believed that the next generation of antiplasmodials or the templates necessary for their synthesis may be found in plants currently used in African Traditional Medicine (Addae-Mensah *et al*, 2011; Efange *et al*, 2002; Fabricant *et al*, 2001; Willcox *et al*, 2011).

Most of the drugs used for the treatment of malaria ranging from the oldest (Quinine) which was extracted from *Cinchona* species to the latest (Artemisinin) from *Artemisia annua* have served mankind effectively but the issue of drugs resistance to plasmodium strains is still worrisome (Baird *et al*, 1996; Carmargo *et al*, 2009). This study can lead to the discovery of novel antiplasmodial drug molecules with low resistance considering the fact that most medicinal plants are underutilised.

MATERIALS AND METHODS

All reagents and chemicals were of analytical grade and commercially purchased. RPMI 1640 culture medium and fetal bovine serum were provided by Gibco (NY, U.S.A).Double beam T80+ UV/Visible spectrometer (PG instruments Ltd., USA) was used to obtain the absorbance of analytes. Ascorbic acid, gallic acid, 2, 2-diphenylpicryl-1- hydrazyl (DPPH) and reducing power (RP) were obtained from Sigma-Aldrich, Germany.

Plant Collection and Extraction

The stem bark of *Tectona grandis* were collected from university of Lagos, Akoka campus Nigeria in April, 2015. The plant material was authenticated and Identified by Mr Oyebanji of the herbarium unit of the Department of Botany, Faculty of Science, University of Lagos Nigeria with voucher number LUH 6569. Voucher specimen was deposited at the center.The stem bark were air dried within 14 days under a shade at room temperature before it was pulverized by grinding into a fine powder. Two portions each of 150g Powdered samples were then subjected to cold maceration in 1500ml methanol and hexane respectively for three days and filtered with a whatman filter paper. The same procedure was repeated twice more for maximum yield before concentration in a rotary evaporator at 40^oC (Heidolph Rotavapo model 4010) and later oven dried at 42^oC to remove the remaining solvent. The dry extracts were weighed and stored in sample bottles at 4^oC in a refrigerator until they were analysed.

Phytochemical Screening

Phytochemical screenings were carried out on the extracts using standard procedures to identify the chemical constituents as described by Trease and Evans (1989).

In Vitro Antioxidant Assay

The 2,2-Diphenylpicryl-1-hydrazyl (DPPH) free radical scavenging activity and reducing power (RP) methods were used to investigate the antioxidant activity of methanol and n-hexane extracts from *Tectona grandis* stem bark respectively.

DPPH Free Radical Scavenging Activity

The ability of the plant extracts to scavenge 2, 2diphenyl-1-picryl hydrazyl (DPPH) free radicals was determined by the standard method (Hirano *et al*., 2001). The stock solution of the extracts was prepared in methanol to achieve the concentration of 200 µg/ml. Dilutions were made to obtain concentrations of 10, 50, 100, 150 µg/ml. Diluted solutions (2 ml each) were mixed with 0.5ml of 0.1M DPPH methanol solution in test tubes. The mixture was shaken and allowed to stand for 20 min at room temperature and the reduction of the DPPH free radical was measured at absorbance of 517nm using UV-Visible Spectrometer. The blank mixture contains equal volume of methanol and DPPH solution and the absorbance measured as control. Ascorbic acid and garlic acid were used as standards. The experiments were carried out in triplicate. Percentage inhibition was calculated using equation shown below.

DPPH Scavenging Activity (% inhibition) = $[A_x - A_y / A_x] \times 100$

Where $\mathbf{A_x}$ = Control Absorbance

$\mathbf{A_y}$ = Absorbance of the analyte / standard.

The lower the absorbance values of the prepared solutions the better the free radical scavenging activity.

Reducing Power (RP) Assay

The reducing power of both the methanol and n-hexane stem bark extracts from *Tectona grandis* was investigated with slight modification of the method by Oyaizu (1986) hence, increase in absorbance of the reaction mixture indicates the reducing power of the samples (Jayaprakash *et al*,2001). Ascorbic acid and gallic acid were used as standard antioxidants. Substances which have reduction potential react with potassium ferricyanide at absorption maximum of 700nm. Serial dilutions of 10µg/ml, 50µg/ml, 100µg/ml, 150µg/ml and 200µg/ml were prepared for each sample extracts and standards. All the solutions were made with methanol. 1ml of each preparation was placed in each test tube. According to Oyaizu, 2.5ml of 0.2M phosphate buffer(pH 6.6) and 2.5ml of 1% w/v potassium ferricyanide ($K_3Fe(CN)_6$ was added to 1.0ml of each sample dissolved in distilled water in a test tube .The resulting mixture was incubated for 30 min at 50°C before addition of 2.5ml Trichloroacetic acid (10%w/v). The mixture was centrifuged at 3000 rpm for 10 min and filtered. Then 2.5ml of the filtrate was added to 2.5ml of distilled water and 0.5ml of 0.1% w/v, ferric chloride ($FeCl_3$), shaken and allowed to stay on the bench for 10min at room temperature before reading the absorbance at 700nm against the blank using UV-Visible spectrometer.

***In Vitro* Antiplasmodial Assay**

The methanol and hexane extracts were tested in triplicate on one occasion against chloroquine-sensitive (CQS) strain of *Plasmodium falciparum* (NF54). Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen (1976). Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler (1993). The test samples were prepared to a 20 mg/ml stock solution in 100% DMSO. Samples were tested as a suspension if not completely dissolved. Stock solutions were stored at -20ºC. Further dilutions were prepared on the day of the experiment. Chloroquine (CQ) and artesunate were used as the reference drugs in all experiments. A full dose-response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth (IC_{50}–value). Samples were tested at a starting concentration of 100 µg/ml, which was then serially diluted 2-fold in complete medium to give 10 concentrations; with the lowest concentration being 0.2µg/ml. The same dilution technique was used for all samples. Reference drugs were tested at a starting concentration of 1000 µg/ml. The highest concentration of solvent to which the parasites were exposed to had no measurable effect on the parasite viability (data not shown). The IC_{50}-values were obtained using a non-linear dose-response curve fitting analysis via Graph Pad Prism v.4.0 software (San Diego, CA).

Parasite Culture and *In Vitro* Extracts Testing

In vitro culture of chloroquine-sensitive (CQS) strain of *Plasmodium falciparum* (NF54) strain were maintained in human erythrocytes suspended in RPMI 1640 containing 37.5mM HEPES , supplemented with7mM D-glucose, 6mM NaOH, 25ml gentamicin sulphate ,2mM L-glutamine and 10% human serum albumin.The strains were maintained in human erythrocytes in a gas mixture containing 5% O_2, 5% CO_2, and 90% N_2.The parasites were synchronised to achieve a very high prevalence of young ring stages(>95%) by sorbitol lysis treatment(10% w/v sorbitol (BDH) .The antimalarial activity was measured using the microdilution technique in vitro. Red cells with parasitemia between 1-2% and 2% hematocrit were incubated with the methanol and hexane extracts for 48h.Samples were dissolved in DMSO and serially diluted with culture medium. To evaluate parasitemia, Giemsa staining and flow cytometric analysis were used. The concentration of the drug required to inhibit parasite growth was determined by comparing the flouriscence incorporated into the treated and control cultures. The concentration causing 50% inhibition was determined from the

drug concentration response curve. DMSO were used at the maximum concentrated of 0.1% and did not inhibit parasite growth.

RESULTS

The phytochemical screening of the methanol extract of *Tectona grandis* stem bark revealed the presence of phenolics, tannins, saponins, alkaloids, terpenes while flavonoids and steroids in the n-hexane extract.Cardiac glycosides ,reducing sugar and anthraquinones were absent in both samples as shown in Table 1. Methanol and n-hexane solvents were used for the extraction of the chemical constituents present in *T. grandis* stem bark. . Both methanol and n-hexane extracts gave 20.60g and 20.54g corresponding to 13.73 and 13. 69 % (w/w) yield respectively. This indicates that either of the solvents can be used to extract the phytochemicals present in *T.grandis* stem bark. Variation in the percentage yield of the extracts might be due to the chemical composition of the plant, polarity of the solvent, nature of the soil and agro-climatic condition as well as the effectiveness of the extracting solvent to dissolve endogenous compounds. The results of the DPPH percentage inhibition activity of the two extracts are presented in table 2 (Figure 1) while that of the reducing power assay are as shown in table 3 (Figure 2) respectively.

Table 1: Phytochemical constituents of methanol and n-hexane stem bark extracts form *Tectona grandis* .

Phytochemicals	Methanol extract	n-hexane extract
Flavonoids	_	+
Steroids	_	+
Phenolics	+	_
Tannins	+	_
Saponins	+	_
Cardiac glycosides	_	_
Alkaloids	+	_
Terpenes	+	_
Anthraquinones	_	_

+ = present - = absent

Table2: Percentage inhibition of DPPH against concentration of methanol and n-hexane stem bark extracts from *Tectona grandis* (* SEM, n = 3).

Conc. (µg/ml)	Methanol sample % inhibition	n-hexane sample % inhibition	Ascorbic acid % inhibition	Gallic acid % inhibition
10	38.44± 0. 38	19.42±0.47	40.22±0.21	42.35±0.19
50	41.49±0.24	21.40±0.16	45.63±0.27	46.33±0.52
100	43.86±0.39	26.56±0.23	51.75±0.45	63.64±0.37
150	60.32±0.51	41.67±0.64	70.45±0.11	81.82±0.30
200	63.67± 0. 29	54.32±0.33	84.09± 0.41	85.31±0.09

*SEM= standard error of mean

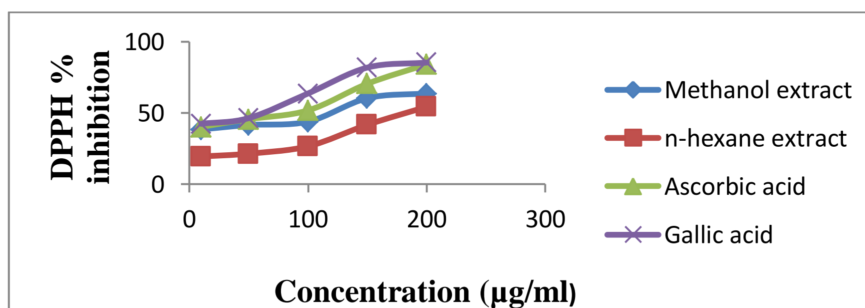

Figure 1: Line graph showing percentage inhibition of methanol and n-hexane extracts from *Tectona grandis* stem bark

Table 3: Result of reducing power assay for methanol and n-hexane stem bark extracts from *Tectona grandis* (SEM, n=3)

Conc. (µg/ml)	Methanol extract absorbance	n-hexane extract absorbance	Ascorbic acid absorbance	Gallic acid absorbance
10	0.133± 0.07	0.124± 0.16	0.129± 0.06	0.220± 0.23
50	0.360± 0.44	0.299± 0.04	0.343± 0.17	0.476± 0.33
100	0.829± 0.19	0.766± 0.12	0.802± 0.22	0.539± 0.14
150	0.980± 0.21	0.790± 0.05	0.961± 0.31	1.107± 0.09
200	1.076± 0.02	0.850± 0.42	1.470± 0.13	1.333± 0.11

The methanol and n-hexane extracts of the stem bark of *T. grandis* were evaluated in vitro against *Plasmodium falciparum* chloroquine-sensitive FN54 strain in comparison to standard chloroquine and artesunate drugs with their respective IC50 as shown in table 4.

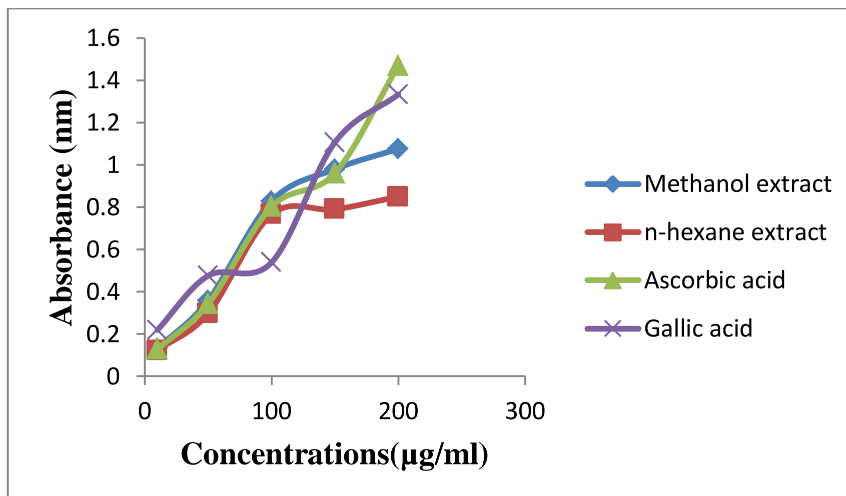

Figure 2: Line graph showing the reducing power assay of methanol and n-hexane extracts from *Tectona grandis* stem bark

Table 4. *In vitro* antiplasmodial activity of methanol and hexane extracts from *Tectona grandis* (n=3)

Extract / Drugs	IC_{50} µg/ml [SEM, n]	Activity
Methanol	2.54±0.44	good
n-Hexane	36.14±0.37	moderate
Chloroquine	0.03± 0.01	excellent
Artesunate	<0.02± ND	excellent

DISCUSSION

The *Tectona grandis* plant had been reported to exhibit several medicinal activities due to the presence of a couple of secondary metabolites hence, the methanol and n-hexane extracts from the stem bark were investigated for phytochemical screening, *in vitro* antioxidant and antiplasmodial activity. The Phytochemical screening on the leaves of *T. grandis* indicated the presence flavonoids, phenols and tannins (Komlaga *et al*., 2016). A previous study on the stem bark methanolic extract showed the presence of alkaloids and absence of flavonoids and steroids (Gupta and Singh, 2004). In the present study, the methanolic extract of the stem bark from *T.grandis* contained secondary metabolites such as phenolics, tannins, saponins, alkaloids, terpenes while flavonoids and steroids in the n-hexane extract. However,Cardiac glycosides ,reducing sugar and anthraquinones were absent in both samples as shown in Table 1. A research conducted on the ethyl acetate extract of the *T.grandis* stem bark showed the absence of glycosides (Goswami *et al*, 2010). This may be as a result of the different polarity of the solvents.

The presence of phytochemicals with phenolic groups gives plants acidic properties and could possibly be responsible for its antimicrobial activities (Harbone, 1973). Tannins are a group of polymeric phenolic substances capable exhibiting antioxidant activity (Cruz, 2013) and prevention of local tumor formation (Khaomek *et al*., 2008).

Several workers have also reported the analgesic and anti-inflammatory properties of alkaloids. They are used in medicine as an anaesthetic agents (Stray, 1998).It also has an adaptogenic effect which helps the host (man and animal) to develop resistance against disease and endurance against stress (Gupta, 1994).

The presence of saponins in the stem bark of the methanol extract supports the potentials of *T.grandis* to fight infections caused by parasites and in humans, saponins serves as immune system booster. The non-sugar part of saponins has a direct antioxidant activity which may result in reduced risk of cancer, heart diseases and aging (Prohp and Onoagbe, 2012). . They exhibit expectorant actions which are very useful in the management of inflammation of the upper respiratory tract.

Research has shown that they are cardio tonic in nature (Traore-Keita, 2000; Trease and Evans, 1989). The steroids and saponins are responsible for central nervous system activities. They can be hydrolyzed to produce aglycone (Sapogenin), which may be steroids or triterpenes (Okwu *et al*, 2004). Steroids are known to have stimulatory effect on bone marrow resulting in increased erythropoiesis (Stray, 1998). The presence of steroids in the n-hexane stem bark extract is an indication that it may have erythropoitic properties. Terpenes are multi-bioactive in nature such as antimalarial .antiviral,antifungal among others. Flavonoids are used to treat various disease conditions such as oedema, toothache, fever, diarrhoea and dental caries. They are known to inhibit protein synthesis in bacteria (Das *et al*, 1990). Flavonoids have antioxidant activities as well as health promoting effects such as antiallergic, anticancer, antioxidant, anti-nflammatory, antifungal, antibacterial, antipyretic antithrombotic, vasoprotective and antiviral effects. These effects have been associated with the influence of flavonoids on arachidonic acid metabolism (Trease and Evans, 2002).

The antioxidant properties of the plant extracts were determined using 2, 2-diphenylpicry-1-hydrazyl (DPPH) free radical scavenging activity and the reducing power method. The DPPH radical scavenging activities of the two extracts were expressed in terms of IC_{50} value with respect to ascorbic acid and gallic acid as standards. Lower IC_{50} value shows more antioxidant potential.The IC_{50} value for methanol extract of the plant part was 120 µg/ml while that of n-haxane extract was 190 µg/ml .The antioxidant activity of the methanol extract was comparatively lower than of ascorbic acid 98µg/ml and gallic acid 70µg/ml respectively (see table 2, Figure 1) .However, it shows that the methanol extract can serve as an alternative antioxidant in scavenging free radicals formed. However, the methanol extract antioxidant activity was quite better when compared to the n-hexane extract. The variability of the percentage inhibition in the plant extracts is due to variation in concentration of phytochemicals in the methanol and n-hexane extracts of *T.grandis* stem bark.

The reducing power of each of the extracts was tested against ascorbic acid and gallic acid as control (see table 3, Figure 2). The In this assay, the yellow colouration of the methanol and n-hexane extracts in solution turned greenish depending on the reducing power of the samples. The ability to reduce Fe^{3+} to Fe^{2+} may be attributed to the donation of hydrogen atom which is related to the presence of reductant. Therefore, an increase in absorbance of the sample is proportional to an increase in the reducing power. The reducing power for methanol extract is 100% better than ascorbic acid but less than gallic acid. Therefore its antioxidant activity is higher than n-hexane extract. Thus, the methanol and n-hexane extracts of *Tectona grandis* stem bark can be used for their antioxidant activities against certain disease case arising from reacting oxidative stress.

***In Vitro* Antiplasmodial Activity**

The methanol extract exhibited a good antiplasmodial activity (IC_{50} =2.54±0.44) while the n- hexane extract showed a moderate activity (IC_{50}=36.14±0.37) when compared to chloroquine (0.03± 0.01) and artesunate (<0.02± ND) standards respectively against *P.falciparum* chloroquine sensitive (FN54) strain .Though both extracts showed antiplasmodial activity however, the phytochemical responsible for a better activity may be present in the methanol extract. Similarly, *in vitro* antiplasmodial activity of aqueous, methanol, ethyl acetate and petroleum ether leaf extracts from *Tectona grandis* respectively against *Plasmopdium falcipa rum* chloroquine sensitive 3D7 and chloroquine resistant W2 strains gave IC_{50}= 7.18 ± 1.22 µg/ml(3D7) and >100 µg/ml for W2 (Komlaga *et al*,2016).This indicates that the aqueous leaf extract of *T.grandis* were active against the chloroqiune sensitive(3D7) strain when compared to the chloroquine standard (IC_{50}= 0.021± 0.0024µM) whereas the extract showed no activity on the chloroquine resistant(W) strain. The organic solvent fractions of the leaf extracts displayed significant antiplasmodial activity against chloroqiune sensitive (3D7) *P.falciparum* strain with IC_{50} of 4.48±1.42µg/ml for petroleum ether; 14.79± 3.19µg/ml for ethyl acetate and 0.92± 0.25µg/ml for methanol in comparison to same chloroquine standard value respectively (Komlaga *et al*.,2016).

Both *in vitro* and *in vivo* antiplasmodial activities of different plants stem barks from various families and species with promising IC_{50} results has been reported(Iwalewa *et al*,2008; Kayser *et al*,2003) and the criteria for considering the *in vitro* antiplasmodial activity of a given extract or compound as “good”, “moderate”, “low” or “inactive” differs. For instance, earlier studies by Basco *et al*., (1994) have adopted the following criteria: IC_{50} < 10 µg/mL, good activity; IC_{50} of 10-50 µg/mL, moderate activity; IC_{50} of 50-100 µg/mL, low activity; and IC_{50} > 100 µg/mL, inactive. However, Basco and co-workers’ criteria have been used for classifying the *in vitro* antiplasmodial activity of crude extracts which was also adopted in this study.

CONCLUSION

Based on the results obtained it can be concluded that this plant part can be a good source of valuable antioxidants useful to cure diseases caused by oxidative stress. The antiplasmodial activity of the plant can be exploited for malaria treatment. This is the first time the antiplasmodial activity of the stem bark of this plant will be reported. .Further work is currently on-going to isolate and identify the active constituents responsible for the antiplasmodial activity.

ACKNOWLEGMENT
This work was supported by grant and financial encouragement from the University of Lagos and Tertiary Education Trust Fund (TETFUND), Nigeria of which we are very grateful.

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