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Hepatoprotective effect of *Vernonia amygdalina and Ocimum gratissimum* on Wistar rats exposed to long-term administration of artemisinin-based combination therapies

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Abstract

In this study the protective effect of *Vernonia amygdalina* (VA) *and Ocimum gratissimum* (OG) on rats exposed to long term oral administration of artesunate-amodiaquine and arthemeter-lumefantrine were investigated. Forty-two albino rats were divided into seven groups. They were given the drugs, artesunate amodiaquine (AA) and artemether lumefantrine (AL) base on their body weight. Group 1: Control, received distilled water, group 2, received of 2.86 mg/7.7 mg AA, group 3, received of 1.14 mg/6.86 mg AL, group 4 received of 2.86 mg/7.7 mg AA + 200 mg VA, group 5 received of 1.14 mg/6.86 mg AL + 200 mg VA, group 6 received of 2.86 mg/7.7 mg AA + 200 mg OG and group 7 received of 1.14 mg/6.86 mg AL + 200 mg OG. The animals were sacrificed and blood samples obtained through cardiac puncture for biochemical investigations. Biochemical assay for total protein, albumin, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (**γ-**GT) were done. Co-administration of artesunate-amodiaquine and arthemeter-lumefantrine significantly decreased ($P<$ 0.05) total protein and albumin while there was significant increase ($P<$ 0.05) in total bilirubin, direct bilirubin, AST, ALT, ALP and **γ-**GT when compared with control group. The administration of VA and OG significantly increased the total protein and albumin and significantly decreased ($P<$ 0.05) total bilirubin and liver enzymes when compared with control group. The results indicate hepatic injury in the rats exposed to long term administration of artemisinin-based combination therapies (ACTs) which was reversed by the administration of VA and OG. There is need for caution while taking ACTs as malaria chemotherapy.

Keywords: Artemisinin; Herbs; Malaria; Hepatocytes

1 Introduction

The malaria burden in Nigeria accounts for 25% of global cases. The causes include climate, high transmission potential, socioeconomic development, overstretched health care systems, and displaced populations [1, 2, 3]. The disease is frequently treated in Nigeria through self-prescription as well as the utilization of nearby herbs and health facilities/hospitals [4]. Additionally, normal control measures incorporate the utilization of medication (prophylaxis), insect sprays (coil and sprays), insecticide-treated nets (ITNs), and window and door nets [5, 6]. Artemisinin-based combination therapy (ACT) is used as recommended treatment for uncomplicated malaria in Africa. In Nigeria, artemether-lumefantrine is used as an essential drug because of its efficacy in the treatment of malaria [7].

Artemisinin-based combination therapy (ACT), like other drugs is metabolized in the liver and the toxicity of some these drugs on liver on long term is not adequately documented. Hepatic toxicity of artesunate and dihydroartemisinin has been reported by Aprioku *et al.,* [8], Aniefiok *et al.,* [9], Aghahowa *et al.,* [10] and Kaboré *et al.,* [11]. Frequent mild adverse events caused by amodiaquine also the combination of amodiaquine and artesunate revealed the common

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adverse events of hepatotoxicity and leucopenia [12]. Several shortcomings have been observed in the adverse event reports when ACTs were used in different patients [13, 14, 15]. In all of these past studies, few ACTs were studied, and limited organ/system were explored [14, 15] and there is little or no information available concerning toxicity of ACTs.

Vernonia amygdalina (VA) is commonly called bitter leaf in English language. In many parts of Nigeria, the plant has been domesticated and used in the treatment of various infection and diseases. *Vernonia amygdalina* is reported to have a broad spectrum of medicinal relevance [16, 17]. *Ocimum gratissimum* (OG) of the family lamiaceae, popularly known as scent leaf is a perennial plant commonly used as spice [18]. *Ocimum gratissimum* is a plant distinguished for its therapeutic value [19, 20, 21]. Therefore, this research is very crucial to assess the prolong use of ACTs as they are usually taken overdose in Nigeria and other developing countries and the protective effect of *Vernonia amygdalina and Ocimum gratissimum* leaves.

2 Material and methods

2.1 Materials

2.1.1 Drugs

The study was conducted using ACTs; Artesunate/Amodiaquine (AA) 100/270 mg (Sanofi Aventis), manufactured at Maphar laboratories 20250 Casablanca, Morocco and Arthemeter/Lumefantrine (AL) 20/120 mg (Coartem Novartis) which was purchase from Odonah Pharmacy Okuku, Yala, Cross River State, manufactured by Novartis Pharmaceuticals Corporation Suffern, New York, U.S.A. Drugs were dissolved and reconstituted in distilled water and administered to the animals orally for 21 days based on their body weight.

2.1.2 Plant Materials

Fresh leaves of *Vernonia amygdalina and Ocimum gratissimum* were harvested from a garden in Okuku in Yala Local Government of Cross River State, South-South, Nigeria. The plants were identified at the herbarium unit of the Department of Biological Sciences, University of Calabar. Their fresh leaves were washed with clean water and dried under the shade for six days. Their dried leaves were milled using pestle and mortar to get a powder that was used for extraction.

2.1.3 Preparation of extract

The powdered samples of *Vernonia amygdalina and Ocimum gratissimum* 100 g were soaked separately into 100 ml of distilled water, they filtered after 48 hours and filtrates were concentrated in water bath. The solutions were diluted with corn oil, to produce a solution 100 mg/ml. The administration of extract was totally by gavage. Proper concentrations were administered by the use of oropharyngeal canula and calibrated hypodermic syringe.

2.1.4 Experimental animals

Forty-two (42) healthy adult albino rats of average weight (50-100 g) were obtained from Animal House, Department of Medical Biochemistry, Cross River State University of Technology, Okuku Campus. The rats were weighed, marked and grouped into seven groups with six rats in each group. They were housed in clean well-ventilated cages and fed with vital feed and given water *ad libitum* for two weeks to acclimatize them to laboratory condition. The study lasted for three weeks. The principles governing the care of laboratory animals as laid out by the Department of Medical Biochemistry, Cross River State University of Technology, were duly observed.

2.2 Methods

2.2.1 Preparation of Drugs

One tablet (100/270) mg of Artesunate/Amodiaquine (AA) was dissolved in 35 ml of distilled water and this was vigorously shaken for proper dissolution. 20/120 mg Arthermether/lumefanthrine (AL) was dissolved in 17.5 ml of distilled water with vigorous shaking for proper dissolution. Volumes corresponding to dose calculated for each rat was taken out of this stock and administered to the rats orally.

2.2.2 Experimental design

The rats were given two different types of drugs, artesunate amodiaquine (AA) and artemether lumefantrine (AL) base on their body weight. Group 1: Control, received distilled water, group 2, received of 2.86 mg/7.7 mg AA, group 3,

received of 1.14 mg/6.86 mg AL, group 4 received of 2.86 mg/7.7 mg AA + 200 mg VA, group 5 received of 1.14 mg/6.86 mg AL + 200 mg VA, group 6 received of 2.86 mg/7.7 mg AA + 200 mg OG and group 7 received of 1.14 mg/6.86 mg AL + 200 mg OG

2.2.3 Sample collection

The rats were anaesthetized with chloroform and 5 ml of blood was collected from the rats through cardiac puncture. The blood was dispensed into a plane sample bottle and sera were gotten from the blood by centrifugation and were used for the biochemical investigations.

2.2.4 Assay of Serum Aspartate Aminotransferase (AST) Activity

The assay of the blood serum aspartate aminotransferase (AST) activity was assayed by examining the level of oxaloacetate hydrazone produced with 2, 4-dinitrophenylhydrazine [22].

2.2.5 Assay of Serum Alanine Aminotransferase (ALT) Activity

Serum alanine aminotransferase (ALT) activity was analyzed by checking the level of pyruvate hydrazone produced with 2, 4-dinitrophenylhydraine [22].

2.2.6 Assay of Serum Alkaline Phosphatase (ALP) Activity

The activity of serum alkaline phosphatase was assayed by using the kinetic colorimetric technique of optimized Deutsche Gesellschaft for Klinische Chemie (DGKC) by the German Society of Clinical Chemists, GSCC [23].

2.2.7 Assay of Gamma Glutamyltransferase (γ-GT) Activity

The serum activity of gamma glutamyltransferase was assayed by using the kinetic colorimetric method of Persijin and Van der Slik [24].

2.2.8 Estimation of Serum Total Protein

The most widely used method for measuring serum protein is the biuret reaction [25] which was adopted for this estimation.

2.2.9 Estimation of Serum Albumin

Albumin is generally measured by a dye-binding technique that utilizes the ability of albumin to form a stable complex with bromocresol green dye [25].

2.2.10 Estimation of Serum Bilirubin

Serum bilirubin was estimated by the method described by Jendrassik and Grof [26].

2.3 Statistical Analysis

The experimental data were analysed for statistical significance by one-way analysis of variance and post hoc comparison using the SPSS version. All data were reported as mean ± SD and statistical significance was accepted at $P < 0.05$.

3 Results

Results of the effect of daily oral administration of the *Vernonia amygdalina and Ocimum gratissimum*, artesunate-amodiaquine (AA) and arthemeter-lumefetrine on the Wistar albino rats are presented below

Table 1 Effect of oral administration of *Vernonia amygdalina and Ocimum gratissimum*, Artesunate-amodiaquine (AA) and arthemeter-lumefetrine (AL) for 21 days on serum total protein, Albumin, serum total and direct bilirubin of Wistar albino rat

GROUP	TP (g/d)	ALB (g/d)	TB (g/d)	DB (g/d)
GROUP 1: CONTROL	11.04±0.65^{e}	21.41±0.46^{e}	14.89±0.46^{a}	4.48±0.50^{a}
GROUP 2: 2.86 mg/7.7 mg AA	7.27±0.56^{a}	17.37±0.62^{a}	20.94±1.46^{d}	5.00±0.79^{a}
GROUP 3: 1.14 mg/6.86 mg AL	8.26±0.42^{b}	18.79±0.36^{bc}	19.13±1.17^{c}	4.86±0.81^{a}
GROUP 4: 2.86 mg/7.7 mg AA + 200 mg VA	9.52±0.42^{cd}	19.32±0.88^{cd}	17.74±0.58^{b}	4.57±0.90^{a}
GROUP 5: 1.14 mg/6.86 mg AL + 200 mg VA	9.90±0.83^{d}	19.75±0.18^{d}	17.08±0.60^{b}	4.52±0.27^{a}
GROUP 6: 2.86 mg/7.7 mg AA + 200 mg OG	9.00±0.35^{c}	18.44±0.42^{b}	18.15±0.86^{bc}	5.01±0.60^{a}
GROUP 7: 1.14 mg/6.86 mg AL + 200 mg OG	9.09±0.52^{c}	18.85±0.72^{bc}	18.01±0.99^{bc}	4.99±0.70^{a}

Values were expressed as Mean ± SD of replicate determinations, value bearing super script a, b, c, d are statistically significant along the same column when compared with the control at (P< 0.05)

In the above table, there was significant (P<0.05) decrease in total protein and albumin in all the animals administered with the drugs when compared to the control. There was a significant (P<0.05) increase of serum total bilirubin while there was no significant difference in direct bilirubin in all treated groups when compared to the control.

Table 2 Effect of oral administration of *Vernonia amygdalina and Ocimum gratissimum,* Artesunate-amodiaquine (AA) and arthemeter-lumefetrine (AL) for 21 days on serum AST, ALT, ALP and γ-GT of Wistar albino rat

GROUP	AST (U/I)	ALT (U/I)	ALP (U/I)	γ-GT (U/I)
GROUP 1: CONTROL	33.55±4.09^{a}	25.64±0.68^{a}	45.70±3.21^{a}	16.41±0.33^{a}
GROUP 2: 2.86 mg/7.7 mg AA	61.03±7.24^{d}	40.13±3.17^{d}	72.14±1.16^{d}	22.73±3.76^{c}
GROUP 3: 1.14 mg/6.86 mg AL	56.49±6.44^{cd}	37.16±2.13^{c}	65.36±1.72^{c}	20.37±4.07^{bc}
GROUP 4: 2.86 mg/7.7 mg AA + 200 mg VA	49.11±1.58^{b}	29.49±1.05^{b}	53.21±5.81^{b}	18.08±1.34^{ab}
GROUP 5: 1.14 mg/6.86 mg AL + 200 mg VA	46.45±2.67^{b}	28.04±0.47^{b}	50.78±0.37^{b}	18.03±1.01^{ab}
GROUP 6: 2.86 mg/7.7mg AA + 200 mg OG	51.14±5.94^{bc}	29.63±0.64^{b}	54.03±1.55^{b}	18.88±0.27^{ab}
GROUP 7: 1.14 mg/6.86 mg AL + 200 mg OG	48.23±3.39^{b}	29.22±0.85^{b}	52.15±1.82^{b}	17.99±0.67^{ab}

Values were expressed as Mean ± SD of replicate determinations. Value bearing super script a, b, c, d are statistically significant along the same column when compared with the control at (P < 0.05).

In the table above, there was a significant (P<0.05) increase in serum AST, ALT, ALP and γ-GT in all treated groups when compared to the control.

4 Discussion

In malaria endemic regions, malaria infection may occur repeatedly in individuals within months which warrant the use of repeated doses of antimalarials. This situation occurs more prominently in individuals with increased susceptibility such as children, pregnant women and immunocompromised patients [27, 28, 29] and this action might result to drug toxicity.

The liver is the largest, important organ and the site for essential biochemical reactions in the human body. It has the function to detoxify toxic substances and synthesize useful biomolecules. The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Therefore, damage to the liver leads to grave consequences [30, 31]. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within

therapeutic ranges, may injure the organ. Due to liver's unique metabolism and close relationship with the gastrointestinal tract, it is susceptible to injury from drugs and other substances.

Drug-induced liver injury is a serious adverse drug reaction associated with many pharmaceuticals [32]. Drugs are able to affect liver function which in some cases it leads to liver failure and even patients' death [33]. Hepatic injury is a serious adverse effect associated with malaria drug therapy [34, 35]. Serum levels of many biochemical markers like transaminases, alkaline phosphatase, bilirubin, total protein, albumin, globulin, triglycerides and cholesterol are elevated in liver disease [30].

Total protein test measures the total amount of protein in the blood. The estimation of total proteins in the body is helpful in differentiating between a normal and damaged liver function as the majority of plasma proteins like albumins and globulins are produced in the liver [36]. Hepatotoxicity leads to decrease in albumin production [36]. Estimation of albumin can be used as a supplementary test for hepatic biosynthetic functions.

Decreased in the level of total protein and albumin in rats treated with AA and AL could be as a result of damage to the hepatic cells. Indicating that, these drugs are hepatotoxic and may cause damage to the liver cells resulting in the release of those metabolites into the blood. Most of the toxicity of antimalarial drugs comes from the induction of the generation of reactive oxygen species (ROS). These drugs might have induced oxidative stress and caused oxidative disorders in the cells. This is in line with some previous studies on antimalarial drugs such as halofantrine [37, 38], amodiaquine (mono-therapy) [39], or amodiaquine and sulfadoxine pyrimethamine [40] and chloroquine [41] which were shown to produce elevation in the level of some serum enzymes and metabolites indicating that they may induce hepatic damage.

When the liver cells are damaged, they may not be able to excrete bilirubin in the normal way, causing a build-up of bilirubin in the blood and extracellular fluid. The estimation of serum bilirubin helps in knowing the capacity of liver to transport organic anions and to metabolize drugs or xenobiotics [42]. Increased levels of bilirubin may result due to decreased hepatic clearance and lead to jaundice and other hepatotoxicity symptoms [43]. Increase in total bilirubin in this study may be due to inflammation of the liver. This may be attributed to the effect of the drugs (AL and AA) administered to the animals.

This study reported the increase in liver aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (**γ-**GT) by treatment with artesunate amodiaquine (AA) and artemether lumefantrine (AL) which is concomitant to previous literature [44, 45]. *Vernonia amygdalina and Ocimum gratissimum* exerted a powerful protective effect on the liver toxicity induced by these drugs. In this study, we conclude that *Vernonia amygdalina* (VA) *and Ocimum gratissimum* has a hepatoprotective activity against toxicity caused by long term administration of artesunate amodiaquine (AA) and artemether lumefantrine (AL) in experimental rats.

5 Conclusion

This study revealed that administration of artemisinin-based combination therapy might have some toxic effect on liver on long term and *Vernonia amygdalina* and *Ocimum gratissimum* can be potential candidates for hepatoprotection. The hepatoprotective action of the plants may be associated with the plants' ability to mitigate oxidative stress and well as modulation of metabolic pathways involved in hepatotoxicity. This study may provide a rational for further studies on ACTs and hepatoprotective effects of other medicinal plants.

Compliance with ethical standards

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Statement of ethical approval

The author has carried out experimental animals in this study according to the rules and codes of ethics for using animals

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Author's short biography

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He obtained his B.Sc. degree in Biochemistry from the University of Nigeria, Nsukka (UNN), Enugu State, 2005. The research project was on the effect of medicinal plant on lipid metabolism. He further obtained a Masters' degree in Biochemistry from the Ahmadu Bello University (ABU), Zaria, Kaduna State, Nigeria in 2011 with a research interest in the management of diabetes. Dr. Ugwu got his Doctorate degree in Biochemistry from the University of Calabar, Calabar, Nigeria in 2017 with a research interest in the management of prostate disease.

He has been working on various research projects with several publications in reputed journals. His recent publications include papers on the management of prostate diseases, diabetes and drug toxicity as well as other findings. He is a reviewer for different journal articles and takes much pride in teaching and performing research in biochemistry and biochemistry related fields. Dr. Ugwu has successfully supervised scores of students.