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EFFECT OF METHANOL LEAF EXTRACT OF *Chanca piedra* (*Phyllanthus niruri* Linn.) ON CARBON TETRACHLORIDE-INDUCED HEPATOTOXICITY IN WISTAR STRAIN RATS

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ABSTRACT

This research aims to investigate the effect of methanol leaves extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* on CCl_4-induced liver damage in Wistar strain rats. The sample was collected from Maiduguri, Borno State, Nigeria. Phytochemical analysis, acute toxicity studies and evaluation of the liver marker enzymes were all conducted on the extract using standard laboratory techniques. The quantitative phytochemical analysis showed that the extract contained alkaloids, tannins, flavanoids, cyanogenic glycosides and phenols at 13.60±0.06 (%), 1917.3±23.36 mg/100 g, 0.5400±0.00 mg quo/g, 3242.0±0.58 mg/100 g and 1.520±0.06 mgGAE/ml, respectively. The acute toxicity study showed that no mortality was recorded at various doses of the methanol leaf extract up to a maximum dose of 5000 mg/kg body weight of rats. A significant increase in aspartate aminotransferase (AST), 83.17±3.87 IU/L, alanine aminotransferase (ALT), 67.67±9.15 IU/L and alkaline phosphatase (ALP), 79.83±9.17 IU/L activities were observed upon treatment with carbon tetrachloride (CCl_4) compared to rats in normal control group, which indicates liver injury. However, treatment with various doses of 100, 200 and 400 mg/kg body weight of the methanol leaf extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* caused a significant decreased in aspartate transaminase (AST) 33.17±5.36 IU/L, alanine transaminase (ALT) 42.17±3.81 IU/L and alkaline phosphatase (ALP) activity 69.30±7.60 IU/L, respectively as compared to rats in positive control groups (34.33±10.12, 39.00±0.00, 64.87±6.41 IU/L, respectively). Furthermore, a significant difference ($p<0.05$) existed among the groups. As a result, the methanol leaves extract of *Phyllanthus niruri* Linn. demonstrated ameliorating effect of liver damage caused by carbon tetrachloride (CCl_4).

Keywords: *Phyllanthus niruri* Linn. (*Chanca piedra)*, liver injury, CCl_4, acute toxicity.

INTRODUCTION

Phyllanthus niruri Linn. *(*also known as *Chanca piedra,* gale of the wind, stonebreaker or seed-under-leaf in English and Geron tsuntsaye in Hausa*)* is a plant possessing several pharmacological properties. It grows 50–70 cm tall and bears ascending herbaceous branches. The bark is smooth and light green. It bears numerous pale green flowers which are often flushed with red. The fruits are tiny, smooth capsules containing seeds (Patel *et al.,* 2011). *Phyllanthus niruri* Linn. *(Chanca piedra)* possesses a wide range of therapeutic characteristics. It is well-known in conventional healthcare systems. It is taken for diuretic, hyperglycemia, and in hypertensive situations in addition to treating kidney stones, gallbladder stones, liver-related ailments such as liver cancer and jaundice (Bagalkotkar *et al.,* 2006). Due to their natural origin and apparent safety, herbal remedies in Ayurveda have been suggested for the treatment of liver problems in the absence of a dependable liver protective agent in modern medicine (Bapat *et al.,* 2013). Cellular macromolecules such as nucleic acids, proteins, and lipids can chemically react with reactive species created in the cell during normal biological metabolism, resulting to their oxidative modification, which can change their composition and potentially harm their cellular functions. This study focused on the hepatoprotective effect of the methanol leaves extract of *Phyllanthus niruri.*

MATERIALS AND METHODS

Reagents and Chemicals

The reagents and chemicals used in this research are of analytical grade and were obtained from British Drugs Houses (BDH) Chemicals Ltd. Poole, England.

Plant Collection and Identification

The sample (*Phyllanthus niruri* Linn.*)* was obtained from Maiduguri, Borno State, Nigeria, in December, 2021. The plant sample was identified by a Taxonomist at the Department of Biological Sciences and voucher sample (Vet212B2) was deposited at the Veterinary Pharmacology Laboratory herbarium, University of Maiduguri, Nigeria.

Experimental Animals

Healthy Wistar rats of both sexes weighing between 100 - 250 g were obtained from the Animal House of Department of Biochemistry, University of Maiduguri, Maiduguri, Borno State, Nigeria. The rats were handled in accordance with the guidelines for the care and use of laboratory

animals (United States of America National Research Council, (US-NRC) (2003). Ethical clearance was obtained from the Animal Use and Ethics Committee (AUEC), Faculty of Veterinary Medicine, University of Maiduguri with approval number REF/FP/092020/PGVP/06.

Preparation of Plant Material

After collection, the leaves of *Phyllanthus niruri* Linn. *(Chanca piedra)* were thoroughly washed and shade dried. The leaves were ground into a fine powder using pestle and mortar. Then sieved to remove debris. Powdered form of the sample was stored at low temperature prior to extraction.

Methanol Extract Preparation

Five hundred grams (500 g) powder of *Phyllanthus niruri* Linn. *(Chanca piedra)* leaves was extracted with one liter of 70 % methanol using cold maceration method, the product was concentrated to dryness at low temperature and then stored in a refrigerator until used.

Quantitative Phytochemical Analysis of Methanol Leaves Extract of *Phyllanthus niruri* Linn. *(Chanca piedra)*

Total alkaloids content was determined according to the method described by Harborne (1973). Total flavonoids content was determined according to the methods described by Ejikeme *et al*., (2014) and Boham and Kocipai (1994). Total tannins and cyanogenic glycosides content were assayed according to the method described by Amadi *et al.,* (2004) and Ejikeme *et al*., (2014). Total phenolic content was assessed using the aluminum chloride method (Chew *et al.,* 2012).

Acute Toxicity (LD_{50}) Study

The LD_{50} *Phyllanthus niruri* Linn. *(Chanca piedra)* was determined as described by Lorke, (1983). The methanol leaf extract was administered orally. Then the LD_{50} was estimated by the following formula:

$LD_{50} = \sqrt{D0 * D100}$

Where D0 = Highest dose that gave no mortality

D100 = Lowest dose that produced mortality

Experimental Design for the Determination of Hepatoprotective Effect of Methanol Leaves Extract of *Phyllanthus niruri* Linn. *(Chanca piedra)*

A total of 36 Wistar rats were randomly divided into six (6) different groups of six (6) rats each and the following treatment was done once per day for fourteen (14) consecutive days.

Group I: served as normal control and were given feeds and water *ad libitum.*

Group II: served as negative control and received on the 14th day CCl_4 (1.5 ml/kg, i.p.) in 1:1 dilution with olive oil.

Group III: served as positive control and were administered with silymarin (25 mg/kg body weight) for 14 days orally and on 14th day CCl_4 (1.5 ml/kg, i.p.) in 1:1 dilution with olive oil.

Group IV: served as treatment group and were administered methanol leaves extract (100 mg/kg body weight) of *Phyllanthus niruri* Linn. *(Chanca piedra)* for 14 days orally and on 14th day CCl_4 (1.5 ml/kg, i.p.) in 1:1 dilution with olive oil.

Group V: served as treatment group and were administered methanol leaves extract (200 mg/kg body weight) of *Phyllanthus niruri* Linn. *(Chanca piedra)* for 14 days orally and on 14th day CCl_4 (1.5 ml/kg, i.p.) in 1:1 dilution with olive oil.

Group VI served as treatment group and were administered methanol leaves extract (400 mg/kg body weight) of *Phyllanthus niruri* Linn. *(Chanca piedra)* for 14 days orally and on 14th day CCl_4 (1.5 ml/kg, i.p.) in 1:1 dilution with olive oil (Kandimalla *et al.,* 2016).

Serum Preparation

The blood sample was collected by cardiac puncture with a needle attached to 5 mL syringe and used for the assessment of some liver marker enzymes (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP). The serum was prepared using standard method. The blood samples was allowed to clot for thirty (30) minutes and then centrifuged at four thousand (4000) revolutions per minute (rpm) for 10 minutes and serum was harvested and kept at low temperature until used (Yesufu *et al.,* 2010).

Determination of some Serum Liver Marker Enzymes

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were assayed by the method of Reitman and Frankel (1957), whereas serum alkaline phosphatase (ALP) activity was determined by Phenolphthalein Monophosphate Method (Klein *et al.,* 1960).

Results

Quantitative Phytochemical Constituents of Methanol Leaves Extract of *Phyllanthus niruri* Linn. (*Chanca piedra)*

The result of quantitative phytochemical analysis of the *Phyllanthus niruri* Linn. (*Chanca piedra)* leaves extract as presented on Table 1, revealed that the concentrations of alkaloids, tannins, flavanoids, cyanogenic glycosides and phenol are 13.60±0.0600 (%), 1917.3±23.36, 0.5400±0.000 mg quo/g, 3242.0±0.58 mg/100g and 1.520±0.0600 mg/GAE, respectively.

Table 1. Quantitative Phytochemical Constituents of Methanol Leaves Extract of *Phyllanthus niruri* Linn. (*Chanca piedra)*

Constituents	Results
Alkaloids (%)	13.60±0.06
Tannins (mg/100g)	1917.3±23.36
Flavonoids (mg quo/g)	0.54±0.00
Cyanogenic glycosides (mg/100g)	3242.0±0.58
Phenols (mgGAE/ml)	1.52±0.06

Data are expressed as mean ± SEM, of three determinations.

Acute Toxicity (LD_{50}) of Methanol Leaves Extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* in Wistar Strain Rats

The phase I and phase II of the oral acute effect of the *Phyllanthus niruri* Linn. (*Chanca piedra)* is shown in Table 2. The results showed that no mortality at various doses of the methanol leaves extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* extract up to a maximum dose of 5000 mg/kg body weight of rats both in the phase I and phase II of the study using the method of Lorke (1983).

Table 2. Acute Toxicity (LD_{50}) of Methanol Leaves Extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* in Wistar Strain Rats

Experiment	Doses (mg/kg Body Weight)	Number of Experimental Rats	Number of Dead Rats after 24 and 72 Hours
Phase 1	10	3	0/3
	100	3	0/3
	1000	3	0/3
Control	0	3	0/3
Phase 2	1600	1	0/1
	2900	1	0/1
	5000	1	0/1

Key: 3=Number of Experimental Rats

1 = Number of Experimental Rats
0 = Mortality Recorded
MTD = Maximum Tolerated Dose

Effect of Methanol Leaves Extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* on some Liver Marker Enzymes in Wistar Strain Rats

The result for the effect of methanol leaves extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* on the liver marker enzymes is presented in Table 3. A significant increase in AST, ALT and ALP activities were observed as a result of carbon tetrachloride (CCl_4) administration. However, treatment with various doses of the methanol leaf extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* caused decreased liver enzymes in the treatment groups. Group treated with 100 mg/kg extract had AST activity of 33.17±5.36 IU/L as against 83.17±3.87 IU/L found in the negative control (CCl_4) group. Group treated with 200 mg/kg extract had AST activity of 55.67±4.06 IU/L as against 83.17±3.87 IU/L found in the negative control (CCl_4) group. Group treated with 400 mg/kg extract had AST activity of 50.00±1.90 IU/L as against 83.17±3.87 IU/L found in the negative control (CCl_4) group. The activity of AST in all the treatment groups was found to be significantly lower than the hepatotoxic (negative control) group. Furthermore, significant difference was observed between groups treated with 200, 400 mg/kg b.wt. and that treated with 100 mg/kg b.w.

Table 3: Effect of Methanol Leaves Extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* on some Liver Marker Enzymes in Wistar Strain Rats

Experimental Groups	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Normal control (Distilled water)	29.33±0.76^{a}	26.33±1.69^{a}	58.83±3.19^{a}
Negative control (CCl_4 (1.5 ml/kg)	83.17±3.87^{d}	67.67±9.15^{d}	79.83±9.17^{b}
Positive control (Sylimarin, (25 mg/kg body weight)	34.33±10.12^{b}	39.00±0.00^{c}	64.87±6.41^{b}
100 mg/kg extract + CCl_4	33.17±5.36^{b}	42.17±3.81^{c}	72.30±7.60^{b}
200 mg/kg extract + CCl_4	55.67±4.06^{c}	40.50±3.61^{c}	69.98±4.38^{b}
400 mg/kg extract + CCl_4	50.00±1.90^{c}	28.33±0.67^{b}	67.93±11.0^{b}

Data are expressed as mean ± SEM, n=3. Values with different superscripts vertically down the column are significantly different. ($P < 0.05$)
Key:
AST = Aspartate Aminotransferase
ALT = Alanine Aminotransferase
ALP = Alkaline Phosphatase
IU/L = International Unit per Liter

CCl_4 = Carbon Tetrachloride

DISCUSSION

Phytocompounds are known to perform distinct biological activities in plants, and may have different kind of biochemical and pharmacological activities in different species of animals. These biological activities include cell toxicity to cell protective effects (Trease and Evans, 2002). The quantitative phytochemical analysis of the methanol leaves extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* showed reasonable concentrations of alkaloids, tannins, flavanoids, andcyanogenic glycosides and phenols that are known to possess a variety of health benefits are high as reported by Hasler and Blumberg, (1999).

The protective effects of these phytochemicals have received more attention against free radical induced liver toxicities (Frei and Higdon, 2003). Flavonoids played an important role in the protection against oxidative stress, (Okada *et al.,* 2001) especially in the case of cancer (Babich *et al.,* 2005). Also known as natural antioxidants, phytocompounds strengthen the endogenous antioxidants defenses from reactive oxygen species (ROS) and restore the optimal balance by neutralizing reactive species (Al-Mamary *et al.,* 2002); (Fetouh and Azab, 2014).

The first step in identifying negative effects of drugs in 24 hours and within 14 days following administration of a single dosage is to perform an acute toxicity test (Rhiouani *et al.,* 2008; Bhardwaj and Gupta, 2012). To find the median lethal dose (LD_{50}) for a certain dangerous drug in testing animals, it is typically given orally (Gadanya *et al.,* 2011). The liver and kidneys are the main organs that are impacted by the metabolic reactions of toxicants (Dybing *et al.,* 2002), and they are helpful in anticipating the toxicity effects of phytotherapeutic items or medications (Bello *et al.,* 2016). Due to its prior exposure to foreign toxins absorbed in the intestine before reaching the blood circulation, the liver is the primary target for hazardous compounds (Samuel *et al.,* 2012; Rhiouani *et al.,* 2008).

The treatment of rats with methanol leaves extract of *Phyllanthus niruri* (10 mg/kg to 5000 mg/kg) did not have any negative effects. Physical characteristics including changes in fur, the mucous membranes of the eyes, behavioral patterns, or tremors did not differ between the treated groups and the control group. Throughout the treatment period, no fatalities or harmful effects were noticed in any of the treated groups.

Because the median lethal dose (LD_{50}) for *Phyllanthus niruri* is higher than 5000 mg/kg body weight (Table 2**)**, it could be possible to classify it as non-toxic. This corresponds to the finding of Samuel *et al.* (2012) which showed that the LD_{50} is greater than 5000mg/kg body weight.

Liver marker enzymes (aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) are good biomarkers used to evaluate the extent of damage to a specific tissue (Tu *et al.,* 2015). As shown in Table 3, a significant increase in aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) activities were observed upon treatment with of carbon tetrachloride (CCl_4) compared to normal control group which indicate liver injury. However, treatment with various doses (100, 200 and 400 mg/kg body weight) of the methanol leaves extract of *Phyllanthus niruri* Linn. (*Chanca piedra)* and standard drug (sylimarin) caused their decrease in the treatment and the positive control groups, respectively.\

Restoring the elevated liver marker enzymes levels (aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) to normal might be attributed to its anti-oxidative property (Harish and Shivanandappa, 2006) as well as the phytocomponents such as flavonoids, alkaloids and phenolic compounds present in the plant extract indicating the hepatoprotective effect of *Phyllanthus niruri* Linn. (*Chanca piedra)* extract against liver damage caused by carbon tetrachloride (CCl_4).
This agreed with the findings reported by Padma and Setty, (1999) which stated that the extract of the plant *Phyllanthus niruri* Linn. *(Chanca piedra)* exert a significant activity against carbon tetrachloride (CCl_4) induced mitochondrial dysfunction. Furthermore, the methanol leaves extract of *Phyllanthus niruri* Linn. *(Chanca piedra)* demonstrates hepatic protection against ethanol-induced liver damage, (Toyin *et al.,* 2008) alloxan (Raphael *et al.,* 2002) and cyclophosphamide-induced oxidative stress in Wistar strain rats (Kumar and Kuttan, 2005).

CONCLUSION

In conclusion, the methanol leaves extract of *Phyllanthus niruri* Linn. *(Chanca piedra)* have shown the potential to ameliorate carbon tetrachloride (CCl_4)-induced liver injury in Wistar strain rats.

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