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# Evaluation of hepatotoxicity effect of methanol leave extract of *Gongronema latifolium* in Albino rats

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## Abstract

*Gongronema latifolium* is highly medicinal in nature. The fundamental ingredients used for medicinal purposes are stored in the various parts of the plant such as the fruits, seeds, leaves, root and stem. This present study is aimed to evaluate the hepatotoxicity effect of methanolic leaf extract of *Gongronema latifolium* on albino rats. This study was divided into five groups normal control groups: received commercial rat feed and water, group 2: received 1000 mg/kg b.w. of leaf extract of *Gongronema latifolium*, group 3: received 500 mg/kg b.w of leaf extract of *G. latifolium*, group 4; received 250 mg/kg of leaf extract of *Gongronema latifolium*, and group 5: received 125mg/kg of leaf extract of *Gongronema latifolium.* The result shows a significant ($p<0.05$) increase in serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and conjugate bilirubin when compared to the normal control not giving the extract. Administration graded dosage of 1000mg/kg and 500mg/kg body weight significantly ($p<0.05$) increased the liver damage marker enzymes when compared with groups that received low dosage of 250mg/kg and 125mg/kg body weight and the normal control groups. The histopathological study revealed severe portal inflammation without steatosis and moderate portal inflammation in groups that received 1000mg/kg and 500mg/kg. Therefore, these results suggested that methanol leaf extracts of *Gongronema latifolium* possess hepatotoxic properties and strict caution must be observed when using the plant extract as a natural remedy of any disease.

**Keywords:** Medicinal; Aminotransferase; *Gongronema latifolium*; Inflammation; Hepatotoxic.

## 1. Introduction

Hepatotoxicity refers to *liver dysfunction* or liver damage that is associated with an overload of drugs or xenobiotics (Navarro and Senior, 2006). The chemicals that cause liver injury are called hepatoxins or hepatoxicants. Hepatoxicants are exogenous compounds of clinical relevance and may include overdoes of certain medicinal drugs, industrial chemicals, natural chemicals like microcystins, herbal remedies and dietary supplements (Willett *et al*, 2004; Papay *et al*, 2009).

Hepatotoxicity may result not only from direct toxicity of the primary compound but also from a reactive metabolite or from an immunologically-mediated response affecting hepatocytes, biliary epithelial cells and/or liver vasculature (Saukkonen *et al*., 2006; Deng *et al*., 2009). The hepatotoxic response elicited by chemical agents depends on the concentration of the toxicant which may be either parent compound or toxic metabolite, differential expression of enzymes and concentration gradient of cofactors in the blood across the acinus (Bleibel *et al.,* 2006)

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Liver is the largest organ of the human body weight approximately 1500g and is located in the upper right corner of the abdomen on top of the stomach, right kidney and intestines and beneath the diaphragm. The liver performs more than 500 vital metabolic function. Bile aid in the removal of toxic substances and serves as a filter that separates out harmful substances from the bloodstream and excretes them (Saukkonen *et al.,* 2006). An excess of chemical hinders the production of bile thus leading to the body's inability to flush out the chemicals through waste. The central role played by the liver in the clearances and transformation of chemicals expose it to toxic injury (Saukkonen *et al.,* 2006)

*Gongronema latifolium* is a leafy vegetable which belongs to the family of plants called Asclepiadaceous and a genus called Gongronema. It is harvested from forest in southeastern states of Nigeria and some other parts of Sub-Saharan Africa. It has been reported that aqueous and methanolic extracts of *Gongronema latifolium* exhibited hypoglycaemic, hypolipidemic, antioxidative, antibacterial activities and emulsifying properties (Ugochukwu *et al.,* 2003, Ugochukwu and Badady, 2002, Ugochukwu and Badady, 2003, Ogundipe *et al.,* 2003, Oshodi *et al.,* 2004, Eleyinmi, 2007). Therefore, this study aimed at evaluating the hepatotoxic effect of methanol leaf extract of *Gongronema latifolium* in albino rats.

## 2. Methodology

### 2.1. Collection of plant Materials

The leaves of *Gongronema latifolium* were obtained from Michael Okpara University of Agriculture, Umudike and its botanical identification was authenticated by Dr Ibeh of the department of forestry, College of natural resources and environmental management.

#### *2.1.1. Plant Extraction*

*Gongronema latifolium* leaves were air dried, and ground into fine particles using electric blender. Then, 200g of the leaves was soaked into 600ml of methanol for 72 hours with intermittent shaking. The resulting mixture was filtered and the filtrate was collected while the residue was discarded. The filtrate was then evaporated using water bath at 50 $^{0}$C until the methanol was fully evaporated leaving only the gel like green substance which is the plant extract.

#### *2.1.2. Experimental Animals*

The animals were obtained from the Animal House of the College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike. They were housed in clean cages and the animals were fed with standard vital feed. They were given access to water from public supply *ad libitum* till the end of the experiment. They were allowed to acclimatize for a period of ten (14) days prior to the commencement of the study.

All the extracts where administered through the oral route using a gavage intubation. Animals used for this experiment were identified using a simple coded identification which was applied using concentrated picric acid solution which was re-applied whenever fading was observed. This study was conducted in the Animal House of the Department of Biochemistry, College of Natural Science, Michael Okpara University of Agriculture, Umudike.

### 2.2. Experimental Design and protocol

The Twenty four male albino rats (between 100g-160g body weight) were randomly placed into five (5) groups with (4) rats in group one (5) rats in the other groups.

Group one: Served as the normal control (it received commercial rat feed and water for 21 days).

Group two: (Received 1000 mg/kg b.w. of leaf extract of *Gongronema latifolium*).

Group three: (Received 500 mg/kg b.w of leaf extract of *G. latifolium)*.

Group four: Received 250 mg/kg of leaf extract of *Gongronema latifolium)*.

Group five: Received 125mg/kg of leaf extract of *Gongronema latifolium)*.

The test animals (groups 2, 3, 4 and 5) received the leaf extract as stated above for twenty-one consecutive days.

### 2.3. Collection of Animal sample

At the end of 21 days, the rats were fasted overnight and were euthanized by cervical dislocation and blood was collected by cardiac puncture into both EDTA contained sample tube and plain sample tube and allowed to clot. Serums

were separated within one hour of blood clotting by centrifugation at 3000g for about 20mins after which they were collected using Pasteur pipette. The serum samples were stored in a refrigerator until required for use. The serum samples were used for serum assay of liver function. The organ of interest (Liver) was excised, rinsed in ice cold 1.15% KCl, bottled and weighed using an electronic weighing balance.

### 2.4. Liver enzymes assay

#### *2.4.1. Alanine Amino Transferase (ALT) activity*

The ALT activity was assayed using the method of Reitman and Frankel (2007) as outlined in Randox test kit (USA).

Principle: The ALT activity was by monitoring the concentration of pyruvate hydrazine formed with 2, 4-dinitrophenylhydrazine. The colour intensity is measured against the black at 540nm.

#### *2.4.2. Aspartate Amino Transferase (AST) activity*

The *in-vitro* activity of AST was assayed by Reitman and Frankel (2007) using Randox test kit (USA).

Principle: The AST activity was generally assayed by monitoring the concentration of oxaloacetate hydrzone formed with 2, 4-dinitrophenylhydrazine. The colour intensity is measured against the black at 540 nm.

#### *2.4.3. Alkaline phosphate (ALP) activity*

The ALP activity was assayed using the method described by Reitman S, Frankel (2007)

Principle: The principle of this based on the reaction involving serum ALP and a colourless substrate of phenolphthalein monophosphate, giving rise to phosphoric acid and phenol phthanlein at alkaline pH values, turns pink that can be determine photo metrically.

#### *2.4.4. Total Bilirubin Test*

The total bilirubin activity was assayed using the method described by Reitman S, Frankel (2007)

Principle: Bilirubin reacts with diazotized sulfanilic acid to produce azobilirubin which has an absorbance maximally at 560nm in the dimethyl sulfoxide (DMSO) solvent. The intensity of the colour produced is directly proportional to the amount of total bilirubin concentration present in the sample.

#### *2.4.5. Conjugate bilirubin Test*

The conjugate bilirubin activity was assayed using the method of Reitman and Frankel (2007) as outlined in Randox test kit (USA).

Principle: Bilirubin reacts with diazotized sulfanilic acid to produce azobilirubin which has an absorbance maximum at 560nm in the aqueous solution. The intensity of the colour produced is directly proportional to the amount of direct bilirubin concentration present in the sample.

### 2.5. Liver histopathological examination

#### *2.5.1. Tissue preparation*

The surviving experimental animals were humanely sacrificed at the end of the study. Sections of Liver from the animals in the experimental groups were collected for histopathological examination. The samples were fixed in 10% phosphate buffered formalin for a minimum of 48 hours. The tissues were subsequently be trimmed, dehydrated in 4 grades of alcohol (70%, 80%, 90% and absolute alcohol), cleared in 3 grades of xylene and embedded in molten wax. On solidifying, the blocks were sectioned, 5µm thick with a rotary microtome, floated in water bath and incubated at 60˚C for 30 minutes. The 5µm thick sectioned tissues were subsequently cleared in 3 grades of xylene and rehydrated in 3 grades of alcohol (90%, 80% and 70%). The sections were then stained with Hematoxylin for 15 minutes. Blueing was done with ammonium chloride. Differentiation was done with 1% acid alcohol before counterstaining with Eosin. Permanent mounts were made on degreased glass slides using a mountant; DPX. (Distrene, Pasticizer and Xylene).

### 2.6. Slide examination

The prepared slides were examined with a Motic™ compound light microscope using x4, x10 and x40 objective lenses. The photomicrographs were taken using a Motic™ 5.0 megapixels microscope camera at x160 and x400 magnification.

## 3. Results and discussion

### 3.1. Histopathological result

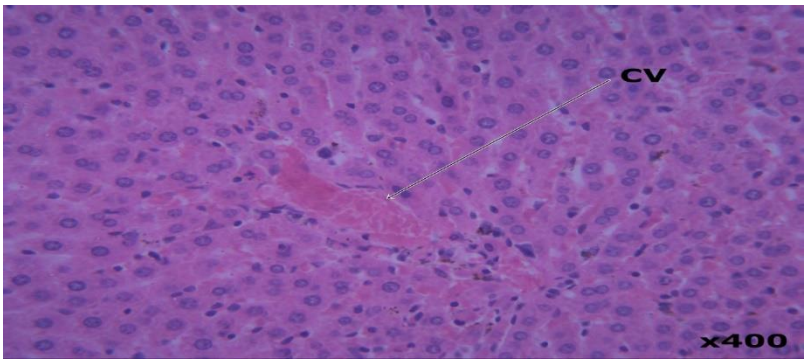


**Plate 1** Photomicrographs show well preserved liver architecture. There is no pathology found on the normal control

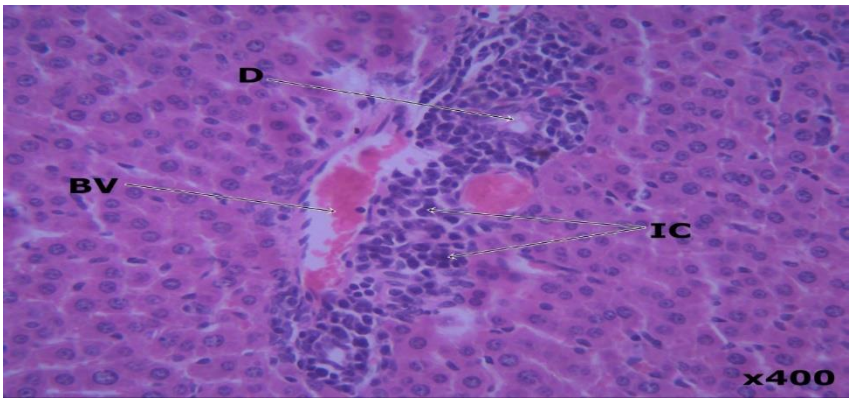


**Plate 2** Photomicrographs show group of 1000mg/kg dosage of *G .Llatifolium* leaves extract on Albino Rat. When compared to normal control group there is a severe portal inflammation with interface (piecemeal) necrosis without fibrosis or steatosis. There is also moderate centrilobular haemorrhage.

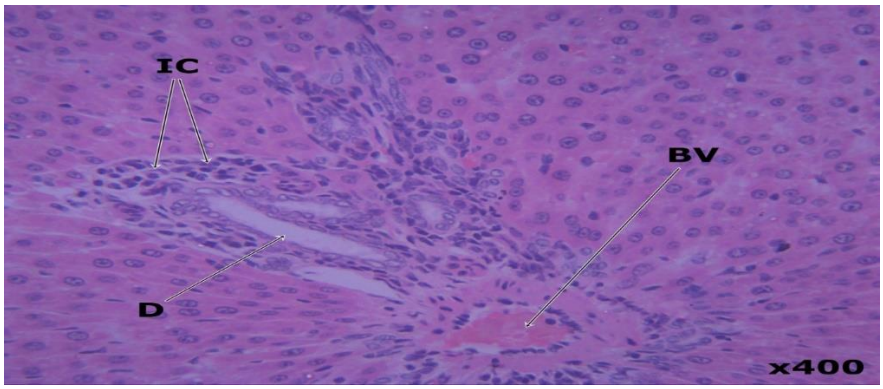


**Plate 3** Photomicrographs show group that received 500mg/kg dosage of *G. latifolium* leaves extract on Albino Rats. When compared to normal control there is moderate portal inflammation without interface necrosis or fibrosis. There is no steatosis.

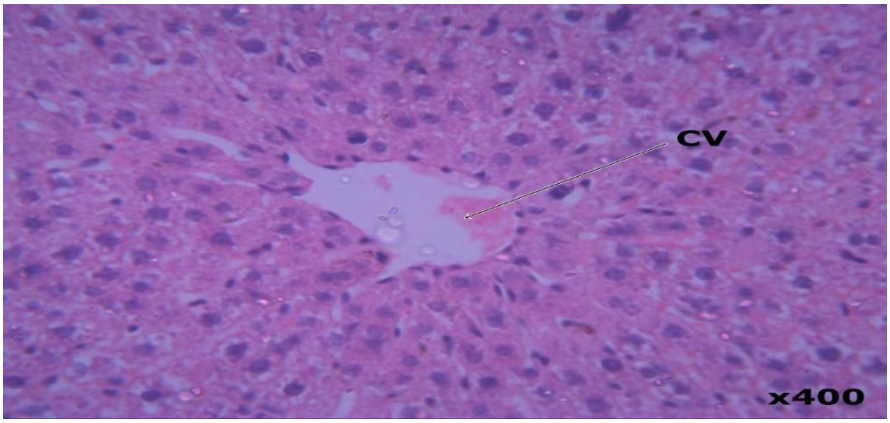


**Plate 4** Photomicrographs show group that received 250 mg/kg dosage of *G. latifolium* leaf extract on Albino Rats. When compared to normal control there is mild steatosis without portal inflammation.

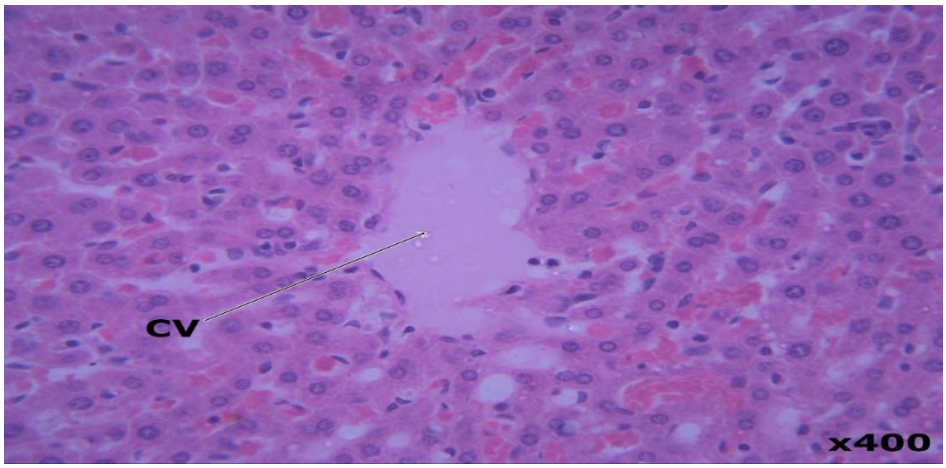


**Plate 5** Photomicrographs show group that received 125mg/kg dosage of *G. latifolium* leaf extracts. When compared to normal control the portal triads are evenly spaced around a central vein and there is mild portal inflammation without interface necrosis or fibrosis. There is no steatosis

**Table 1** Effect of *G. latifolium* leaves extract on conjugate bilirubin concentration in albino rat.

| Groups(mg/kg) | Week1(mg/kg) | Week 2(mg/kg) | Week 3(mg/kg) |
|---|---|---|---|
| Normal Control | $4.94\pm0.17^{e}$ | $4.94\pm0.17^{a}$ | $4.94\pm0.17^{a}$ |
| 1000 mg/kg | $4.50\pm0.14^{d}$ | $7.30\pm0.14^{c}$ | $9.30\pm0.14^{e}$ |
| 500 mg/kg | $4.10\pm0.14^{c}$ | $5.85\pm0.49^{b}$ | $8.50\pm0.14^{d}$ |
| 250 mg/kg | $3.70\pm0.14^{b}$ | $5.55\pm0.35^{b}$ | $7.70\pm0.14^{c}$ |
| 125 mg/kg | $2.90\pm0.14^{a}$ | $4.75\pm0.35^{a}$ | $6.25\pm0.21^{b}$ |

Means with the same alphabet as superscript are non-significantly ($p>0.05$) difference

Table 1: showed the effect of different doses of *G. latifolium* on conjugate bilirubin concentration. There was a significant ($p<0.05$) difference in all the extract groups in week 1 and 3 when compared to the normal control. There was a significant ($p<0.05$) increase in 1000 mg/kg, 500 mg/kg, 250mg/kg when compared to the normal control, while 125 mg/kg was non-significantly ($p>0.05$) decrease when compared to the normal control in Week 2.

**Table 2** Effect of *G. latifolium* leaves extract on total bilirubin concentration in albino rat

| Groups(mg/kg) | Week1(mg/kg) | Week 2(mg/kg) | Week 3(mg/kg) |
|---|---|---|---|
| Normal Control | 10.40±0.27$^{d}$ | 10.40±0.27$^{d}$ | 10.40±0.27$^{a}$ |
| 1000 mg/kg | 10.50±0.14$^{d}$ | 15.05±0.77$^{d}$ | 18.50±0.14$^{d}$ |
| 500 mg/kg | 9.40±0.28$^{c}$ | 13.10±0.14$^{c}$ | 15.10±0.14$^{c}$ |
| 250 mg/kg | 8.75±0.21$^{b}$ | 12.25±0.91$^{b,c}$ | 13.95±0.07$^{b}$ |
| 125 mg/kg | 7.70±0.14$^{a}$ | 11.50±0.42$^{b}$ | 14.00±0.28$^{b}$ |

Means with the same alphabet as superscript are non-significantly (p>0.05) different

The table above shows the effect of different doses of *G. latifoluim* on Total bilirubin concentration on albino rat. There was a significant (p<0.05) increase in 1000mg/kg, 500mg/kg, 250mg/kg, 125mg/kg in week 1, week 2 and week 3 when compared to normal control while 1000mg/kg in week 1 was non significantly (p>0.05) decrease when compared to normal control.

**Table 3** Effect of *G. latifolium* leave extract on aspartate amino transferase concentration in albino rat.

| Groups(mg/kg) | Week1(mg/kg) | Week 2(mg/kg) | Week 3(mg/kg) |
|---|---|---|---|
| Normal Control | 17.32±0.36$^{a}$ | 17.32±0.36$^{a}$ | 17.32±0.36$^{a}$ |
| 1000 mg/kg | 17.60±0.28$^{a}$ | 22.25±0.21$^{c}$ | 26.35±0.07$^{e}$ |
| 500 mg/kg | 16.30±0.42$^{c}$ | 22.15±0.63$^{c}$ | 24.50±0.14$^{d}$ |
| 250 mg/kg | 13.90±0.14$^{b}$ | 19.90±0.14$^{b}$ | 22.20±0.28$^{c}$ |
| 125 mg/kg | 12.90±0.14$^{a}$ | 17.75±0.35$^{a}$ | 19.70±0.42$^{b}$ |

Means with the same alphabet as superscript are non-significantly (p>0.05) different.

Table 3 shows the effect of different doses of *G.Latifoluim* on Aspartate Amino Transferase concentration on albino rat. There was a significant (p<0.05) increase in all the extract groups in week 3and 500mg/kg, 250mg/kg in week 1 and week 2 when compared to normal control while there was a non-significant (p>0.05) decrease in 1000mg/kg and 125mg/kg in week 1 and week 2 when compared to normal control.

**Table 4** Effect of *G. latifolium* leaves extract on alkaline phosphate concentration in albino rat.

| Groups(mg/kg) | Week1(mg/kg) | Week 2(mg/kg) | Week 3(mg/kg) |
|---|---|---|---|
| Normal Control | 89.20±0.48$^{a}$ | 89.20±0.48$^{a}$ | 89.20±0.48$^{a}$ |
| 1000 mg/kg | 92.40±0.28$^{c}$ | 111.30±1.83$^{c}$ | 118.80±0.28$^{e}$ |
| 500 mg/kg | 89.55±0.91$^{a,}$ | 105.85±1.48$^{b}$ | 116.95±0.70$^{d}$ |
| 250 mg/kg | 90.50±0.14$^{b}$ | 101.15±0.35$^{b}$ | 115.30±0.14$^{c}$ |
| 125 mg/kg | 88.60±0.14$^{a}$ | 93.60±6.22$^{a}$ | 105.45±0.77$^{b}$ |

Means with the same alphabet as superscript are non-significantly (p>0.05) different.

Table 4 shows the effect of different doses of *G.Latifoluim* on Alkaline Phosphate concentration on albino rat. There was a non-significant (p>0.05) decrease in all the extract groups in week1 and week 2 when compared to normal control while there was a significant (p<0.05) increase in all the extract groups in week 3 when compared to normal control.

**Table 5** Effect of *G. latifolium* leaves extract on alanine amino transferase concentration in albino rat.

| Groups(mg/kg) | Week1(mg/kg) | Week 2(mg/kg) | Week 3(mg/kg) |
|---|---|---|---|
| Normal Control | 16.00±0.31$^{d}$ | 16.00±0.31$^{b}$ | 16.00±0.31$^{a}$ |
| 1000 mg/kg | 16.60±0.28$^{e}$ | 19.75±0.91$^{d}$ | 24.30±0.14$^{e}$ |
| 500 mg/kg | 13.90±0.14$^{c,}$ | 18.40±0.56$^{c}$ | 21.90±0.14$^{d}$ |
| 250 mg/kg | 11.70±0.14$^{b}$ | 17.30±0.42$^{c}$ | 19.400±0.28$^{c}$ |
| 125 mg/kg | 10.00±0.28$^{a}$ | 14.45±1.06$^{a}$ | 17.00±0.28$^{b}$ |

Means with the same alphabet as superscript are non-significantly (p>0.05) different.

Table 5 shows the effect of different doses of *G.Latifoluim* on Alanine Amino Transferase concentration on albino rat. There was a significant (p<0.05) increase in week 1, week 2 and week 3 in all the extract groups when compared to the normal control

## 4. Discussion

The results obtained, the examined liver showed a highly significant difference between the control groups and the groups administered with *G. latifolium*. This is so because, any derangement of biochemical processes in experimental animals due to the presence of a xenobiotic would reflects an increase or decrease in the activity of such enzyme including ALT, AST and ALP used as indicator of liver injury (Rahman and Hodgson, 2000). *G. latifolium* leave extract administered to the groups at different dosage exhibited varying hepatic alteration in the liver compared to those of normal controls. This finding is in consonance with our result in this present study which showed a significant increase in the liver dysfunction enzymes. There is a significant increase (p<0.05) in total bilirubin (TB) as the days of administration increases as shown in Table 2. Week three (3) recorded a highest significant in TB with a value of 18.50±0.14 when compared with the normal control with a value of 10.40±0.27. This may be as a result of dose concentrations.

The study also show a non-significant changes in ALP, AST, and ALT values following week one (1) to week two (2) of administration and a significant changes in week three (3) of administration as agreed with the result obtained by (Nwanjo *et al.,* 2006).

Assay for liver enzymes: ALT, AST, and ALP are important in assessing optimal liver function increase in the level of liver enzymes in the plasma is an indicator of liver dysfunction (Dame, 2009). ALT I a good indicator of liver dysfunction and this further substantiate the possible hepato-protective effect of administration of the plant extract especially at low dose following from week one and week 2 of administration may be attributed to the glycosides and phytosteroids (constituent of leaves extract of *G. latifolium*) (Emeka and Obidoa, 2009) which has been shown to inhibit antioxidant activities in hepatocytes and also cause some hepatotoxic effect as the administration continues following the continues administration of the extract as shown in week 3. Continuous administration of *G. latifolium* leaf extract was observed from this study to increase CB, TB, ALT, AST, and ALP. This is conformity with the finding is as agreed by Rahman and Hodgson (2000).

*G. latifolium* administration caused significant (p<0.05) increased of serum ALT, AST and ALP activities which parallel to the histopathological changes in the liver. These finding is in agreement with the finding obtained by (Effiong *et al.,* 2012). This increase in the activities of ALT, AST, ALP might be due to the damage of cellular membranes of hepatocytes which in turn leads to an increase in the permeability of cell membrane and facilitates the passage of cytoplasm enzymes outside the cell leading to the increase in the aminotransferase activities in blood serum (Gaur and Bhatia, 2009).

In the histopathological result, the study showed a severe portal inflammation with interface necrosis without fibrosis or steatosis in groups that received 1000mg/kg body weight when compared to normal control groups, there was a moderate portal inflammation without interface necrosis fibrosis and there was no steatosis in group administered 500mg/kg body weight when compared to normal control groups, there was a mild steatosis without portal inflammation in groups that received 250mg/kg body weight when compared to normal control groups and in groups that received 125mg/kg body weight, there was a mild portal inflammation without interface necrosis or fibrosis and these was cause due to the degeneration of hepatocytes in periportal zones and inflammatory infiltration.

The liver is the major organ involved in drugs biotransformation. Level of serum liver biomarkers enzymes are biochemical parameters usually performed in order to evaluate any toxic effects on the liver (Mukinda and Syce, 2007). Increase in the level of AST, ALT, and ALP in the serum are associated with liver toxicity by drugs or medicinal plants or any other hepatotoxin. However; ALT is more specific to liver and thus a better parameter for detecting liver injury as AST is also associated with disease of other organs such as heart and muscle (Ozer *et al.,* 2008).

## 5. Conclusion

All compounds undergoes xenobiotic metabolism which requires multiple biochemical transformations. The result of this present study showed that *G. latifolium* shared a significant increase in the hepatic enzyme levels particularly at high dose concentration. We conclude that the methanol leaf extracts of *Gongronema latifolium* (Utazi) have a hepatotoxic effect in the model studied. Therefore strict caution must be observed when using the plant extract as a natural remedy of any disease.

## Compliance with ethical standards

### *Acknowledgments*

Authors wish to acknowledge Dr Onoja,who took proper care of the animals throughout this study.

### *conflict of interest*

Author declared that no conflict of interest existed in this paper.

### *Ethical approval and consent to participate:*

The study was conducted by following the guideline set by National Institute of Health,USA as approved by the College of Veterinary Medicine,Mcheal Okpara University of Agriculture ,Umudike.THE ETHICAL COMMITTEES REFERENCE NUMBER IS: MOUAU/CVM/REC/202015.

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