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Phytochemical Screening, Acute (LD_{50}) and Sub-Chronic Toxicity Studies of Aqueous Stem Bark Extract of Cinnamomum Verum

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Abstract: Cinnamon has a long history both as a spice and as a medicine. This study was carried out to screen the phytochemicals of the extract as well as to evaluate the acute (LD_{50}) and sub-chronic toxicities of aqueous bark extract of *Cinnamomum verum* in rats. A total of twenty eight rats were used in this study, thirteen for acute toxicity test and fifteen for sub chronic toxicity. The acute toxicity study was done in two phases; in phase I, nine rats were divided into three groups of three rats each and were administered the aqueous bark extract of *Cinnamomum verum* at different doses of 10, 100 and 1000mg/kg body weight orally. The rats were observed for mortality and general behavior for 24hrs. In phase II, four rats were administered with aqueous bark extract of *Cinnamomum verum* at higher doses of 1500, 2500, 3500 and 5000mg/kg and were observed for mortality and other signs of toxicity for 24hrs. For the sub chronic toxicity experiment, fifteen rats were divided into five groups of three rats each. Group 1 was the control group, groups II to V were orally administered 50, 100, 150 and 200mg/kg of aqueous bark extract of *Cinnamomum verum* respectively for four weeks. The rats were sacrificed and blood samples collected for biochemical analysis of liver and kidney functions. The result of phytochemical screening revealed the presence of saponins, reducing sugars, flavonoids, steroids, resins and cardiac glycosides. Acute toxicity revealed that the extract was practically non-toxic with oral LD_{50} greater than 5000mg/kg body weight. The levels of ALP, ALT, AST and TP of the test groups decreased significantly ($p<0.05$) with respect to control group while serum TB, ALB increased with respect to control group. A significant decrease ($p<0.05$) in serum electrolytes, creatinine and urea and an increase in serum bicarbonate was observed in extract administered groups in a dose dependent pattern compared to normal control. In conclusion, these results showed that the extract is rich in phytochemicals and was found to be relatively safe at administered doses.

Keywords: *Cinnamomum verum*, toxicity, aqueous, stem bark, extract

INTRODUCTION

Plants, either as traditional preparations or pure active principles, have always been among the common sources of medicines [1]. Over 5000 plants are known to be used for medicinal purposes in Africa, but only a few have been studied [2]. A great number of Nigerian higher plants are traditionally noted for their medicinal properties, but regrettably only few have so far been studied for their active constituents. The use of herbal remedies can be attributed to their perceived efficacy and the fact that they are a cheap source of medicines [3].

There is an assumption that that the use of plants in traditional medical practice for treatment of various ailments is harmless and safe because they are derived from natural sources [4]. This assumption is based on the common belief that herbs are by nature safer and gentler than orthodox drugs and plant-based medicine have been used in the treatment of diseases over many centuries [5]. However, herbal preparations assumed to be safe may contain contaminants such as pathogenic microbes, heavy metals and aflatoxins due to the manner in which they are prepared [6]. Moreover, many studies have reported various toxic effects of herbal medicines, such as hepatotoxicity [7] and nephrotoxicity [8].

Cinnamomum verum, called "true cinnamon", Ceylon cinnamon or Sri Lanka cinnamon is a small evergreen tree belonging to the family Lauraceae, native to Sri Lanka. Among other species, its inner bark

is used to make cinnamon. *Cinnamomum verum* trees are 10–15 metres (32.8–49.2 feet) tall. The leaves are ovate-oblong in shape, 7–18 cm (2.75–7.1 inches) long. The flowers, which are arranged in panicles, have a greenish color, and have a distinct odor [9].

Cinnamon's unique healing abilities come from three basic types of components in the essential oils found in its bark. These oils contain active components called *cinnamaldehyde*, *cinnamyl acetate*, and *cinnamyl alcohol*, plus a wide range of other volatile substances [10]. *Cinnamomum verum* reported to possess Anti-Microbial Activity [11], hypoglycemic activity [12], Cinnamon's Scent Boosts Brain Function [13] and Antioxidant [14]. In addition to the active components in its essential oils and its nutrient composition, cinnamon has also been valued in energy-based medical systems, such as Traditional Chinese Medicine, for its warming qualities. In these traditions, cinnamon has been used to provide relief when faced with the onset of a cold or flu, especially when mixed in a tea with some fresh ginger [15].

Therefore, the current study was aimed at investigating the phytochemical composition, and determining the acute (LD_{50}) and sub-chronic toxicity of the aqueous stem bark extract of *Cinnamomum verum* in albino rats.

MATERIALS AND METHODS

Collection and preparation of plant material

Cinnamomum verum bark was bought from Kurmi market Kano. It was made into powder and 500 g was soaked in 5 litres of distilled water, and vigorously shaken, for 48 hours, at room temperature. The mixture was filtered with muslin cloth and later with Whatman Number 1 Filter Paper. The filtrate (extract) was concentrated to dryness in an oven at 45˚ C. Percentage yield was calculated, and the extract was stored in a plastic container until required. The dried extract was reconstituted in distilled water; the volume administered to each rat was calculated according to Muhammad *et al* [16].

Phytochemical screening

Phytochemical tests were carried out by using the standard methods of Harborne [17], Sofowora [18], Trease and Evans [19], Kokate [20], Rasal [21] and Savithramma *et al* [22].

Animals

Twenty eight *wistar* albino rats of both sexes, weighing 100-150 g, were obtained from Department of Physiology, Bayero University Kano, Nigeria. They were kept, at room temperature, in wire-mesh cages, to acclimatise for 1 week. They were fed with animal feeds (Vitalised Feeds, Jos, Nigeria), and tap water *ad libitum*.

Lethal mean dose (LD_{50}) determination

Twenty eight rats were used in this study, thirteen for acute toxicity test and fifteen for sub chronic toxicity. The acute toxicity study was done in two phases; in phase I, nine rats were divided into three groups of three rats each and were administered the aqueous bark extract of *Cinnamomum verum* at different doses of 10, 100 and 1000mg/kg body weight orally. The rats were observed for mortality and general behaviour for 24hrs. In phase II, four rats were administered with aqueous bark extract of *Cinnamomum verum* at higher doses of 1500, 2500, 3500 and 5000mg/kg and were observed for mortality and other signs of toxicity for 24hrs.

Sub-chronic toxicity studies

For the sub chronic toxicity experiment, fifteen rats were divided into five groups of three rats each. Group 1 was the control group, groups II to V were orally administered 50, 100, 150 and 200mg/kg of aqueous bark extract of *Cinnamomum verum*, respectively for four weeks. On the 29^{th} day, weight was taken, and the rats were humanely sacrificed. Blood samples were taken in plane containers, for biochemical analysis. Analysis was performed on sera obtained after centrifugation of the whole blood. Standardized diagnostic kits (Labkit®) (Randox) and Teco diagnostic kits were used for spectrophotometric determination of biochemical parameters.

STATISTICAL ANALYSIS

Results were expressed as mean ± standard error. The data collected were subjected to one-way Analysis of Variance (ANOVA) using Graphad Instat, Version 3.02, Benferoni, (San Diego, USA) [23].

RESULTS

Various phytochemical constituents from aqueous bark extract of *Cinnamomum verum* such as saponins, reducing sugars, alkaloids, tannins, flavonoids, steriods, coumarins, resin were detected as shown in table1. The Quantitative analysis showed that the extract has high concentration of saponins (1.998±0.04) followed by reducing sugars (1.099±0.01) then cardiac glycosides (0.646±0.06), tannins (0.200±0.03) and flavonoids (0.094±0.01).

Table-1: Phytochemical Screening of aqueous bark extract of Cinnamomum verum

Constituents	Inference	Content (g%)
Saponins	+	1.998± 0.04
Flavonoids	-	-
Flavonoids	+	0.094±0.01
Reducing Sugars	+	-
Resins	+	-
Coumarins	-	-
Tannins	+	0.200±0.03
Steroids	+	-

Key: (+) = Present (-) = Absent

Acute Toxicity Test

In the initial phase of the determination of acute toxicity, mortality and toxic symptoms were not observed when the aqueous bark extract of *Cinnamomum verum* was administered orally to the experimental rats (Table 2a). In the second phase, no mortality was observed although some rats exhibited symptoms of weakness (Table 2b).

Table−2a: Phase I LD_{50} (oral, rat) of the aqueous bark extract of *Cinnamomum verum*

Doses (mg/kg)	Mortality
10	0/3
100	0/3
1000	0/3

Table−2b: Phase II LD_{50} (oral, rat) of the aqueous bark extract of *Cinnamomum verum*

Doses (mg/kg) Mortality	
1500	0/1
2500	0/1
3500	0/1
5000	0/1

Sub chronic toxicity studies

Table 3 present liver function indices of rats administered with aqueous extract of *Cinnamomum verum.* The Mean serum Alkaline phosphatase (ALP), Alanine amino transferase (ALT), Aspartate amino transferase (AST) and Total protein (TP) activities of the rats administered with the aqueous bark extract of *Cinnamomum verum* were found to decrease significantly ($p<0.05$) (table 4), while serum Total Bilirubin and Albumin increased significantly ($p<0.05$) with respect to control group.

Table 3: Mean Serum Liver Enzymes, Bilirubin, Albumin and Total Proteins of rats administered with aqueous bark extract of *Cinnamomum verum* for 4 weeks.

Grouping/Dose	AST(U/L)	ALP(U/L)	ALT(U/L)	TB(U/L)	ALB(g/dl)	TP(g/dl)
GI(Normal)	88.50 ±1.23^{a}	90.46 ±6.13^{b,c}	25.91 ±0.70^{c,d}	15.70 ±1.05^{d}	2.89 ±0.07^{e,d}	5.49 ±0.14^{f}
GII (50mg)	87.47 ±1.27	89.93 ±5.22	21.43 ±0.07	18.27 ±0.53	3.67 ±0.29	4.40±1.04
GIII (100mg)	84.87 ±5.45	85.13 ±2.93	21.08 ±1.99	19.23 ±3.64	4.13 ±0.20	4.37 ±0.25
GIV (150mg)	84.53 ±5.37	83.57 ±4.13^{b}	17.23 ±0.45^{c}	19.76 ±0.31	4.63 ±0.60^{e}	4.03 ±0.17
GV (200mg)	67.8 ±3.37^{a}	71.23±2.05^{c}	15.83 ±1.11^{d}	20.77 ±0.69^{d}	4.53 ±0.76 ^{d}	3.37 ±0.41^{f}

Values are expressed as mean±SD, n=5. Values with similar superscript on the same column are significant ($p <0.05$). Key: AST= Aspartate amino Transferase, ALP= Alkaline phosphatase, ALT= Alanine amino Transferase, TB= Total Bilirubin, ALB= Albumin, TP= Total protein.

The mean serum levels of sodium (Na^{+}), potassium (K^{+}), chloride (Cl^{-}), Creatinine and Urea of the rats administered aqueous bark extract of *Cinnamomum verum* significantly decreased ($p<0.05$) when compared to the control group while bicarbonate ($HCO3^{-}$) increased significantly ($p <0.05$) (table 4).

Table−4: Mean Serum Electrolytes levels of rats administered with aqueous bark extract of *Cinnamomum verum* for 4 weeks

Groupings	Na^+(MEq/L)	Cl^-(MEq/L)	K^+(MEq/L)	Urea(mmol/L)	HCO_3^-(mmol/L)	Crea(mmol/L)
GI (Normal)	95.61±5.69[a,b]	80.34±3.84[a,b]	4.07±0.02[a,b]	8.73±0.49	22.90±1.85[a,b,c]	79.64±3.26[a,b]
GII (50mg)	94.67±4.78	78.67 ± 1.25	3.87 ±0.12	7.93±0.25	30.33±1.65	76.29±1.65
GIII(100mg)	93.33±3.52	75.33 ± 3.40	3.80 ±0.08	7.53±0.04	36.23±2.11[a]	75.73 ±2.51
GIV(150mg)	85.30±6.24[a]	74.33 ± 2.62[a]	2.87 ±0.87[a]	7.08±0.22	38.51±1.23[b]	73.06 ±2.67[a]
GV (200mg)	80.00±2.94[b]	71.00±2.16[b]	2.63±1.20[b]	7.07±0.16	38.51±1.23[b]	71.71±1.81[b]

Values are mean±SD, n=5. Values with similar superscript on the same column are significantly different ($p < 0.05$). Key: Na^+= Sodium, Cl^- = Chloride, K^+ = Potassium, $HCO3^-$ = Bicarbonate

DISCUSSION

Secondary metabolites are biosynthesized in plants for different purposes including growth regulation, inter and intra-specific interactions and defense against predators and infections [24]. Plants are recognized for their ability to produce a wealth of these secondary metabolites and mankind has been using many species for centuries to treat a variety of diseases [25]. Many of these natural products have been shown to demonstrate interesting biological and pharmacological activities and are used as chemotherapeutic agents or a starting point in the development of modern medicine. However, some plant extracts could be inherently dangerous, containing naturally occurring toxins, which may be cytotoxic or carcinogenic [26].

The acute toxicity test result of this study showed that the LD_{50} of the aqueous bark extract of *Cinnamomum verum* was greater than 5000mg/kg body weight. The fact that the experimental rats survived the acute toxicity testing up to a dose of 5000mg/kg showed that the aqueous bark extract of *Cinnamomum verum* is practically non-toxic [27] This is in accordance with a study by Shah *et al*. [28] who demonstrated that the ethanolic extract of *Cinnamomum zeynalicum bark* was non-toxic after acute toxicity tests. Rabiatu *et al*. [29] also reported that *Cinnamomum verum* possess low moderate toxicity, evidenced by high LD_{50} values with no lethality, thus the low toxicity of *Cinnamomum verum* offers a wide margin of safety for beneficial doses.

Biochemical parameters are useful in toxicity studies by providing information about *in vivo* effects of test substances [30]. Liver is considered the key organ in the metabolism, detoxification, and secretory functions in the body, and its disorders are numerous with no effective remedies. Liver plays a key role in many metabolic processes of not only itself but of other tissues as well. Severe hepatic injury, as a result of metabolism of some of the toxic phytochemicals found in medicinal plants and failure of the metabolic products to be eliminated by the liver [31], may be associated with marked distortion of its functions. Liver enzymes, aspartate and alanine aminotransferases (AST and ALT) are involved in amino acid metabolism. Large amounts of AST are present in the liver, kidney, cardiac muscle, and skeletal muscle. Serum ALT and AST are always found to increase in liver cell damage and the greater the degree of the liver damage the higher the activities of both enzymes [32]. The result of sub-chronic toxicity of the liver showed a significant decrease ($p<0.05$) in activities of AST, ALT ALP and Total protein as well as increase in serum Albumin and Total Bilirubin. This is in agreement with various studies which reported decreased activity of transaminases in liver of rats administered with aqueous bark extract of *cinnamomum verum* [33]

Kidney is the major excretory organ in the body, it function is affected by a number of factors, which may ultimately result in its failure [34]. Renal function indices such as urea, creatinine, electrolytes, and uric acid can be used to evaluate the functional capacity of the nephrons of study animals and are considered as good indicators of kidney function. Similarly, the serum concentrations of electrolytes, uric acid and creatinine could give an insight into the effect of plant extract on the tubular and or glomerular part of the kidney. The significant decrease in serum Na^+, K^+, Cl^-, creatinine and urea with significant increase in serum HCO_3^- indicates the beneficial effect of the extract on kidney which is in accordance with the work of Rabiatul *et al* [35].

CONCLUSION

According to the findings of this study, *Cinnamomum verum* aqueous stem bark extract is rich in phytochemicals that may be responsible for the reported pharmacological activities of this plant. It is also shown that aqueous bark extract of *Cinnamomum verum* is practically non-toxic, evidenced by high LD_{50} value with no lethality. It may be considered that the extract is safe at the tested sub-chronic doses, and well tolerated for the 28 days study period. Thus, have potential for safe use as herbal medicine.

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