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Biochemical and histological effects of methanolic extract of *Carica papaya* seeds in Albino Wister rats infected with *Trypanosomal brucei brucei*

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Abstract

In this study, the biochemical and Histological effect of methanolic extract of *Carica papaya* seed in Albino Wister Rats were determined. Eighty Wister rats of both sexes, randomly divided into 8 groups, were used. Exactly 100 mg/kg, 200mg/kg, 400mg/kg and 800mg/kg of the plant extract was administered to each group for the experimental rats infected with *Trypanosomal brucei brucei* for period of 5 days. At the end of the experimental period, animals were sacrificed and blood collected by cardiac puncture. Biochemical parameters were determined. The level of serum biochemical parameter shows significantly $P<0.05$ increased in AST at the concentration of 100mg/kg 200mg/kg, 400mg/kg, 800mg/kg, berenil drug control and negative control when compared with normal control and extract control. While significantly increased in serum level of ALT and ALP were observed at concentration of 400mg/kg, 800mg/kg, berenil drug control and negative control when compared with normal control and extract control. The elevation in serum biochemical parameter in this study could be as a result of tissue inflammation caused by the parasite infection. Histopathological examination of selected organs (liver and brain) revealed histological alterations among different treated groups with their respective controls. The histology of the brain Sections from Suprachiasmatic region of brain. All treatment groups show mild diffuse infiltration by chronic infiltrates and increased kupfer cell population. The negative control shows proliferation glial cells and fewer neuronal cell bodies exhibiting shrunken (pyknotic) nuclei.

Keywords: Biochemical parameters, Histological Changes, Extract and methanolic

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1. Introduction

The use of herbal medicines in human and animal health care systems is well documented in ancient literature. In many parts of the World, ethno-therapies are no longer seen as myth, superstition, witchcraft or ungodly practices and indeed is gaining popularity with the belief that "natural is better". It is believed that nearly 80% of world population relies primarily on herbal remedies for the treatment of human and animal diseases. It is in this light that World Health Organization encourages the use of herbal preparations for the treatment of some local health problems particularly in developing countries where they are readily available, easily affordable and already integrated into the people's cultures. Several medicinal plants have been proved beneficial through extensive laboratory tests [1]. *Carica papaya* is regarded as a wholesome fruit, the daily requirements of some of the essential nutrients like proteins, minerals and vitamins can be met from this fruit. The vitamin C content increases as the maturity progresses. Its carbohydrate content is mainly in invert sugar which is a form of predigested food [2]. Its main medicinal use is as a digestive agent; it is prescribed for people who have difficulty digesting protein and is used to break up blood clots after surgery, which is due to the presence of enzyme papain in the plant's latex. The latex from the trunk of the tree is also applied externally to speed the healing of wounds, ulcers, boils, and warts. The seed is used to expel worm and the flower may be taken in an infusion to induce menstruation [2]. It has been documented that black seeds of papaya are highly beneficial in the treatment of cirrhosis of the liver caused by alcoholism, malnutrition etc. It has also been reported that annonaceous acetogenins derived from the extracts of the twigs of the pawpaw tree may be good chemotherapeutic agents for cancer as these compounds inhibit enzymes necessary for metabolic processes in tumor cells [2]. Aqueous extract of unripe *Carica papaya* has been documented to possess antisickling properties. Oduola et al. [2] confirmed this property and established the minimum concentration of the unripe *Carica papaya* that achieved

maximum antisickling to be 1g/ml in physiological saline. Solvent partitioning revealed that the antisickling agent resides in the ethyl acetate fraction of the extract. The results of the acute oral toxicity study in Wister albino rats showed the LD_{50} of the aqueous extract of the unripe *Carica papaya* to be 2520mg/kg. This plant has therapeutic uses such as anti-parasitic, anti-amoebic, anti-microbial, anti-fertility activity, anti-ulcerogenic, anti-fungal, antitumor, hypolipidaemic and employ in wound-healing activity, free radical scavenging activity, diuretic activity, uterotonic activity [3].

This paper seeks is designed to assess the effect of the *carica papaya* seeds extract on biochemical parameters and histological changes of the liver and brain tissues of some Wister albino rats.

2. Materials and methods

2.1. Collection of plant materials

Fresh mature seed of *Carica papaya* was collected in Vom, Jos south local government area of Plateau state. Nigeria. The plant specimen was identified and authenticated in the herbarium unit at Federal College of Forestry, Jos, Nigeria.

2.2. Methods

2.2.1. Preparation of plants materials

Seed of *Carica papaya*, was washed thoroughly with tap water in order to remove the dust and soil particles. Then the plant was air dried under the shade to prevent ultra-violet rays from inactivating the chemical constituents and was pulverized (ground into powder form) separately, using pestle and mortar [2].

2.2.2. Methanolic extraction of seed of Carica papaya

The pulverized seed of *Carica papaya*, (600g) was extracted with methanol. The maceration process was performed at room temperature by adding 600g of the powder form to 2600 mL of methanol it was then extracted by cold maceration with daily shaking for three days and was filtered using Whatman filter No.1 Paper. The filtrated was air dried. It was harvested and weight, the dried extracts was preserved in a desiccator [4].

2.2.3. Experimental design

Albino rats weighing between 80-120 grams of either sex were used for the study. The albino rat was kept in clean wire meshed cages under standard animal condition in accordance with the recommendations in Guide for the Care and Use of Laboratory Animal [5]. Then, the animals were given standard feed diet and water and bilirubin during the entire period of the experiment**.**

2.3. Test organism

Trypasonoma brucei (*Fe*dere strain) used for this work was obtained from Nigeria Institute for Trypanosomiasis Research (NITR), Vom Plateau State, Nigeria. The parasite was maintained in their laboratory by continuous passage in albino rats, until commencement of the work

2.3.1. Serum, liver and brain preparation

On the last day of the extract administration, the animals were anaesthetized and sacrificed, 5 ml of the blood will also collected in a plane container which was used for biochemical parameters. The blood samples were separated using refrigerated centrifuge at 3000rmp for 5 minutes. The plasma was harvested and stored at $4^{\circ}C$ period to time of used. Liver and brain tissues were removed from the rats and trimmed down to a size of 3mm × 3mm thick and fixed in buffered formalin solution ready for histological studies. The tissue slides were prepared in the Laboratory.

2.3.2. Effect of extract on biochemical parameters

Serum was harvested from blood kept for 2 h at room temperature (25-26 °C) in glass test-tubes and centrifuged at 3000 g for 5 minutes. Albumin, total protein, conjugated bilirubin, total bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase.

2.3.3. Determination of alkaline phosphatase

The principle stated that alkaline phosphatase (ALP): The substrate p-nitrophenyl phosphate is hydrolyzed by alkaline phosphatase from the sample in the presence of magnesium ions, to form nitrophenol which is yellow and can be read at 405 nm. The intensity of color produced is proportional to the activity of alkaline phosphatase. ALP Para nitrophenol phosphate HOH [5].

In a cuvette, 10 µl of sample was mixed with 50µl of the reagent. The initial absorbance was read at 405nm, and subsequently over 3minutes. The mean absorbance per minute was used in the calculation: ALP activity (IU/l) = 2742×ΔA 405 nm/min; Where: 2742 = Extinction coefficient; ΔA 405 nm/min = change in absorbance per minute for the sample.

Assay of alanine transaminase (ALT) activity: The method described by IFCC] using Randox kits. To 50µl of the sample, 500 µl of the ALT reagent was added and mixed in a test tube, and the initial absorbance at 340 nm was read after 1 minute. The timer will start simultaneously and further readings of the absorbance were taken after 1, 2, and 3 minutes. ALT activity (nm/min) = 1746 × ΔA 340nm/min, ΔA 340 nm/min = change in absorbance per minute for the homogenate sample, 1746 = Extinction coefficient.

Assay of aspartate transaminase (AST) activity: The same assay method described for ALT was used with the exception that the ALT reagent was replaced with the AST reagent. AST activity (nm/min) = 1746 × ΔA 340nm/min; ΔA 340 nm/min = change in absorbance per minute for the homogenate sample; 1746 = extinction co-efficient.

2.3.4. Determination of bilirubin

Principle of Reaction Bilirubin stated that sulfanilic acid reacts with sodium nitrite to form diazotized sulfanilic acid. Total bilirubin reacted with diazotized sulfanilic acid in the present of TAB form azobilirubin [4]. 1000µl of direct bilirubin reagent was added to a test yubr label sample blank and tested respectively. 20µl activator direct was added into the test only and followed by 50 µl of the serum into the sample blank and tested. It was then mixed and incubated for 5 minutes at room temperature. The absorbance of test against respective blank was measured at 546nm.

Calculation with factor:

$$\text{Direct bilirubin} = \text{OD of test} - \text{OD of sample blank} \times 16$$

$$\text{Bilirubin concentration} = \frac{\text{OD of test} - \text{OD of blank}}{\text{OD of calibration} - \text{OD of calibrator blank}} \times \text{concentrator of calibrator}$$

Total bilirubin: 1000µl of direct bilirubin reagent was added to a test tube label sample blank and test respectively. 20µl activator total was added into the test only and followed by 50 µl of the serum/calibrator into the sample blank and test. It was then mixed and incubated for 5minutes at room temperature. The absorbance of test against respective blank was measured at 546nm.

Calculation with factor:

$$\text{Total bilirubin} = \text{OD of test} - \text{OD of sample blank} \times 25$$

$$\text{Bilirubin concentration} = \frac{\text{OD of test} - \text{OD of blank}}{\text{OD of calibration} - \text{OD of calibrator blank}} \times \text{concentrator of calibrator}$$

2.3.5. Determination of total protein

Principle of reactions: Cupric ions in an alkaline medium interact with protein peptide bonds resulting in the formation of a coloured complex [4]. 1000µl of the reagent was added to 20µl of the sample and incubated at room temperature for 5 minutes. The absorbance against blank was recorded at 546nm.

2.3.6. Determination of albumin

Principle of the reaction: The measurement of serum albumin is based on the indicator 3,3',5,5'-tetrabromo-m cresol sulphonephthalein (bromocresol green, BCG) which absorbs at 578nm, the absorbance being directly proportional to the concentration of albumin in the sample [4]. 1000µl of the reagent was added to 10µl of the sample and incubated at room temperature for 1 minute. The absorbance was measure at 600nm against the blank.

2.3.7. Statistical Analysis

Values was expressed as mean ± SEM n=5.Data was subjected to one-way analysis of variance (ANOVA), followed by SPSS version 23. Tukey's comparison *post-hoc* test used to compare the differences between the experimental groups. (GraphPad Software, San Diego, CA, USA). Values of $p < 0.05$ was considered significant.

3. Results and discussion

3.1. Biochemical parameters of rat infected with T. brucei and treated with Carica papaya seed methanol extract

The result of serum biochemical parameter shows significantly P<0.05 increased in AST at the concentration of 100mg/kg 200mg/kg, 400mg/kg, 800mg/kg, berenil drug control and negative control when compared with normal control and extract control. While significantly increased in serum level of ALT and ALP were observed at concentration of 400mg/kg, 800mg/kg, berenil drug control and negative control when compared with normal control and extract control. The elevation in serum biochemical parameter in this study could be as a result of tissue inflammation caused by the parasite infection. These results differ from Bakari, *et al*., [6], which didn't show any significant different in AST, ALT and ALP in both the infected and uninfected cattle but they are broadly consistent with earlier results of Ibrahim, *et al*., [7] in which they recorded increased in ALT, AST and ALP. And stated that the changing is as a result of the trypanosomes induced hepatocellular damage, monitor by AST, ALT and ALP hepatic cell linkage. Although Significant P<0.05 decreased in serum level of AST, ALT and ALP where observed in infected and treated with different concentration of extract when compared with negative control. These could be all attribute to ability of the extract to reduce the level of parasitemia and presence of antioxidant which serves as anti-inflammatory. Not much significant difference was observed between the extract control and the normal control. The serum albumin and total protein concentration of negative control decreased significantly ($p < 0.05$) when compared to normal control rats. Whereas there was no significant ($p< 0.05$) difference in that of the normal control, extract control, standard drug control (Berenil) and Prophylactic. The decreased in mean value of total serum protein level of rats agrees with previous findings of (Allam, *et al*., [8]; Katunguka-Rwakishaya *et al*., [9], but contradicts observations made in sheep infected with T. brucei by Taiwo *et al*., [10], who observed no change in levels of total plasma proteins from pre-infected values at the initial stage of the infection, but in the later stage the levels increased significantly above pre-infection levels. The decreased could be due to reduced protein synthesis arising from damaged liver or as a result of excessive protein breakdown arising from reduced feed intake as observed in all the infected animals and also could be arise from low level of albumin caused by catabolism, uptake of albumin by trypanosomes or heamodilution [9]. Significant ($p< 0.05$) increased in serum level of bilirubin was also observed in negative control when compared with all the others groups. Increased in serum level of bilirubin in this study corroborates with the earlier findings of Ekanem and Yusuf [11] (2010). Who

stated that Bilirubin is transported to the liver bound to albumin, High plasma conjugated bilirubin concentration indicates impaired hepatic excretory function.

3.2. Histopathological changes on the liver and brain of Trypanosoma brucei brucei infected rats treated with methanolic extract of seed of Carica papaya

The tissues of rat infected with *T. brucei* treated with various concentration of extract were also subjected to histopathological analysis for 7 to 21 days post-infection. The section of liver tissue of negative control i.e. (infected rat and not treated) shows a moderately preserved hepatic lobular architecture with hepatocytes generally exhibiting reactive nuclei. Mild diffuse chronic inflammatory infiltrates and increased kupfer cell population are observable. There are also extensive areas of hepatocyte necrosis, with hepatocytes losing nuclear details these were compared with liver of normal control and extract control rat which shows a well-preserved hepatic lobular architecture with normal-appearing hepatocytes. All treatment groups show mild diffuse infiltration by chronic infiltrates and increased kupfer cell population. The mild damaged to the liver cells could be probably as a result of the extract causing inhibitory effect on the trypanosomes. These observation matches with those finding observed in earlier study by Vincent *et al*., [12] who showed inhibitory activity of *C. papaya* leave extract on *T. evansi*, the liver cell of the infected rat returned to normal.

The histopathological investigation of the brain Sections from Suprachiasmatic region of brain. The negative control shows proliferation glial cells and fewer neuronal cell bodies exhibiting shrunken (pyknotic) nuclei. Some large reactive astrocytes surrounded the inflamed blood vessel are also seen. A few amount of *T. brucei* were also seen. This study confirmed the work of Shuaibu *et al*., [13] who demonstrated the presence of *T. brucei* in brain parenchyma cells of infected rat. Investigation by many researchers had shown that the trypanosomes were able to cross the brain blood barrier (BBB). As the disease progress, the parasite destroyed the BBB and advances to brain [14, 15]. Others studies also indicate that the laminin composition of the basement membrane plays an important role in trypanosome transmigration into the CNS [16, 17]. All the treated groups did not show much liver cells damage when compared to the normal control group, this could be as a result of the extract that have anti-inflammatory effect.

Table 1. The Biochemical parameters of Rat infected with *T. brucei* and treated with *Carica papaya* seed methanol extract

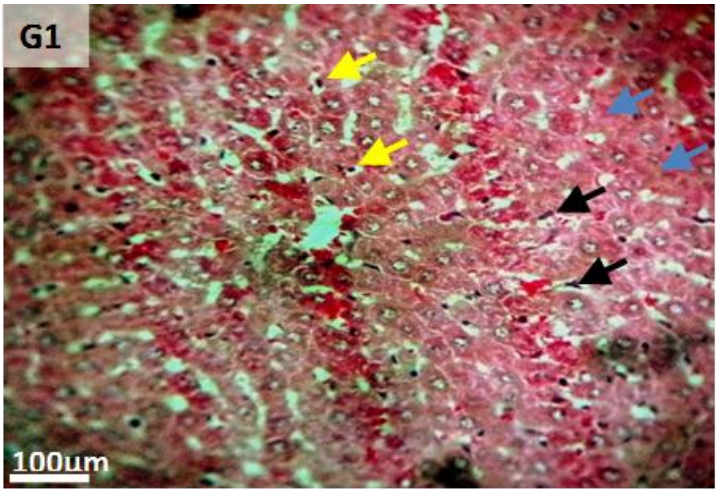
TREATMENT GROUPS	AST (U/L)	ALT (U/L).	ALP (U/L)	ALBUMIN (g/dl)
100 mg/Kg	105.00±42.97*	109.00±85.42	127.17±133.74*	40.50±8.36*
200 mg/Kg	99.83±101.37*	101.50±84.77	144.50±64.27	35.50±3.39*
400 mg/Kg	108.83±39.17*	123.17±70.00*	145.00±62.71	29.00±6.23*
800 mg/kg	73.77±51.44*	102.67±58.36*	115.00±149.98	33.72±1.27*
Berenil	88.50±73.50*	92.67±58.20*	72.83±78.61	51.33±7.12*
cNormal Cont.	48.00±34.16*	25.67±3.20*	65.50±12.08*	48.00±5.90*
Neg. Control	192.67±50.54*	271.50±102.88	270.05±173.07	16.00±4.60
Extract Contr	18.50±41.74*	16.17±42.94*	46.17±27.15*	41.00±9.23*
Prophylactic	154.67±55.03	88.50±161.71	114.83±74.07*	36.83±8.68*

*Significantly different from negative control down the group at P<0.05
Values are Mean ± SEM for determinations n=7

Table 2. The Biochemical parameters of Rat infected with *T. brucei* and treated with *Carica papaya* seed methanol extract

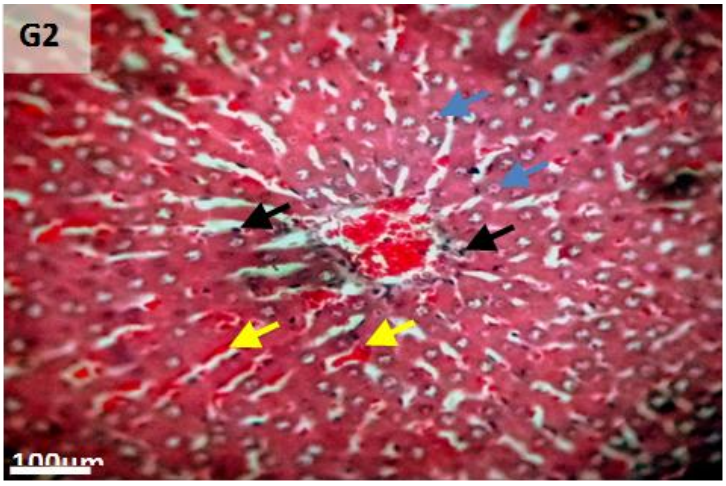
TREATMENT GROUPS	TB (mg/dl)	DB (mg/dl)	TP (g/dl)
100 mg/Kg	13.00±3.95*	1.30±0.11*	44.33±10.09*
200 mg/Kg	12.17±1.17	1.22±0.08*	43.67±8.98*
400 mg/Kg	12.50±2.08*	1.25±0.11*	36.83±8.70*
800 mg/kg	13.17±1.17*	1.22±0.15*	41.83±10.17*
Berenil	21.67±3.50*	2.20±0.48*	70.50±3.94*
cNormal Cont.	14.50±5.47*	1.13±0.52*	72.50±5.32*
Neg. Control	59.33±12.44	2.65±0.75	19.50±8.62
Extract Contr	21.83±8.38*	0.55±0.45	73.17±4.36*
Prophylactic	18.00±8.46	1.32±0.21	48.17±14.93*

*Significantly different from negative control down the group at P<0.05
Values are Mean ± SEM for determinations n=7



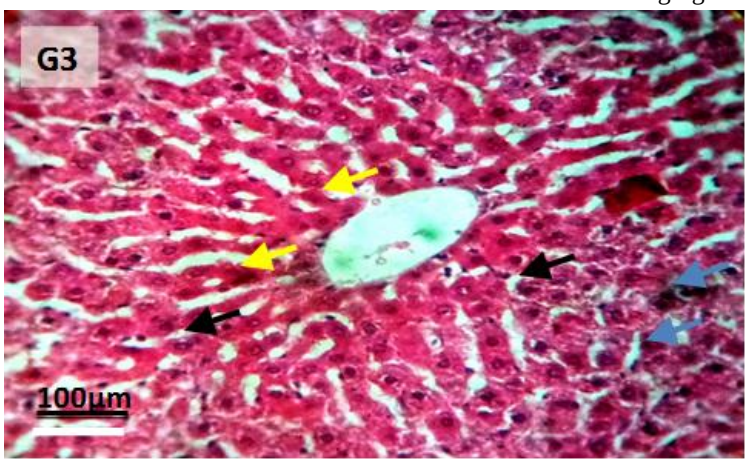
Section of liver tissue shows a moderately preserved hepatic lobular architecture. Mild diffuse chronic inflammatory infiltrates (yellow arrows) and increased kupfer cell population (black arrows) are observable. There are also extensive areas of hepatocyte necrosis (blue arrows), with hepatocytes losing nuclear details. *H&E stain.*

Figure 1. Histopathology of the liver of rat infected with *T. brucei* and treated with 100mg/kg of *Carica papaya* seed extract



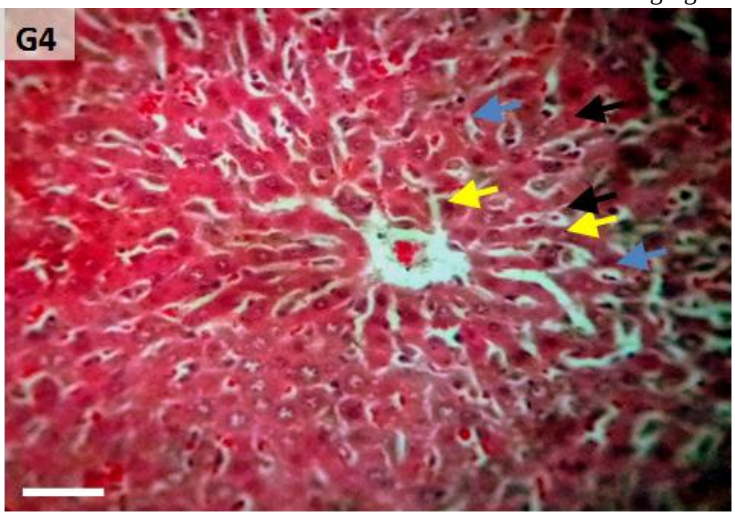
Section of liver tissue shows a well preserved hepatic lobular architecture with hepatocytes exhibiting reactive nuclei (blue arrows). There is mild dilatation and congestion of hepatic sinusoids (yellow arrows), as well as a mild diffuse infiltration by chronic inflammatory cells (black arrows). *H&E stain*.

Figure 2. Histopathology of the liver of rat infected with *T. brucei* and treated with 200mg/kg of *Carica papaya* seed extract



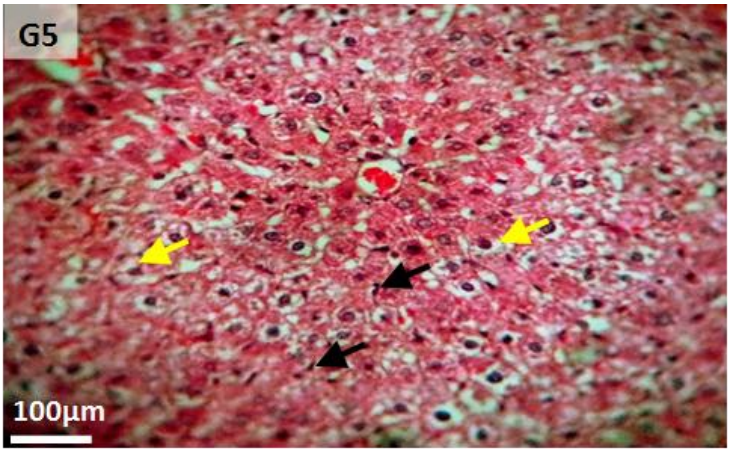
Section of liver tissue shows a moderately preserved hepatic lobular architecture with hepatocytes in zone 2 exhibiting ballooning degeneration (blue arrows). There is marked dilatation of hepatic sinusoids (yellow arrows), as well as a mild diffuse infiltration by chronic inflammatory cells (black arrows). *H&E stain*.

Figure 3. Histopathology of the liver of rat infected with *T. brucei* and treated with 400mg/kg of *Carica papaya* seed extract



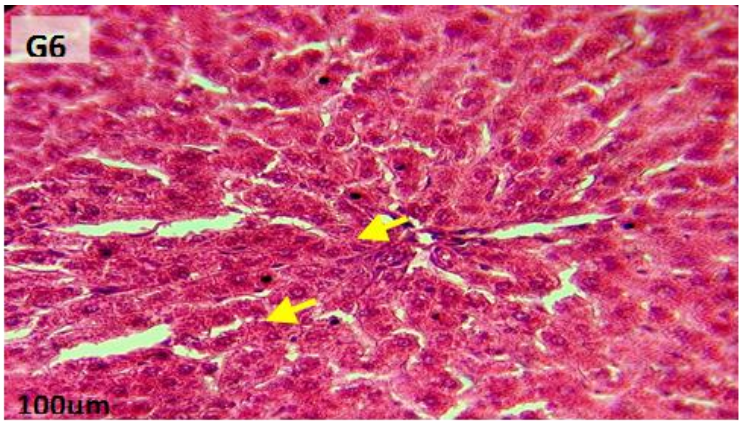
Section of liver tissue shows a poorly preserved hepatic lobular architecture with hepatocytes generally exhibiting reactive nuclei (blue arrows). There is congestion of hepatic sinusoids (yellow arrows), as well as an increase in kupfer cell population (black arrows). *H&E stain*.

Figure 4. Histopathology of the liver of rat infected with *T. brucei* and treated with 800mg/kg of *Carica papaya* seed extract



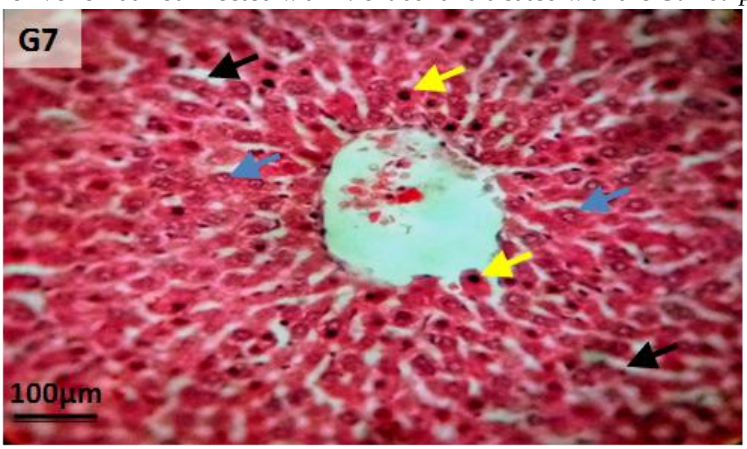
Section of liver tissue shows a poorly preserved hepatic lobular architecture with hepatocytes generally exhibiting ballooning degeneration (yellow arrows). There is also an increase in kupfer cell population. *H&E stain*.

Figure 5. Histopathology of the liver of rat infected with *T. brucei* and treated with standard drug berenil (positive control)



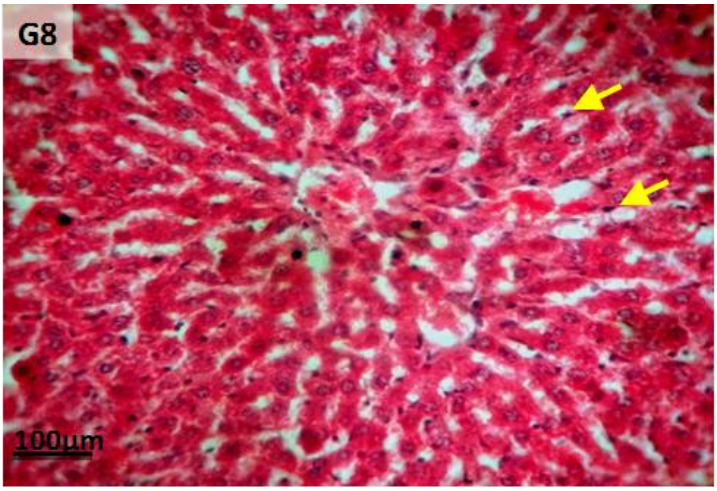
Section of liver tissue shows a well preserved normal-appearing hepatic lobular architecture. A few karyopyknotic hepatocytes (yellow arrows) are also seen. *H&E stain*.

Figure 6. Histopathology of the liver of rat not infected with *T. brucei* and treated with the *Carica papaya* seed methanol extract



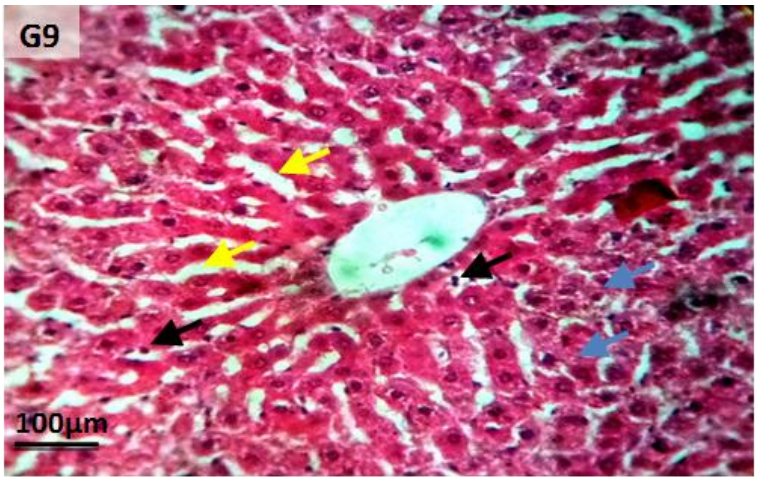
Section of liver tissue shows a moderately preserved hepatic lobular architecture with hepatocytes generally exhibiting reactive nuclei (blue arrows) while some hepatocytes are seen with pyknotic nuclei (yellow arrows). There is mild dilatation of hepatic sinusoids (black arrows), as well as an increase in kupfer cell population. *H&E stain*

Figure 7. Histopathology of the liver of rat infected with *T. brucei* and not treated (negative control)



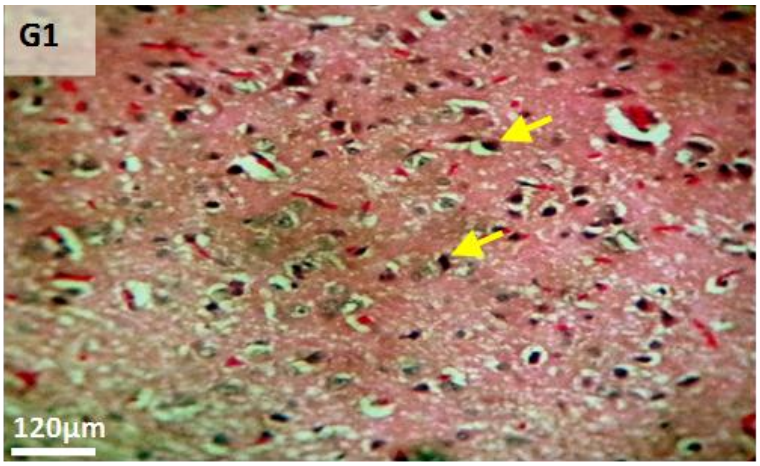
Section of liver tissue shows a well-preserved hepatic lobular architecture with normal-appearing hepatocytes A scant population of lymphocytes (yellow arrows) are also seen. *H&E stain*

Figure 8. Histopathology of the liver of rat not infected with *T. brucei* but treated with 800mg/kg of *Carica papaya* seed extract. (extract control)



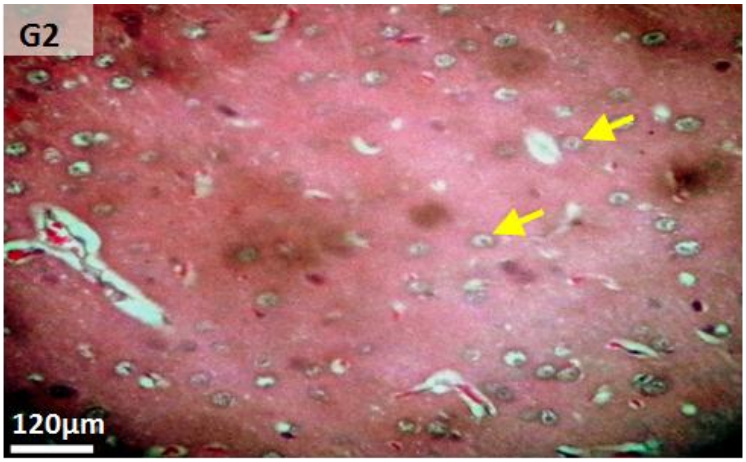
Section of liver tissue shows a moderately preserved hepatic lobular architecture with hepatocytes in zone 2 exhibiting ballooning degeneration (blue arrows). There is marked dilatation of hepatic sinusoids (yellow arrows), as well as a mild diffuse infiltration by chronic inflammatory cells (black arrows). *H&E stain*

Figure 9. Histopathology of the liver of rat treated with 800mg/kg of *Carica papaya* methanol extract before infected with *T. brucei* (prophylactic control)



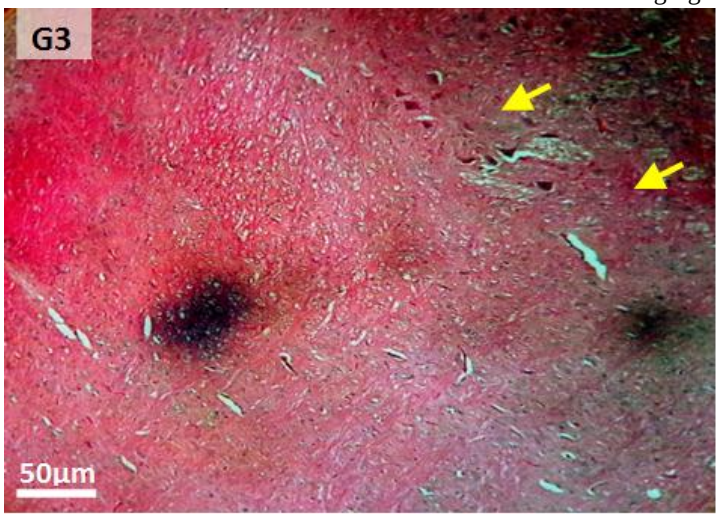
Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A proliferation of neuronal cell bodies was seen exhibiting shrunken (psychotic) nuclei (yellow arrows). *H&E stains*

Figure 10. Histopathology of the brain of rat infected with *T. brucei* and treated with 100mg/kg of *Carica papaya* seed extract



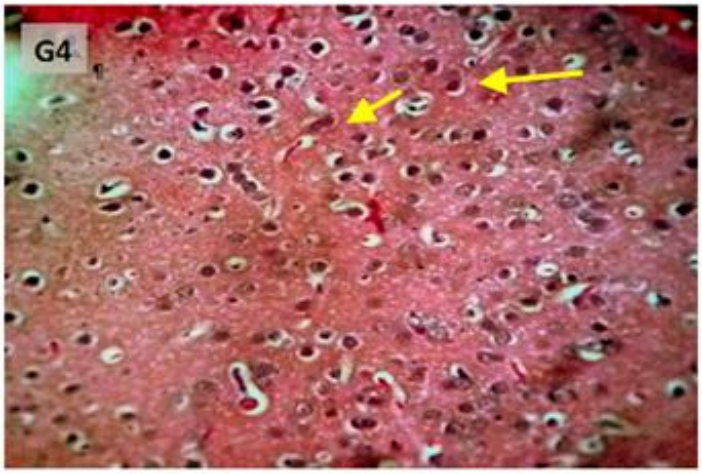
Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A proliferation glial cells and neuronal cell bodies are seen exhibiting shrunken (pyknotic) nuclei (yellow arrows).

Figure 11. Histopathology of the brain of rat infected with *T. brucei* and treated with 200mg/kg of *Carica papaya* seed extract



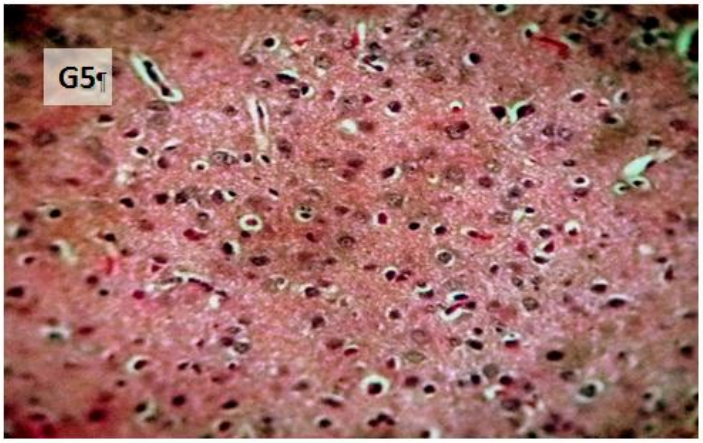
Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A few neuronal cell bodies are seen in the upper right corner with normal nuclear features (yellow arrows). No obvious proliferation of glial cells was observed.

Figure 12. Histopathology of the brain of rat infected with *T. brucei* and treated with 300mg/kg of *Carica papaya* seed extract



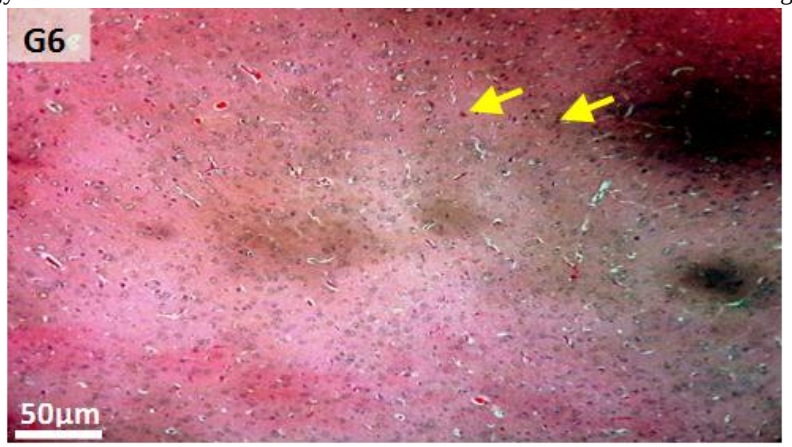
Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A proliferation glial cells and neuronal cell bodies are seen exhibiting shrunken (pyknotic) nuclei (yellow arrows).

Figure 13. Histopathology of the brain of rat infected with *T. brucei* and treated with 400mg/kg of *Carica papaya* seed extract



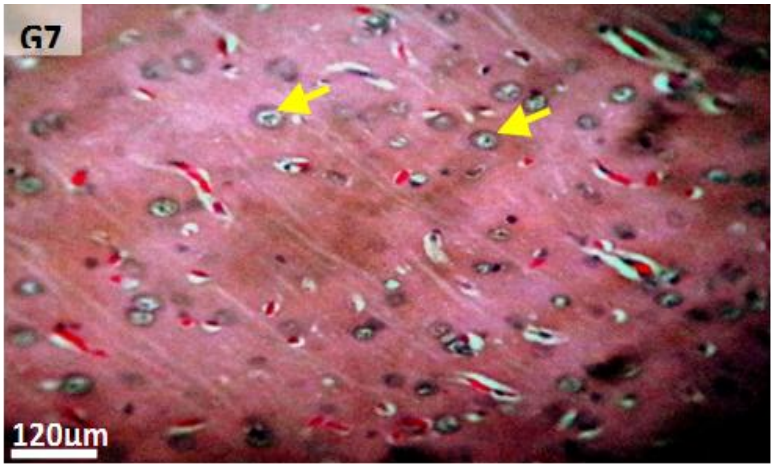
Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A proliferation glial cells and fewer neuronal cell bodies are seen exhibiting shrunken (pyknotic) nuclei.

Figure 14. Histopathology of the brain of rat infected with *T. brucei* and treated with standard drug berenil (positive control)



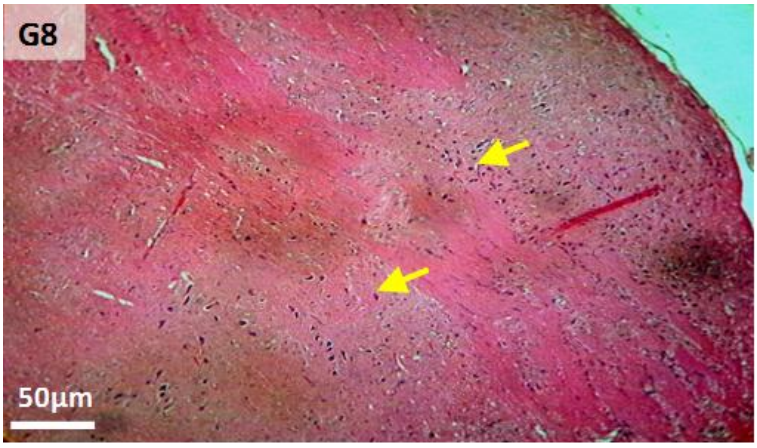
Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A few neuronal cell bodies are seen with normal nuclear features. No obvious proliferation of glial cells was observed.

Figure 15. Histopathology of the brain of rat not infected with *T. brucei* and also not treated with *Carica papaya* seed methanol extract. (normal control)



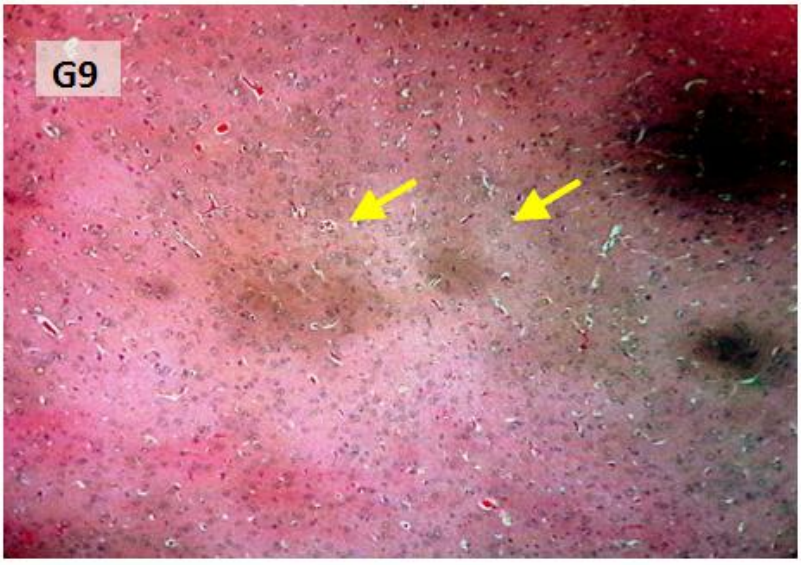
Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A proliferation glial cells and fewer neuronal cell bodies are seen exhibiting shrunken (pyknotic) nuclei.

Figure 16. Histopathology of the brain of rat infected with *T. brucei* and not treated (negative control)



Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A few neuronal cell bodies are seen with normal nuclear features (yellow arrows). No obvious proliferation of glial cells was observed.

Figure 17. Histopathology of the brain of rat not infected with *T. brucei* but treated with 800mg/kg of *Carica papaya* seed extract. (extract control)



Sections from Suprachiasmatic region of brain, showing well preserved CNS tissue architecture. A proliferation of neuronal cell bodies was seen exhibiting shrunken (pyknotic) nuclei.

Figure 18. Show Histopathology of the brain of rat treated with *Carica papaya* seed methanol extract before infected with *T. brucei* (Extract control)

4. Conclusions

The Parasite (*Trypanosomal brucei brucei*) have induced adverse alterations in biochemical parameters such as serum AST, ALT, ALP, Albumin, TB, DB and TP and histopathological lesions have been observed in liver or brain tissues of experimental animals. However, all the treated groups did not show much liver cells damage when compared to the normal control group, this could be as a result of the parasite that have anti-inflammatory effect.

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