



Protective properties of *Ficus platyphylla* extract of Nupe land origin on oxidative stress in acetaminophen-induced albino rats

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ABSTRACT

Acetaminophen is a common and widely used analgesic and antipyretic agent, but at high doses, it leads to undesirable side effects, such as liver damage. The study investigates the protective properties of *Ficus platyphylla* against acetaminophen-induced oxidative stress in albino rats. About 30 albino rats were randomly divided into five (5) groups each consisting of six albino rats. The group 1 and 2 served as the negative and positive control, respectively. Group 3, 4 and 5 were served with 1000, 3000 and 5000 mg of extracts, respectively, with addition of acetaminophen (100mg/100g/day) to each group for 28 days. The analysis of serum marker enzymes, hematological indices, lipid profiles, and antioxidant enzymes were analyzed. A significant increase ($p < 0.05$) in red blood (RBC), white blood cell (WBC), hemoglobin (Hb), platelet (PLT), decrease in serum liver enzymes (ALP, ALT, AST, and MDA) were dictated in rats treated with acetaminophen and various doses of *F. platyphylla* extracts compared to acetaminophen treated rats. Similarly, increase levels of antioxidant enzymes, high-density lipoprotein (HDL) and calculated CPI, and decrease levels of lipid profiles (TC, TG, LDL, VLDL, AI, and CRI) were observed in rats administered acetaminophen and various doses of extracts compared to rats treated with the only acetaminophen. Therefore, various doses of *F. platyphylla* extracts could be toxic-free and may be used to combat tissue damage caused by oxidative stress.

Keywords: Acetaminophen, *Ficus platyphylla*, liver enzyme, oxidative stress, rats

INTRODUCTION

In so many diseases, reactive oxygen species (ROS) have been implicated (Ali *et al.*, 2001). A wide variety of ROS-scavenging antioxidants such as bioactive compounds and antioxidant vitamins have been established in various medicinal plants (Sun *et al.*, 2002, Liu *et al.*, 2003). The utilization of medicinal plants that contain high levels of phytochemicals has been recommended to prevent or reduce oxidative stress in the human body [Sun *et al.*, 2002, Chu *et al.*, 2002). The natural antioxidant defense mechanisms can be insufficient and hence dietary intake of antioxidant components is important and recommended (Duh, 1998).

The World Health Organization estimated that about 80% of the people that are living in developing countries use exclusively traditional medicines to treat their health problems. In developed countries more recently, interest has risen in the value of plants as sources of new drug candidates and in herbal medicines for healthy lifestyles. Traditional medical practitioners make claims of successful treatments of diseases using a variety of herbal

medicines often with little supporting evidence. A proper scientific evaluation of these herbal medicines with pertinent emphasis on established pharmacological and toxicological paradigms is imperative to determine their efficacy and safety.

Ficus platyphylla Del. Holl. (Moraceae) is a deciduous plant locally known as “Gamji” and widely distributed throughout the savannah region of the West African coast. Preparations of the plant have been used in the Nigerian traditional medicine for the management of insomnia, epilepsy, psychosis, depression, pain, and inflammation for many years and their efficacy is widely acclaimed among the Nupe communities of north-central, Nigeria (Audu, 1989). The cold water extract, decoction or powder of the stem or root bark are usually taken

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orally, while the powder is often mixed with food and eaten, or placed in burning charcoal and inhaled (Audu, 1989). Previous studies revealed that the plant contains biologically active substances with the potential central nervous system, antinociceptive, anti-inflammatory, and gastrointestinal activities in rodents (Amos *et al.*, 2001, Chindo *et al.*, 2003 & 2008).

Paracetamol (PC) is commonly used as an analgesic and antipyretic drug (Kanno *et al.*, 2016). It is safe at therapeutic levels, but at high doses, it can lead to undesirable side effects such as hepatotoxicity and nephrotoxicity (Ahmad *et al.*, 2012). Although high doses of it establish a conjugated bond with glucuronic acid or sulfate in which a significant portion is metabolized by the cytochrome P450 system. This probably leads to the production of reactive toxic metabolites such as *N*-acetyl-*p*-benzoquinone imine (NAPQI) interacting with sulfhydryl groups in the glutathione (GSH) molecule (El-Din *et al.*, 2013; Gamal *et al.*, 2013; Abdel-zaher *et al.*, 2018). Therefore, PC induces depletion of cellular GSH stores. Binding cellular proteins, the remaining portion of NAPQI begins lipid peroxidation and ultimately induces kidney damage (Das *et al.*, 2015; El-shafey *et al.*, 2015). Therefore, PC toxicity is determined by the amount of NAPQI produced and the inadequate GSH for PC detoxification (Naguib *et al.*, 2014). Decreases in antioxidant enzyme levels and increases in the production of reactive oxygen species (ROS) are observed as a result of acetaminophen-induced tissue damage (Gul *et al.*, 2012). Oxidative stress and the formation of free radicals in PC-induced kidney and liver damage have been reported in several studies (Abdel-zaher *et al.*, 2018; El-shafey *et al.*, 2015). Furthermore, some studies have reported that high doses of acetaminophen reduce tubular epithelial cell vitality by leading to kidney toxicity (Yu *et al.*, 2014; Ucar *et al.*, 2013). Hence, one of the alternative therapeutic approaches against acetaminophen-induced tissue toxicity is the use of natural compounds that are used for medical purposes and have antioxidant activities (Sener *et al.*, 2003). Indeed, several antioxidants were proved efficient in protecting the body tissues against the deleterious effect of acetaminophen overdose (Williams *et al.*, 2011) In view of these and due to the different utilizations, well established and proven effectiveness of *F. platyphylla* parts

extract in the Nigerian traditional medicine and lack of optimum effective doses in the management of oxidative stress-related human diseases, this study is aimed to evaluate the protective properties of *F. platyphylla* extracts against acetaminophen-induced oxidative stress in albino rats.

METHODOLOGY

Materials

F. platyphylla parts were collected from Lapai, Nigeria. The water used in the analysis was glass distilled. The weaning albino rats used were of the same litter origin obtained from the rat colony of the Department of Biochemistry, Federal University of Technology, Minna, Nigeria. Acetone was purchased from sigma-Aldrich Company (St. Louise, MO, United State). Albumin, alkaline phosphatase (ALP), alanine and aspartate aminotransferase (ALT and AST), antioxidant enzyme assay kits were obtained from Roche Diagnostic GmbH, Mannheim, Germany.

Sample Collection

The selected part of *F. platyphylla* (stem bark) was collected from Lapai in Lapai Local Government Area of Niger State, Nigeria, around in March 2016. The botanical identification and authentication of the selected plant were confirmed in the Biological Department, Faculty of Natural Sciences, Ibrahim Badamasi Babangida University, Lapai. The debris on the stem bark was removed and air-dried at room temperature. Dried samples were pounded into fine powder using mortar and pestle and stored in a labeled air-tight container for future use.

Preparation Of Crude Extract

The extractant used was acetone due to its selective property of extracting tannin and flavonoid (Islam and Kato-Noguchi, 2014). Eight (80) grams of *Ficus platyphylla* stem bark powder in one (1) litre capacity conical flask containing 500 ml of cold acetone (Sigma-Aldrich, Europe) was prepared, kept in a cupboard with intermittent shaking for five days. The mixture was filtered using a muslin cloth and the filtrate was evaporated in a rotary evaporator to give a yield of 12.47 g., the paste was poured into beaker and placed in a water bath for complete evaporation of the solvent. This was reconstituted separately in distilled water to give the required doses of 1000, 3000 and 5000 mg/kg of the extract used in this study.

Experimental Animals

The healthy thirty (30) adult male rats of Wister strain weighing between 125 and 160 g body weight were obtained from the Animal House of the Biochemistry Department, Federal University of Technology, Minna, Niger State. They were housed in clean metabolic cages placed in well-ventilated house conditions (temperature $23 \pm 1^\circ\text{C}$; photoperiod: 12 h natural light and 12 h dark; humidity: 45–50%) and also allowed free access to Balanced Trusty Chunks and tap water freed of contaminants before and during the experiment. The rats were acclimatized after randomized into different groups for seven (7) days in standard environmental conditions before the experiments. The methods used were following that of the Organization for Economic Development (OECD) guidelines on good laboratory practice (OECD).

Experimental Animal Group Design

The rats were grouped into five (5) with six rats per group, and orally administered as follows:

Group1: Healthy control rats administered with distilled water for 28 days

Group2: Healthy rats treated with only 100 mg/100g/day of acetaminophen for 28 days

Group3: Healthy rats treated with 1000 mg/kg of extract + 100 mg/100g/day of acetaminophen for 28 days

Group4: Healthy rats treated with 3000 mg/kg of extract + 100 mg/100g/day of acetaminophen for 28 days

Group5: Healthy rats treated with 5000 mg/kg of extract + 100 mg/100g/day of acetaminophen for 28 days

The animals were anaesthetized and sacrificed after the 28th day of treatments and blood were collected by cardiac puncture. The collected blood from each group were pulled, dispensed in to plain bottles and allowed to clot and centrifuged at 3500 rpm for 10 min. The sera were separated, stored at -4°C and used for evaluation of hematological indices, serum liver enzymes, antioxidant enzymes and lipid profile.

Determination of Hematological Parameters

EDTA-added whole blood samples were used for hematological examination. Hematological parameters like number of red blood cell (RBC), white blood cell (WBC), lymphocytes (LYM), platelets (PLT), hemoglobin (Hb) concentration

and hematocrit (Ht) values were determined by standard methods using automated hematology analyzer (Abacus 360, Japan) (Jain, 1986).

Determination Of Anti-Oxidant Enzyme

Superoxide dismutase (SOD) activity was determined using the Epinephrine method (Pajovic *et al.*, 2003). Briefly, 0.1ml of serum was added to 2.5ml of 0.05M phosphate buffer (pH 7.8). Beside the spectrophotometer, 0.3ml of adrenaline solution (0.059%) was added to the mixture and the absorbance was read at 750nm for 1minute. One unit SOD activity was given as the amount of SOD necessary to cause 50% inhibition of the oxidation of adrenaline. The international unit of SOD activity is in U/L. Increase in absorbance for substrate is calculated using the formula: $A_3 - A_0 / 3$, and the % inhibition is calculated using this formula: $100 - \text{IAS} / \text{IAB} \times 100$; A_3 : Absorbance after 15seconds, A_0 : Absorbance after 90seconds, IAS: Increase in absorbance of substrate, IAB: Increase in absorbance of blank.

Catalase (CAT) activity was determined according to U.V. analysis method (Aebi, 1974; Arief *et al.*, 2010). In this method, 0.1ml of hemolysate was added to 5ml of water, mixed and allowed to stand for 5 min. In duplicate, 1ml of phosphate buffer was added to 2ml of hemolysate. Then, 1ml of 30mM hydrogen peroxide solution was added beside the spectrophotometer and the absorbance was monitored at 750nm for 3min. The Catalase activity was calculated using the equation: $K = 2.3/\Delta_t \times \log W_1/E_2$; E_1 = Absorbance after 15seconds, E_2 = Absorbance after 18seconds, Δ_t = Change in time. The Catalase content of the sample is expressed in activity of Catalase per second (K).

Reduce glutathione (GSH), glutathione reductase (GR), glutathione peroxidase (GPx) and glutathione S-transferase (GST) was determined using the method described by Reitman and Frankel (1957); Arief *et al.*, (2010). The enzymes were assayed following the manufacturer's instruction by using reagents kit (CHEMELEX, S.A Industries, Spain).

Liver Function Test

The determination of Serum Alanine Transaminase (ALT), Aspartate Transaminase (AST), alkaline phosphatase (ALP) and malondialdehyde (MDA) was performed using the methods described by Reitman and Frankel (1957). The enzyme was assayed according to

manufacturer's instruction using reagents kit (CHEMELEX, S.A Industries, Spain).

Lipid Parameters

The serum total cholesterol (TC), high-density lipoprotein (HDL) and triglyceride (TG) concentrations in rats were analyzed using spectrophotometric enzyme assay kits (Bowers and McComb, 1966; Jagetia *et al.*, 2003). The serum Low-density lipoprotein (LDL) and Very low-density lipoprotein (VLDL) concentrations were calculated following the Friedewald formulae (Friedewald *et al.*, 1972). Cardioprotective index (CPI), atherogenic (AI) and coronary risk indices (CRI) were calculated using the formulae; CPI = HDL/LDL; AI = TC-HDL/HDL and CRI = TC/HDL.

Data Analysis

Data were presented as mean + standard deviation. One way analysis of variance (ANOVA) and the least significant difference (LSD) was applied. Significance was accepted at $p < 0.05$.

RESULTS

The results of hematological indices are presented in Table 1. It reveals that there were significant changes ($p < 0.05$) on all hematological indices in acetaminophen-induced albino rats treated with different concentration (1000mg, 3000mg and 5000mg) of *F. platyphylla* and those treated with the only acetaminophen as compared to the normal control. At all doses of concentrations (1000, 3000 and 5000 mg/mL) of *F. platyphylla*, a significant increase ($p < 0.05$) in hematological indices were experienced in acetaminophen-induced rats when compared with acetaminophen control rats. However,

significant decreases in all hematological indices were recorded in PCM treated rats when compared to healthy rat control groups (Table 1). However, a significant decrease in antioxidant activities were observed in acetaminophen-induced rats compared to normal healthy rats. Thus, co-administration of 1000, 3000 and 5000 mg/mL of *F. platyphylla* extract, separately, to acetaminophen-induced rats elevated the antioxidant values above those of acetaminophen control rats (Table 2). High values of all liver enzymes (ALT, AST, ALP, and MDA) were recorded in the acetaminophen treated groups compared to the normal control and *F. platyphylla* treated groups ($p < 0.05$). Upon administration of 1000, 3000 and 5000 mg/mL of *F. platyphylla* extracts, separately, to acetaminophen-induced rats drastically reduce the liver enzyme activities when compared to acetaminophen treated rats (Table 3). The results of lipid indices in all studied rats are presented in Table 4. All rats treated with acetaminophen alone had high significant values of TC, TG, LDL, VLDL, AI, and CRI while decrease significant values of HDL and CPI were observed in acetaminophen treated rats when compared to healthy control rats. Upon co-administration of 1000, 1000 and 5000 mg/mL of *F. platyphylla* extracts, separately, to acetaminophen treated rats drastically reduce the values for TC, TG, LDL, VLDL, AI and CRI and elevated the values for HDL and CPI when compared with acetaminophen-induced rats (Table 4).

Table 1. Effect of *F. platyphylla* extract concentrations on hematological indices in acetaminophen-induced albino rats.

Treatment	WBC($10^9/L$)	LYM($10^9/L$)	RBC($10^{12}/L$)	Hb(g/dl)	Ht(PCV %)	PLT ($10^9/L$)
NC	2.03±0.02 ^c	1.54±0.01 ^c	2.53±0.01 ^c	4.33±0.09 ^c	15.48±0.01 ^c	190.03±0.09 ^b
PCM	1.23±0.01 ^a	0.63±0.01 ^a	1.28±0.01 ^a	3.23±0.09 ^a	12.33±0.09 ^a	92.03±0.09 ^a
1000mg+PCM	2.11±0.02 ^d	1.57±0.01 ^d	2.97±0.03 ^d	5.03±0.09 ^d	15.42±0.01 ^b	190.00±0.40 ^b
3000mg+PCM	2.02±0.01 ^b	1.23±0.01 ^b	3.00±0.01 ^e	4.37±0.13 ^c	15.83±0.01 ^e	190.07±0.03 ^b
5000mg+PCM	2.25±0.26 ^e	1.87±0.01 ^e	2.47±0.03 ^b	4.17±0.09 ^b	15.69±0.01 ^d	190.00±0.06 ^b

WBC: white blood count; LYM: lymphocyte; RBC: red blood count; Hb: hemoglobin; Ht: hematocrit; PLT: platelet; PCM: paracetamol. The data are presented in mean ± SEM (n = 6/group) and horizontal values with different superscript are significant different ($p < 0.05$) while those with the same superscript are not significance difference ($p > 0.05$).

Table 2. Effect of *F. platyphylla* extracts concentrations on antioxidant activities in acetaminophen-induced albino rats

Treatment	SOD (u/g)	CAT (k/g)	GSH (nmol/min/mg)	GR (nmol/min/mg)	GPx (nmol/min/mg)	GST (nmol/min/mg)
NC	34.41±0.21 ^d	67.42±1.21 ^d	711.7±0.4 ^b	8.5±0.6 ^b	10.5±0.5 ^b	9.6±0.7 ^b
PCM	26.30±0.16 ^a	49.32±0.62 ^a	401.2±0.3 ^a	4.6±0.4 ^a	6.6±0.5 ^a	5.3±0.6 ^a
1000mg+PCM	35.41±0.21 ^e	67.62±0.22 ^e	761.2±0.5 ^c	8.8±0.7 ^c	11.5±0.2 ^c	10.5±0.3 ^c
3000mg+PCM	35.56±0.62 ^f	68.60±0.31 ^f	810.1±0.7 ^d	10.5±0.2 ^d	12.1±0.2 ^d	10.8±0.5 ^d
5000mg+PCM	34.32±0.31 ^c	67.31±0.39 ^c	825.3±0.5 ^e	10.7±0.3 ^c	12.6±0.3 ^e	11.2±0.3 ^e

SOD: Superoxide Dismutase, CAT: Catalase, GSH: reduced glutathione, GR: glutathione reductase, GPx: glutathione peroxidase, GST: glutathione S-transferase. NC: Normal control, PCM: Paracetamol. The data are presented in mean ± SEM (n = 6/group) and horizontal values with different superscript are significantly different (p<0.05) while those with the same superscript are not significance difference (p>0.05).

Table 3. Effect of *F. platyphylla* extracts concentrations on liver enzyme activities in acetaminophen-induced albino rats.

Treatment	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	MDA (nmol/min/mg)
NC	39.10±1.2 ^c	137.20±1.0 ^c	21.8±0.3 ^a	10.8±0.3 ^d
PCM	56.40±2.1 ^f	167.42±3.8 ^f	45.3±0.4 ^e	11.3±0.4 ^e
1000mg+PCM	39.01±0.8 ^b	137.09±1.0 ^b	25.5±0.5 ^c	9.5±0.5 ^b
3000mg+PCM	38.19±0.2 ^a	136.62±2.1 ^a	24.6±0.7 ^b	8.6±0.7 ^a
5000mg+PCM	40.11±1.0 ^d	138.71±2.8 ^d	27.2±0.5 ^d	10.2±0.5 ^c

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, MDA: malondialdehyde, NC: Normal control, PCM: Paracetamol. The data are presented in mean ± SEM (n = 6/group) and horizontal values with different superscript are significantly different (p<0.05) while those with the same superscript are not significance difference (p>0.05).

Table 4. Effect of *F. platyphylla* extracts concentrations on lipid indices in acetaminophen-induced albino rats.

Treatment	TC (mmol/L)	HDL (mmol/L)	TG (mmol/L)	LDL (mmol/L)	VLDL (mmol/L)	AI	CRI	CPI
NC	3.7±0.2 ^a	1.3±0.1 ^b	1.3±0.1 ^a	1.1±0.1 ^a	2.3±0.1 ^c	1.9±0.3 ^d	2.8±0.2 ^d	1.2±0.4 ^d
PCM	4.4±0.3 ^e	0.7±0.1 ^a	2.2±0.1 ^d	2.8±0.5 ^d	2.8±0.3 ^d	5.3±0.2 ^e	3.0±0.5 ^e	0.3±0.2 ^a
1000mg+PCM	3.8±0.3 ^b	1.5±0.1 ^c	1.4±0.1 ^b	2.0±0.5 ^c	1.5±0.3 ^a	1.5±0.2 ^c	1.1±0.5 ^b	0.8±0.2 ^b
3000mg+PCM	4.0±0.2 ^d	1.6±0.1 ^d	1.4±0.3 ^b	1.7±0.3 ^b	1.7±0.1 ^b	1.5±0.1 ^b	1.0±0.1 ^a	0.9±0.2 ^c
5000mg+PCM	3.9±0.1 ^c	1.5±0.2 ^c	1.6±0.4 ^c	2.0±0.2 ^c	1.5±0.2 ^a	1.6±0.3 ^a	1.9±0.2 ^c	0.8±0.4 ^b

TC: total cholesterol, HDL: high-density lipoprotein, TG: triglyceride, LDL: low-density lipoprotein, AI: atherogenic index, CRI: coronary risk index, CPI: Cardioprotective index. The data are presented in mean ± SEM (n = 6/group) and statistically significant from healthy control rats at p<0.05 by ANOVA and Dunnett's test was performed.

DISCUSSION

Hepatoprotective properties of *F. platyphylla* bark extract at different concentrations against acetaminophen-induced liver injury by oxidative stress were evaluated. Blood parameters are key factors in diagnosing the actual physiological states of organisms. An organism must keep its

blood composition and constituent relatively constant under natural conditions to function properly (Maina, 2015). The present study shows that bark extracts of *F. platyphylla* and acetaminophen demonstrated varying degrees of hematological changes at the dose levels of 1000, 3000 and 5000mg/mL

The results of hematology as indicated in Table 1 revealed that there was a significant decreased ($p < 0.05$) in all hematological indices observed in acetaminophen-induced rats when compared with healthy control rats. The drastically reduction in hematological parameters in acetaminophen treated rats could be due to the overdose of acetaminophen administered that produced oxidative stress in rats. Low levels of hematological parameters in treated rats with an overdose of acetaminophen signified abnormality in rats. This finding is in correlation with the report of Baker *et al.* (1998) that mega doses of acetaminophen administered to rats generate oxidative damage on their erythrocytes and ultimately lead to hemolytic anemia. It is also in line with earlier work reported by Young *et al.*, (1990) and El-Din *et al.* (2013) that over-consumption of acetaminophen induces hemolytic anemia in hk phenotype dogs. However, a significant increased ($p < 0.05$) in all hematological indices observed in rats treated with acetaminophen and various doses of *F. platyphylla* extracts as compared with those on the only acetaminophen could be due to the ability of all doses of extracts to neutralize the effects of free radicals generated by mega dose of acetaminophen in rats. This ultimately can prevent the occurrence of acetaminophen-induced hemolytic anemia in rats. Anderson and Theron (1990) have demonstrated that *F. platyphylla* possess high antioxidant properties that are free radical neutralizers. The ability of extract concentrations in to elevate white blood cells in rats administered with acetaminophen and various doses of extracts could be that bioactive compounds in extracts stimulated the sensitivity of the committed stem cells, responsible for the production of white blood cells. Iranloye (2002) and Adeneye (2008) have shown that *F. platyphylla* possess immune-boosting properties of white blood cells similar to those reported for medicinal plants. Likewise, high levels of platelet counts experienced in rats treated with acetaminophen and various doses of

extracts may suggest the presence of some bioactive compounds in extracts that stimulated thrombopoietic process rats. This finding is in line with the report of Subenthiran *et al.* (2013) that leaf juice of many medicinal plants consumed during dengue infection had the potential to induce platelet production.

Besides, antioxidant activities (CAT, SOD, GSH, GR, GPx, and GST) in rats treated with only acetaminophen and the extracts of *F. platyphylla* were studied as indicated in Table 2. The low profile of antioxidant enzymes observed in rats administered with an only mega dose of acetaminophen as revealed in Table 2 may signify that the natural defense mechanisms of the animals have been overwhelmed by free radicals generated by paracetamol. The antioxidant enzymes can prevent the production of lipid peroxidation and base modification by scavenging ROS (James *et al.*, 2014). The increased levels of these antioxidant enzymes demonstrated in rats treated with acetaminophen and various doses of extracts could suggest their inhibitory potency of free radicals production and from overwhelming the natural defense system of the animals. These are indications of extracts antioxidant potentials as supported that *F. platyphylla* extracts possessed antioxidant properties and important bioactive compounds (Anderson and Theron, 1990). Drug metabolizing enzymes are a diverse group of proteins that are responsible for metabolizing a vast array of xenobiotics such as drugs, environmental pollutants, and endogenous compounds. Phase II drug detoxification mechanisms involve the conjugation of toxic agents with compounds such as glutathione and glucuronic acid (James *et al.*, 2014). Megadose of acetaminophen administered alone can deplete the levels of these enzymes and coadministration of various doses of the extract could induce/restore the activities of drug-metabolizing enzymes. Thus, the significant induction in the levels of these enzymes by the extract might enhance the elimination/clearance of

acetaminophen from the body before it is metabolized to the potential toxic agent(s) (Yakubu *et al.*, 2013; Tripathi *et al.*, 2003).

Furthermore, the result of serum ALT and AST, ALP and MDA levels in rats treated with acetaminophen alone and those co-administered with various doses of *F. platyphylla* are presented in Table 3. High profiles of liver enzymes demonstrated in rats treated with megadose acetaminophen alone could signify hepatocytes damage by free radicals generated by the megadose of acetaminophen administered to the rats. Changes in serum levels of marker enzymes are known to be associated with various diseases and high levels of these enzymes are indicative of liver damage (Jackson *et al.*, 2002; Abdel-Wahal *et al.*, (2003). This result correlates with that of Eriksson *et al.* (1992) and Yakubu *et al.* (2013) that a high dose of acetaminophen is toxic and increase levels of marker enzymes which signify hepatocyte damage. Sai *et al.* (1992), Yakubu *et al.* (2013) and El-Din *et al.* (2013) have reported that high levels of serum marker enzymes in rats administered with a megadose of acetaminophen indicate liver damage.

In a normal therapeutic intake of paracetamol, cytochrome P-450 system generates excessive metabolites that can be decreased by glutathione. Thus, under overdose of acetaminophen, the glutathione accumulates will be depleted and the excessive metabolites will react with the macromolecules of liver and lead to hepatocyte death and the hepatic cellular enzymes in serum will therefore increase (Nwana and Oboh, 2007, El-Din *et al.*, 2013). It signifies that hepatotoxicity of acetaminophen is critically dependent on the glutathione cellular depletion, and high reduction in reduced glutathione of the intracellular level can cause the generation of free radicals. (Arnaiz *et al.*, 1995, Tirmenstein and Nelson, 1990, El-Din *et al.*, 2013). In contrast, the administration of mega dose of acetaminophen (100 mg/mL) with various doses of extracts in albino rats

showed a significant decrease ($P \leq 0.05$) in serum AST, ALT, and ALP (Table 3). Low levels of serum marker enzyme signify their hepatoprotection against oxidative damage caused by the megadose of acetaminophen in rats. That's the protection of the hepatocytes by various doses extracts from acetaminophen-induced oxidative stress could involve their antioxidant mechanism. It was suggested that all doses *F. platyphylla* contain high antioxidant properties, which serve as an extracellular neutralizer of free radicals (Anderson and Theron, 1990). In agreement with reported literature, this study demonstrates low levels of serum concentrations of MDA in all rats may indicate extract's potencies in hepatoprotection against cardiovascular disorders.

Subsequently, the results of lipid profiles in rats treated with the megadose of acetaminophen and various doses of *F. platyphylla* extracts are presented in Table 4. The significant elevation of lipid indices (TC, TG, LDL, VLDL, AI, and CRI) and lower levels of HDL and CPI were detected in rats treated with the megadose of acetaminophen alone compared to healthy control rats. These are all evidence of hypercholesterolemia and atherosclerosis that could be attributed to oxidative stress production due to an overdose of acetaminophen. Oboh (2006) has demonstrated that an elevation in the serum cholesterol and LDL levels is attributed to vesicular disorders (hypercholesterolemia and atherosclerosis). This finding is in line with the report of Ravikumar *et al.*, (2010) that elevated total cholesterol levels was noted in rats intoxicated with CCl_4 . This may prevent the production of bile acid and could result in an increased level of cholesterol. High levels of LDL and lower levels of HDL may risk the formation of atherosclerotic plaques (Adaramoye and Akanni, 2014; Anoja *et al.*, 2018). It is also established by epidemiological and clinical studies that high levels of HDL may be associated with a high risk of vascular disorders (Tan, 2016; Anoja *et al.*, 2018;

Yakubu *et al.*, 2013). Contrary, coadministration of various doses of *F. platyphylla* and acetaminophen mega dose yield a significant decrease ($P > 0.05$) in serum TC, TG, LDL, VLDL, AI, and CRI and elevated levels of HDL and CPI were detected in rats compared to acetaminophen-induced rats (Table 4). These are indications of all doses of extracts ability to neutralize free radicals generated by excessive intake of acetaminophen and inhibition of bile acid production. This could be due to rate-limiting enzyme HMG-CoA reductase of cholesterol biosynthesis inhibition and activation of lipolysis by reducing the activity of hormone-sensitive lipase, respectively. This is in line with the reports of Yokozawa *et al.* (2006) and Anoja *et al.* (2018) that medicinal plant extracts exhibited protective effects against hypercholesterolemia, atherosclerosis, and hypertriglyceridemia by counteracting LDL oxidation, leading to inhibition of cholesterol transport pathway by preventing the formation of modified LDL oxidative particle. Low levels of calculated indices like CRI and AI in rats may signify the high protective ability of extracts against hyperlipidemia. In contrast, increased levels of CPI in terms of HDL/LDL ratio in all rats may further strengthen the potency of the plant extracts against atherogenicity.

Conclusion

It can be concluded from the present finding that all various doses of *F. platyphylla* extract experimented could be efficiently used to prevent liver, cardiovascular, erythrocyte and platelet damages caused by high doses of acetaminophen orally administered after successful clinical trials. Besides, the excessive intake of acetaminophen should be discouraged in homes because of its destructive effects on the liver. *F. platyphylla* extract consumption should be encouraged in juices as it can be used as a functional drink to prevent liver damage due to its antioxidant properties, and as such, *F. platyphylla* extract could be recommended for a clinical trial. The findings of this research suggest that the various doses of bark extract of *F. platyphylla* may be toxic-free and useful in

the management and treatment of free radical related diseases like oxidative stress.

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