

# The Journal of Phytopharmacology

(Pharmacognosy and phytomedicine Research)

## Research Article

ISSN 2320-480X

JPHYTO 2017; 6(2): 73-77

Received: 25-03-2017

Accepted: 22-05-2017

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## Toxicity evaluation and protective effect of *Rhus longipes* Engl. leaf extract in paracetamol induced oxidative stress in wister rats

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### ABSTRACT

**Aim:** Acute toxicity and protective effect of ethanol leaf extract of *Rhus longipes* Engl. against Paracetamol induced oxidative stress was investigated. The LD<sub>50</sub> of the leaf extract was determined using up and down technique and the effect of 1/10th and 1/20th/ LD<sub>50</sub> of the extract on antioxidants enzymes and non-enzymes were assessed in the serum and isolated liver of normal and Paracetamol intoxicated rats. Data obtained were analyzed by one-way analysis of variance (ANOVA) and Dunnett's t-test was used as the test of significance. Values were considered significant at P value < 0.05. The results obtained indicated that LD<sub>50</sub> of *Rhus longipes* Engl. leaf extract is greater than 5000 mg/kg/body weight. A significant (p<0.05) increase was observed in the level of hepatic (H) TBARs (81.97%), Catalase (38.42%) and serum (S) TBARs (164.44%) and catalase (64.72%) respectively but, a significant (P<0.05) decrease in hepatic activities of SOD, GPX, GR, vitamin C and E in paracetamol treated groups when compared with the serum and normal control group respectively. The extracts (250 and 500 mg/kg/body/weight) and the standard silymarin significantly (p<0.05) restored the derange antioxidants parameters to near normal in dose dependent manners. The activities of the extract at the highest concentration (500 mg/kg/b.wt) compared favourably with the standard drug. The results suggested that the leaf extract of *Rhus longipes* Engl. contain bioactive compounds which could protect against toxicity induced oxidative stress. The results of this study can be used as a basis for further investigations in the search for the bioactive principle.

**Keywords:** Oxidative stress, Acute toxicity, Paracetamol, Antioxidant enzymes.

### INTRODUCTION

The Imbalance in reactive oxygen species (ROS) (superoxide radicals, hydroxyl radicals, singlet oxygen and hydrogen peroxide) generation and the antioxidant defence systems have been reported to play critical role in the aetiology, pathogenesis and progression of most human diseases [1, 2]. Although, ROS often generated as by-products of biological reactions, drug induced toxicity and degenerative diseases or obtained from external sources, normally play positive role in energy production, phagocytosis, regulation of cell growth and intercellular signalling or synthesis of biologically important compounds [3]. However, their overproduction coupled with decrease antioxidant level may lead to serious health issues if uncontrolled. The delirious effect of ROS may be due to their attack on lipids cell membranes [4, 5] leading to lipid peroxidation and decrease membrane fluidity. It may also cause DNA mutation leading to cancer [6]. It is logical to hypothesis that increase antioxidant status may be protecting against free radical induced toxicity.

Recent global interest in non synthetic and natural drugs has set the search for medicinal plants as potential source of antioxidants. According to Arham [7], medicinal plants are rich sources of antioxidants, anti-inflammatory and they may also serves as food.

*Rhus longipes* or *Searsia longipes* (Engl.) is one of the plants commonly used in the treatment of asthma and malaria infection in Ogbomoso, Southwest, Nigeria and malaria infection. It belongs to the family of Anacardiaceae. *Rhus longipes* is a bush or small tree with pale green leaves; whitish or greenish flowers and dull red fruits that grow up to 12 metres tall. The plant is found in the Savannah, thickets, woodlands of various types and forests. Various parts of this plant are employed in the management human diseases for example the roots extract is use as remedy for infertility in women and to dilate birth canal [8, 9]. A decoction of the root is drunk as a treatment for malaria [10] and for the treatment of cancer [11]. When the root combined with the leaf sap is used as a laxative and abortifacient [12]. Although, other genus of

*Rhus* has been reported demonstrate significant pharmacological activities. Aliakbarlu J *et al* and Kossah R *et al* reported the antibacterial, anti-fungal and antioxidant effect of *Rhus coriaria* respectively [13, 14]. Anti-inflammatory properties and DNA protective effect of the plants was also reported by [15, 16]. To the best of our knowledge, information on the biological and pharmacological activities of *Rhus longipes* is scanty in the literature. The present study was therefore design to evaluate the *in vivo* antioxidant potential of ethanol leave extract of *Rhus longipes* in Paracetamol intoxicated rats.

## MATERIALS AND METHODS

### Plant Collection, Authentication and Extraction

Fresh leaves of *Rhus longipes* were collected from district Katangura Area of Ogbomoso North Local Government, Ogbomoso, Oyo state, Nigeria, in the month of May, 2014. The plant samples were identified and authenticated by a taxonomist, Professor A.T.J Ogunkunle of Department of Pure and Applied Biology, Ladoko Akintola University of Technology, Ogbomoso, Oyo State, Nigeria and was assigned a voucher number SIN052014 after which a voucher specimen was prepared and deposited at the University Herbarium.

### Plant extraction

The plant sample were washed, chopped into small pieces, shade dried at room temperature and powdered mechanically (Electric blender, S-748, SAISHO). Hundred (100 g) grams of the powdered plant material was defatted using 400 ml of petroleum ether in Soxhlet apparatus and extracted with 500 ml acetone for 72 hours. The acetone extract was filtered with Whatman No. 1 filter paper and the resulting filtrate was concentrated with a rotary evaporator (40°C). The product formed was lyophilized to give 12.0 g of the residue, corresponding to a yield of 2.4%. This was then stored in a desiccator for further use.

### Animals

Male albino Wistar rats each weighing 140-190 g was procured from the central animal house, Ladoko Akintola University of Technology Ogbomoso, Oyo State, Nigeria. The animals were fed with commercial pellets and water *ad libitum*, and were maintained on a 12 hour light / dark cycle in a temperature regulated room (20-22°C) during the experiment. The experiment was conducted in compliance with the rules and regulations outlined in NIH Guide for the care and use of laboratory animals; NIH Publication revised (1985) NIPRD Standard Operation Procedures (SOPs).

### Acute toxicity test

Acute toxicity study was carried out according to Miller and Tainter [17] methods in albino Wister rats of either sex (150-190 g). The LD<sub>50</sub> of the acetone extract of *Rhus longipes* when given orally and tested in rats were found to be non-toxic up to the dose of 5.0 g/kg body weight. Based on result of LD<sub>50</sub>, 1/10<sup>th</sup> and 1/20<sup>th</sup> of the LD<sub>50</sub> were taken as therapeutic doses [18].

### Experimental Design

Rats were divided randomly into five groups of six animals each and treated for one week (14 days) as follows.

**Group-I** Animals served as normal control, treated with vehicle (distilled water) 1 ml/kg once daily for 14 days orally.

**Group-II** Animals served as toxic control, received 1ml vehicle for 14 days and on the 13<sup>th</sup> day were given Paracetamol (2 g/kg, b.wt) orally.

**Group III** Animals Received acetone extract of *Rhus longipes* (250 mg/kg b.wt), orally, once daily for 14 days. A single dose of Paracetamol 2 g/kg body weight was administered orally on 13<sup>th</sup> day.

**Group-IV** Received acetone extract of *Rhus longipes* (500 mg/kg b.wt) orally, once daily for 14 days. A single dose of Paracetamol 2g/kg b.wt was administered orally on 13<sup>th</sup> day.

**Group-V** Received *Silymarin* (25 mg/kg b.wt) orally, once daily for 14 days and a single dose of Paracetamol 2g/kg/b.wt was administered orally on 13<sup>th</sup> day.

### Preparation of sample

All rats were killed 12 h after administration of Paracetamol under mild ether anaesthesia. Blood were collected, serum separated immediately and stored in the refrigerator. All serum samples were used within 12 h. The livers were rapidly removed. 500 mg of each liver was weighed and homo-genized, using glass homogenizer with ice-cooled saline to prepare 25% w/v homogenate. The homogenate was divided into two aliquots. The first one was deproteinized with ice-cooled 12% tri-chloroacetic acid and the obtained supernatant, after centrifugation at 1000 × g was used for the estimation of reduced glutathione (GSH) content. The second aliquot was centrifuged at 1000 × g and the resultant supernatant was used for estimation of glutathione peroxidase (GPx), super oxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione reductase (GR) activities and level of malondialdehyde (MDA).

### Estimation of Reduced Glutathione

Reduced glutathione (GSH) in the liver was estimated according to the method of Ellman [19]. Sample (0.75ml) of homogenate was precipitated with 0.75ml of 4% sulphosalicylic acid and centrifuged at 1200 g for 15 min at 4°C. The assay mixture contained 0.5ml of supernatant and 4.5ml of 0.01M, DTNB. (5-5'-dithiobis (2- nitro benzoic acid)) in 0.1M, phosphate buffer (pH 8.0). The yellow colour developed was read immediately at 412 nm. The results were expressed as micromole of GSH per milligram of proteins.

### Catalase (CAT)

Catalase activity was assessed by the method of Luck [20], where the breakdown of H<sub>2</sub>O<sub>2</sub> was measured at 240nm. Briefly the assay mixture consisted of 3ml of H<sub>2</sub>O<sub>2</sub> phosphate buffer (0.0125M; H<sub>2</sub>O<sub>2</sub>) and 0.05ml of supernatant of liver homogenate and the change in the absorbance was measured at 240nm. The enzyme activity was calculated using the milli-molar extension coefficient of H<sub>2</sub>O<sub>2</sub> (0.07). The results were expressed as micromole of H<sub>2</sub>O<sub>2</sub> decomposed per min per milligram of protein.

### Lipid peroxidation assay (LPO)

Malondialdehyde (MDA), a secondary product of lipid peroxidation reacts with thiobarbituric acid at pH 3.5. The red pigment produced was extracted in n-butanol-pyridine mixture and estimated by measuring the absorbance at 532nm [21].

*Superoxide dismutase activity (SOD)*

Superoxide dismutase activity was determined according to the method of Kono [22]. Briefly, the reduction of nitro blue tetrazolium chloride (NBT) was inhibited by superoxide dismutase and measured at 560 nm Spectrophotometric ally. The reaction was initiated by addition of hydroxylamine hydrochloride to the reaction mixture containing NBT and post nuclear fraction of liver homogenate. The results were expressed as units per milligram of protein with one unit of enzyme defined as the amount of SOD required to inhibit the rate of reaction by 50%.

**RESULTS**

**LD<sub>50</sub> Determination**

The results of acute toxicity study revealed that LD<sub>50</sub> values of acetone extract of *Rhus longipes* greater than 5000 mg/kg. The treatment of rat with extract of *Rhus longipes* did not change any autonomic or behavioural response in rats and no mortality was found at the doses of 5000 mg/kg.

**In-vivo antioxidant activity**

The data represented in Table 1 revealed that Paracetamol at dose 2 g/kg b.wt significantly (p<0.05) increased hepatic catalase (CAT) activity by 38.52% and MDA level by 81.97 % with concomitant significant (p<0.05) decrease (43.83%) in glutathione peroxidase (GPX), (58.41 %) superoxide dismutase(SOD), (44.49 %)

glutathione reductase (GR) enzymatic activity and (61.13 %) glutathione (GSH) level when compared to control. Co-administration of the extract at 250 and 500 mg/kg.bwt significantly decreased level of MDA and increased hepatic GSH content and antioxidant enzymatic activities of GPX, CAT, SOD and GR in dose dependent manner when compared to the Paracetamol control. The activities of the extract at the highest dose of 500 mg/kg.bwt compared favourably with the activity of the standard drug.

The results obtained for the effects of ethanol extract of *Rhus longipes* on serum levels of products of lipid peroxidation (malondialdehyde) and activity of antioxidant enzyme (SOD, CAT, GPX, GR) and non-enzymes (GSH, Vitamin E and C) of rats intoxicated with Paracetamol are presented in Table 2 and Fig 1. Treatment of experimental animals with Paracetamol (2 g/kg/b.wt) caused a significant (p<0.05) increase in serum level of malondialdehyde (168.44%) and catalase (64.72%) activity (Table 2). A significant (P<0.05) depletion of serum activities of SOD (60.38%), GPX (59.47%), GSH (56.74%) (Table 2), reduced ascorbic acid (75.05%), α-tocopherol (42.49%) and GR (64.68%) (Fig 1) was obtained in Paracetamol treated rats compared with normal rats. Co-administration of extract of *Rhus longipes* (250 and 500 mg/kg body weight) significantly inhibited the elevated serum levels of malondialdehyde and catalase activity and also restored the activities of SOD, GPX, CAT, GSH (Table 2) and serum ascorbic acid and vitamin E to near normal in dose dependent manner (fig 3). The activity of the extract was also comparable to the standard drug at the highest concentration.

**Table 1:** Effect of acetone extract of *Rhus longipes* on SOD, GPx, CAT, GR and GSH in liver homogenate of Paracetamol treated rats

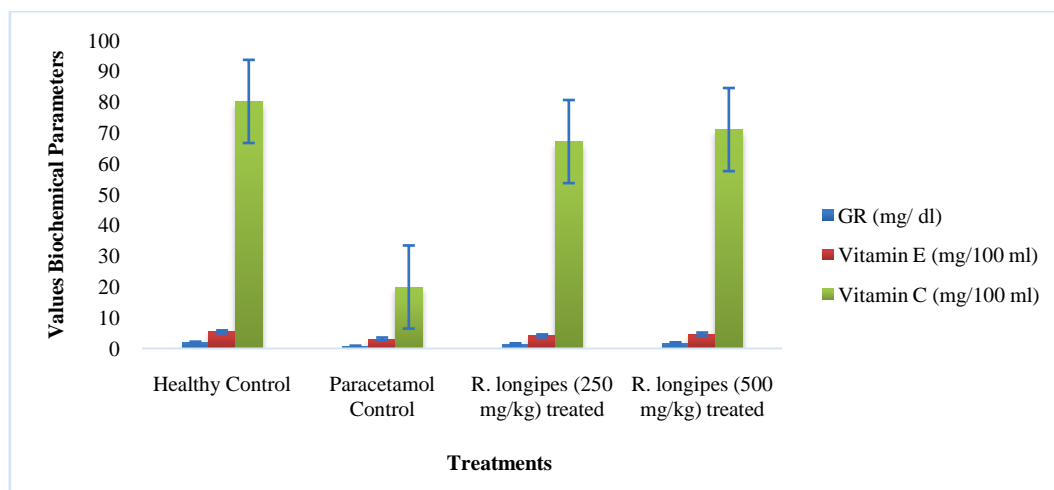
Experimental Groups	GPx U/mg/Protein	CAT (µm/min/mg protein)	SOD (u/mg protein)	GR (mg/ dl)	MDA (moles/ml)	GSH (µmole/g tissue)
Healthy Control	12.32 ± 1.13	187.20 ± 2.4	8.03 ± 0.13	141.07 ± 1.23	160.14 ± 2.02	39.13 ± 0.23
Paracetamol Control	6.92 ± 2.15*	259.30 ± 1.17*	3.34 ± 0.11*	78.21 ± 1.35*	292.09 ± 2.02*	15.21 ± 1.20*
<i>R. longipes</i> (250 mg/kg) treated	8.92 ± 2.01*	126.20 ± 3.16*	5.65 ± 0.22*	109.28 ± 3.15*	182.15 ± 2.10	25.12 ± 0.18
<i>R. longipes</i> (500 mg/kg) treated	9.79 ± 0.23*	145.12 ± 3.20*	6.79 ± 0.33*	110.32 ± 2.02*	170.25 ± 0.11	31.20 ± 0.15
Silymarin Treated	9.16 ± 1.25*	151.10 ± 2.50*	6.60 ± 0.10*	122.18 ± 1.32	169.11 ± 1.16	34.21 ± 0.23

Values are mean ± SEM, n=6 animals in each group. \*p<0.05, when compared to Paracetamol control

**Table 2:** Effect of ethanol leave extract of *Rhus longipes* on serum antioxidant enzyme levels in rat subjected to Paracetamol induced toxicity

Experimental Groups	GPx U/mg/Protein	CAT (n moles of glutathione oxidized/min/mg protein) (mg/ dl)	SOD (Units/mg protein)	MDA (moles/ml)	GSH (µmole/g tissue)
Healthy Control	11.25 ± 0.55	18.34 ± 2.48	10.02 ± 0.29	8.24 ± 1.12	35.60 ± 2.21
Paracetamol Control	4.56 ± 0.18	30.21 ± 1.59	3.97 ± 0.47	22.12 ± 1.67	15.40 ± 1.23
<i>R. longipes</i> (250 mg/kg) treated	6.78 ± 0.24	24.30 ± 1.22	6.34 ± 0.32	15.37 ± 1.21	25.51 ± 0.15
<i>R. longipes</i> (500 mg/kg) treated	9.37 ± 0.45	20.14 ± 0.34	8.34 ± 1.31	10.21 ± 0.36	30.41 ± 0.23
Silymarin Treated	10.21 ± 0.34	19.23 ± 1.42	9.32 ± 0.33	9.41 ± 2.01	31.22 ± 1.22

Values are mean ± SD, n=6 animals in each group. \*p<0.05, when compared to Paracetamol control



**Figure 1:** Effect of ethanol extract of *Rhus longipes* on serum Vitamin C, E and glutathione in paracetamol treated rats

## DISCUSSION

Although, the use of plants to treat human diseases is universal, common, and acceptable practice, most of the herbal preparations do not have drug regulatory approval to demonstrate their safety and efficacy [23]. It is therefore necessary to establish the safety level of some of these plant through toxicological assessments. The LD<sub>50</sub> of ethanol leaf extract of *R. longipes* was found to be greater than 5000 mg/kg; the plant may therefore be thought to be nontoxic as suggested by Lorke [24]. However, additional tests such as sub-chronic and chronic toxicity may be required to guarantee the complete safety of its use.

Endogenous antioxidant defense system consisting of antioxidant enzymes and numerous antioxidant compounds which protects functional and structural molecules against ROS, singlet oxygen, NO, superoxide anion, hydrogen peroxide, hydroxyl radicals, alkoxyl radicals, peroxy radicals, and lipid peroxides-mediated cytotoxicity and tissue damage [25]. Paracetamol, a well known antipyretic agent has been reported to cause oxidative stress when consumed at high dosage [26]. Normal metabolism of Paracetamol usually lead to formation of a highly and very reactive toxic metabolite known as N-acetyl-p-benzoquinoneimine (NAPQI) [27]. NAPQI is detoxified through a well-organized antioxidant enzymes system. The failure of this system lead to accumulation of the free radicals in organs or tissues causing oxidative damage to the membranes and eventually leading to chronic tissue damage [28]. NAPQI has been reported to cause increase production of superoxide anion, hydroxyl radical and hydrogen peroxide, nitric oxide and peroxy-nitrite [29]. The significant decrease in the level of hepatic and serum first line antioxidant enzymes system (Superoxide (SOD), reduced glutathione (GSH), glutathione peroxidase (GPx), observed in the Paracetamol control group in this study (Table 1) is consistent with previous report [30, 31]. GSH is primarily involved with the conjugation of NAPQI to form mercapturic acid [32]. However, excessive formation of NAPQI, increased degradation or decreased synthesis of glutathione as a result of NAPQI induced oxidative damage in the hepatocellular membrane may lead to GSH depletion and this may account for the observed low level of GSH observed in the serum and liver of Paracetamol untreated group of rats in this study (Table 1 and 2). The elevated level of hepatic MDA (81.97 %) and serum (168.44%) MDA in this study, confirm the induction of oxidative stress (Table 1 and 2). This was also reflected in the declined activities of serum glutathione reductase (GR) (Fig 1) which catalyses the NADPH-dependent

regeneration of GSH from the oxidized form (GSSG) and serum and hepatic GPx which offers protection to the cellular and subcellular membranes from the oxidative damage by eliminating hydrogen peroxide and lipid peroxide. The decreased activity of superoxide dismutase (SOD) in this study also support the mechanism of NAPQI provoke oxidative stress. The primary function of SOD is to scavenge O<sub>2</sub> radicals (to molecular O<sub>2</sub> and H<sub>2</sub>O<sub>2</sub>) generated in various physiological processes, thus preventing the oxidation of biological molecules, either by the radicals themselves, or by their derivatives [33]. The observed serum and hepatic decreased in the activity of SOD in the present study may be due to inactivation of the enzymes by increase generation of reactive oxygen species. Therefore, the significant percentage decrease in activities of CAT, SOD, GPx, GSH and elevated level of MDA in both serum and liver of Paracetamol control rats in this study agreed with the previous report of Abraham [34], Lee *et al.* [35] and Taniguchi *et al.* [36] on Paracetamol induced toxicity. The dose dependent improvement in the activities of the antioxidant enzymes and GSH enzymes in the Paracetamol and extract (*R. longipes*) treated rats may be due to the presence of bioactive compounds which are capable of inducing antioxidant enzymes synthesis or hemoxygenase-1, an enzyme which provide cyto-protection against oxidative stress in various experimental model [37]. Although, the present study does not evaluate the phytochemical constituents of *Rhus longipes*, literature reports have shown that other species such as *Rhus coriaria L.* is rich in strong antioxidants called tannins [38]. Glutathione, Vitamin C and E are second line of defence; they scavenge singlet oxygen, peroxy and hydroxyl radicals. Glutathione, one of the most abundant non-protein thiol in mammalian cells provide effective protection for the tissues and organs by acting as reducing agent, free-radical scavenger, xenobiotic detoxification [31, 39, 40] via a self-regulating interplay between vitamin E and C after oxidative challenge, thus providing cells with adequate protection [40]. Vitamin E protects the lipid membrane against free radicals and become oxidized but continuously recycles by a reductase with cytosolic thiol glutathione as cofactors and reduction of oxidized glutathione by dihydrolipoic acid ensure the regeneration of vitamin E to a level high enough to protect the bio-membrane against lipid peroxidation [41]. Considering the high level of MDA observed in the Paracetamol treated group, the reduced level of vitamin E, C and glutathione (Fig 1) observed is in line with previous report. The dose dependent restoration of vitamin E, C and glutathione (GR) to near normal in the extract treated group implies that the leaves extract *Rhus longipes* may be rich anti-oxidant compounds.

## CONCLUSION

The study indicated the restoration of antioxidant systems in the experimental models through the reduction of lipid peroxidation and increasing the serum and tissue antioxidant levels. The study for the first time proves that leave extract of *Rhus longipes* possess antioxidant potentials and can protect against Paracetamol induced toxicity.

## Acknowledgments

The authors express appreciation to the technologist in charge of Biochemistry laboratory, of Department of Biochemistry, Ladoko Akintola University of Technology, Ogbomoso, Oyo State. Nigeria for their technical assistance.

## Conflict of interest

The authors declare no conflict of interest.

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## HOW TO CITE THIS ARTICLE

Olorunnisola OS, Adetutu A, Owoade AO, Adesina BT, Adegbola P. Toxicity evaluation and protective effect of *Rhus longipes* Engl. leaf extract in paracetamol induced oxidative stress in wister rats. *J Phytopharmacol* 2017;6(2):73-77.