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Comparative Antidiabetic Properties of *Ageratum conyzoides* and *Tridax procumbens* Leaf Extracts on Experimental Rats Induced with Diabetes

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Abstract

Plants have been a viable source of antibacterial compounds and have been used in the treatment of a number of infectious diseases. However, their effects on non-infectious diseases are increasingly being evaluated. The comparative studies of the antidiabetic properties of *Ageratum conyzoides* and *Tridax procumbens* leaf extracts and their synergistic effect was carried out using standard methods. The collection of plant materials was from Aganni farm area at Oba-Afunbiowo Estate, Akure, Nigeria. Upon collection, the plants leaves were air-dried, pulverized and subjected to extraction using non-polar and polar solvents including aqueous, chloroform and ethanolic extractions. Furthermore, diabetes was induced in the experimental albino rats using streptozotocin (STZ) dissolved in 0.1M citrate buffer. The biological effect of the extract on the blood samples of the rats were evaluated by measuring the blood glucose levels and other haematological parameters at intervals coupled with histopathological assay to ascertaining further deleterious effects of the extracts on selected vital organs including the heart, brain and kidney. Findings from the research reveal the plants extracts were able to initiate increase in weight of the animals following an initial weight loss observed after diabetes was induced in the experimental rats indicating its therapeutic efficacy. Moreover, the result showed that the group of rats treated with *T. procumbens* extracts exhibited unperceptive recovery in weight gain until the end of the experiment. The initial weight of the experimental rats measured at the beginning of the experiment for this group ranges between 110.40±2.63g and 110.23±1.56g. Additionally, the effect of the induced diabetes on the rats caused a significant increase of the erythrocyte sedimentation rate and white blood cell counts. Conversely, significant decrease of the haemoglobin concentration, packed cell volume, platelets and red blood cell count were observed.

Furthermore, a shrinking or reduction in size of the brain and the heart of the experimental rats were observed, whilst causing a significant increase in the size of the kidneys. In addition, the induced diabetes caused trigeminal nucleus with striated cortex and severe hypostatic central congestion, and neocortex with central mesencephalic nuclei infiltrations coupled with abnormal cell architecture with negative pathology due nuclei gatherings. The plant extract caused these pathologies to be reduced into intact cortical sheath with dilated neocortex of the meninges having an increased nucleus number and intact locus coeruleus. Moreover, it caused heart cardiac striata with profuse haemorrhage and inflammatory cells and congested intra-dilated capillaries. The extracts caused these effects to be corrected but lack proper aorta opening network of systolic transport system. As a result, the induced diabetes caused pathological features that include complete washing away and haemorrhagic unformed kidney nephrons with calcium crystal deposits. However, administration of the extracts caused significant recuperative effects that include nephrons with infiltrated cells and gobble structures. Overall, the results obtained revealed the synergistic potentials of the two plant extracts providing the best therapeutic efficacy against diabetes. As a result, we hereby recommend further purification of both extracts for managing diabetes, especially in the recuperation of vital organs usually affected by diabetes.

Keywords: Antidiabetic properties; Synergistic potentials; Induced; Extracts; Comparative analysis

Abbreviations: STZ: Streptozotocin; EDTA: Ethylene Diamine Tetra Acetic Acid; PCV: Packed Cell Volume; HB: Hemoglobin; ESR: Erythrocyte Sedimentation Rate; RBC: Red Blood cell; WBC: White Blood Cell; H&E: Haematoxylin and Eosin

Introduction

Ethnomedicine is a study or comparison of the traditional medicine based on bioactive compounds in plants and animals and practiced by various ethnic groups, especially those with little access to western medicines for example, the indigenous peoples. In accordance to Younes et al. [1], plants have been demonstrated to be a very viable source of clinically relevant anticancer compounds. As a result, most of these bioactive metabolites such as the phenolic compounds and phytochemicals embedded in

plants are prolific resources for drug production [2]. However, ethnopharmacological information has been poorly utilized in the past in the search for new principles against diseases such as diabetes and cancer [3]. Diabetes is a group of metabolic disorders in which there is high blood sugar levels over a prolonged period [4]. Diabetes is a condition in which the body system does not produce enough insulin to keep the blood sugar levels steady. Additionally, in human system, insulin is a hormone that functions in the removal of sugar (glucose) from the blood when the blood sugar is too high by putting it to work as energy for the somatic cells [5] The symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can lead to many complications including acute complications such as diabetic ketoacidosis, hyperosmolar hyperglycaemic state, or death [5]. Furthermore, serious long-term complications may include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes [6]. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced [7].

In accordance with Islam et al. [8] there are different types of diabetes, but the most common types have been grouped into three. These include: Type 1, Type 2 and gestational type. Findings revealed that the type 1 diabetes is more of an autoimmune disease whereby the body does not produce insulin for itself either completely or too low, because the immune system is attacking the cells in the pancreas that create insulin [9]. The type 2 diabetes has been explained differently by various authors, but it is when the body cannot produce enough insulin for the body, and this is most common in individuals over the age of 50 [8]. The third type of diabetes is gestational diabetes, which occurs only in women during pregnancy, and in most cases goes away after the child birth [8]. However, women who have had gestational diabetes are more at risk of Type 2 diabetes after giving birth [10]. Generally, diabetes and its complications are said to be number seven (7) cause of death in the developed world today as it has a much higher mortality rate in the developing and under-developed countries; especially in Africa and Asia [11]. Currently, findings from research conducted on patients with diabetes in science, drug and herbal medicines reveals that patient can still live well and carry out their daily routines irrespective of their medical state. However, Scientists are constantly in search of effective and affordable medications, even in the application of ethnopharmacological study of plants that can correct the production of insulin in diabetic patients. Hence, this research aims to evaluate the comparative antidiabetic properties of *Ageratum conyzoides* and *Tridax procumbens* leaf extracts on experimental rats induced with diabetes.

Materials and Methods

Collection of plant materials

The collection of the plant materials was carried out in Akure metropolis. They were harvested in Aganni Farm area at Oba – Afunbiowo Estate, Akure, Ondo State, Nigeria.

Extraction from plant samples

Tridax procumbens and Ageratum conyzoides leaves were harvested, rinsed, air dried at room temperature and pulverized into powdered form using an electrical grinding machine (Binatone model BLG-450 XL, 2016 model) China. Moreover, the extractions on the pulverized plant samples were carried out using aqueous, chloroform and ethanol as described by Proestos and Varzakas (2017).

Percentage yield of extracts

Percentage yield of extracts was calculated as follows:

Yield (%) = (Weight after drying/Weight before drying) x 100

Preparation of plant extracts

The preparation of different forms of the extracts for synergistic potentials was conducted using different combination forms of the plant extracts prepared in the ratio of 1:1, 1:2, and 2:2 as outlined in the method of Dawoud et al., 2013 for standard synergistic assay.

Induction of diabetes

Experimental diabetes mellitus was induced by a single intra-venous injection of streptozotocin (STZ) dissolved in 0.1M citrate buffer in the adult experimental rats under anaesthetic condition. They were checked daily to decipher when diabetes had set in. The diabetes was induced fully four days later from observation. Furthermore, the experimental design described by the method of Omoya and Momoh (2019) was employed in grouping the rats. As a result, the rats were grouped into six groups (a-f) consisting three (3) rats per group stated as follows: a= Group induced and treated with *A. conyzoides* extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both *A. conyzoides* and T. procubens extracts; d= Group induced and treated with conventional drug (Melanov); e= Group induced and not treated; f= The Group that was not induced nor treated.

Blood collection

Anaesthetization method as described by Adebolu et al. (2011) was employed in the collection of blood from the experimental rats. The blood samples collected were carefully transferred into ethylene diamine tetra acetic acid (EDTA) bottles for haematological assays and liver functioning tests respectively. Additionally, cardiovascular puncture was used to obtain blood samples from rats whose organs were not required for histopathology analysis.

Organ collection

Histopathological assays were carried out using organs such as the heart, liver, kidney, small intestine and spleen. These organs

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were dissected out using a clean set of dissecting tools from apparently healthy albino rats. Moreover, the organs were collected into specimen bottles containing 10% formalin according to the standard method described by Baker et al. (2018).

Administration of plant extracts orally (treatment)

The effect of the extracts on blood samples in the infected mice was monitored by measuring some hematological parameters such as Packed Cell Volume (PCV), Hemoglobin concentration (Hb), Red Blood Cell Count, WBC counts and differentials as described by Baker et al. (2018) using the following materials: Blood samples, Microscope, grease-free microscopic glass slides, Giesma stain, capillary tube, spectrophotometer, Leishman stain, EDTA bottles, haematocrit centrifuge and reader were used for this assay as documented below:

Erythrocyte Sedimentation Rate (ESR): A wintrobe tube was filled to the top 0 mark and one end of it blocked with plastacine. It was positioned upright and left undisturbed for 1hr. The distance of the fall of red cells in it was read and expressed as the mm fall per hour as the ESR.

Packed Cell volume (PCV): Blood collected into an anticoagulant bottle was mixed and a capillary tube was filled up to 75% (3/4) of its length and placed in the micro-haematocrit centrifuge with the sealant at the outer end and centrifuged at 12,000 rpm for 5 minutes. The result was read as a percentage of packed red cells to total volume of whole blood using an haematocrit reader.

Red Blood cell count (RBC): The blood sample was diluted 1:200 and mixed properly. A portion (0.02 ml) of the blood was pipetted into 4mL of diluting fluid in a bijou bottle and washed thoroughly by alternately drawing up and expelling the diluting fluid. A fine Pasteur pipette was used to fill the counting chamber and the RBC counted using a counter under × 40 objective lens.

White Blood Cell count (WBC): The blood was first diluted in ratio 1:20 and 0.05ml of the blood was pipetted into 0.95ml of diluting fluid. A little portion (0.2 ml) was introduced into the counting chamber and observed using ×10 objective to count the white cells/cubic mm.

Haemoglobin (Hb): Using mouthpiece sucker and a 0.02ml pipette, blood sample was collected and transferred into 4mL Drabkin's solution in a tube. The tube was stoppered, mixed and allowed to stand for 5 minutes for full colour development. A standard blood sample of known haemoglobin concentration was prepared. Using a green (624) filter, the colorimeter was set to zero using plain Drabkin's solution as a blank. In addition, the readings of the sample and the standard were taken and the result calculated as follows:

$$\text{sample haemoglobin concentration} = \frac{\text{Reading of test} \times \text{standard haemoglobin concentration.}}{\text{Reading of standard}}$$

White Blood Cell Differential (WBC Differential) Count: Twenty microliter (0.20 mL) of whole blood was placed on clean grease-free slide and made into a thin film using a glass rod. The film was allowed to air dry before staining with Giesma stain. The stained slides were air dried and observed under immersion using × 100 objective under the microscope. The cells were counted and their numbers recorded individually in terms of neutrophils, eosinophils, basophils, lymphocytes and monocytes based on their shapes as documented by Yamada (2012).

Histopathological tests

Histopathological tests on the vital organs such as liver, heart, kidney, spleen and intestine were performed according to the method of Baker et al., (2018) and Cheesbrough (2006) using the following materials: Animal organs (small intestine, liver, heart and kidney), formalin, xylene, alcohol, microtome, Canada balsam, staining jar, slides, glycerine albumin, microscope, eosin, haematoxylin, water bath, digital camera and oven. The analyses mentioned involve the following processes:

Fixation: Fixation of the tissue was done to prevent further enzymatic activity that usually leads to post-mortem autolysis. It also hardens tissue as well as kills microbes and keep the tissue in its original form. The organs of the animals were collected and fixed in 10% buffered formalin.

Trimming: After fixation, the organs were trimmed to about 1-2cm before dehydration.

Dehydration: Dehydration was done by passing the tissue through different concentrations of ethanol. It was done by the use of automatic tissue processor. They were dehydrated in graded percentages (50%, 70%, 80% and 100%) of ethanol for 1 ½ hours each at 30 ± 2ºC.

Clearing: Clearing of dehydrated tissue was done using 100% xylene. The tissues were left for 2 hours to remove any remnant alcohol completely.

Embedding: This was the placing of the cleared tissue in melted paraffin and allowed to harden. The tissues were left in the molten paraffin wax for 2 hours to embed properly.

Sectioning: This was done using a microtome. The tissues were sectioned to about 3-10µ and floated in water bath at 370C.

Hydration: This is the process of passing the tissue through water by passing it through different concentrations of alcohol. It was passed through xylene, 100%, 90%, 80%,70% and 50% of ethanol for 11/2 hours at each concentration.

Staining: This was done using haematoxylin and eosin (H&E) stains. Haematoxylin stains the nucleus blue while eosin stains the cytoplasm acidophilic.

Dehydration, fixing and microscopy of stained slides: Dehydration was repeated by passing the tissue through different concentrations of ethanol. This was carried out with the aid

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of automatic tissue processor. The tissues were dehydrated in different percentage (50%, 70%, 80% and 100%) of ethanol for 1 ½ hours each and cleared with xylene. The method of Singleton (1999) was employed to removing excess stain under running water. Having cleared in xylene, the fixed tissue on a glass slide was fixed with canada balsam and covered with cover slips. The preparations were left in the oven at 40oC and then placed under the photo-microscope for examination (Pagana, 2007).

Results

Percentage recovery of plant extracts for both *A. conyzoides* and *T. procumbens*

The result of the solvent extraction shows that the highest percentage yield was obtained from ethanolic extract of *Tridax procumbens*, whilst the solvent with the lowest percentage yield was obtained from chloroform extract of *T. procumbens*. Furthermore, the colour description and the percentage yield of each extract from the various solvents are described below:

a) Ethanol extracts: The extracts were light brown; it turned dark brown after evaporation of the ethanol. The percentage yields for both plants were 6.40 and 7.48 respectively.

b) Aqueous extracts: The extract had a dark brown colour with semi-solid sediment after evaporation of the solvent. It had 4.48 and 4.08% yields.

c) Chloroform extracts: The chloroform extracts had a milky white colour with strong fermentative smell. It turned dark brown after evaporation. The percentage yield was 3.88 and 5.80 respectively.

d) The effect of the induced diabetes on the glucose level of the rats' blood is shown for the period of three weeks of treatment with the plant extracts as documented in Table 1. The highest therapeutic effect on the induced diabetes was induced by the standard drug administered (0.5ml of reference drugs for diabetes -Melanov) reducing the sugar level of the rats from 222±4 mg/dL to 102±4 mg/dL within the three weeks of treatment. This was closely followed by the effect of the synergistic effect of the two plants' extracts which reduced the sugar level from 223±6 mg/dL to 182±6 mg/dL within the period of treatment.

Table1: The glucose level of experimental rats.

Groups	Week one	Week two	Week 3
A	220±6 mg/dl	212±6 mg/dl	202±9 mg/dl
B	215±5 mg/dl	190±4 mg/dl	172±6 mg/dl
C	223±6 mg/dl	206±2 mg/dl	182±6 mg/dl
D	222±4 mg/dl	153±4 mg/dl	102±6 mg/dl
E	225±3 mg/dl	214±6 mg/dl	210±9 mg/dl
F	90±4 mg/dl	92±5 mg/dl	95±6 mg/dl

Key: a= Group induced and treated with A. conizoides extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both A. conizoides and T. procubens extracts; d= Group induced and treated with drug; e= Group induced and not treated with anything; f= Group not induced and not treated at all.

e) The result of the effect of the induced diabetes on the weight of the experimental rats within the time of the experiment is noted on Table 2 below. The plants extracts were able to cause an increase in the weight of the animal after an initial loss of weight immediately after the induction of the diabetes in the experimental rats with the exception of the group treated with the *T. procumbens* extract. The result showed that the group treated with *T. procumbens* extract did not recover in weight gain till the end of the experiment. The initial weight at the beginning of the experiment for this group was 110.40±2.63g and ended 110.23±1.56g. Comparatively, all the other groups recorded significant increase between the initial weight and final weight. The group induced with diabetes and not treated had the most significant loss of weight starting with an initial weight of 110.18±5.42g in the beginning of the experiment and ended with a weight of 96.41±2.94g.

f) The result of the haematology of the induced experimental rats is depicted in Figure 1 below. Findings reveal that the effect of the induced diabetes on the rats caused a significant increase of the erythrocyte sedimentation rate and white blood cell counts. Conversely, it caused significant decrease in haemoglobin concentration, packed cell volume, platelets and red blood cell count. As a result, the highest significant effect observed on the plants extracts was exerted by the synergistic combination of both *T. procumbens* and *A. conizoides*.

g) Furthermore, the result of the weight of organs directly affected by the induced diabetes which are the brain, heart and the kidney are shown in Figure 2. The diabetes caused a shrinking or reduction in size of the brain and the heart, whilst causing a significant increase in the size of the kidneys in comparison with other organs.

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Table 2: Effect of induced diabetes on the weight of experimental rats.

Groups	Initial weight before induction (g)	Weight in week 1 (g)	Weight in week 2 (g)	Weight in week 3 (g)
A	110.40±2.63	105.15±3.81	108.28±2.17	110.23±1.56
B	134.10±2.18	137.33±3.03	138.41±2.94	139.23±2.60
C	100.50±5.02	105.10±3.48	101.91±1.12	107.82±1.05
D	102.20±3.15	121.15±1.30	124.02±2.65	121.11±2.29
E	110.20±2.24	106.31±2.12	100.41±1.94	96.41±2.94
F	110.18±5.42	118.43±4.05	125.12±2.20	130.84±4.54

Key: a= Group induced and treated with A. conizoides extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both A. conizoides and T. procubens extracts; d= Group induced and treated with drug; e= Group induced and not treated with anything; f= Group not induced and not treated at all.

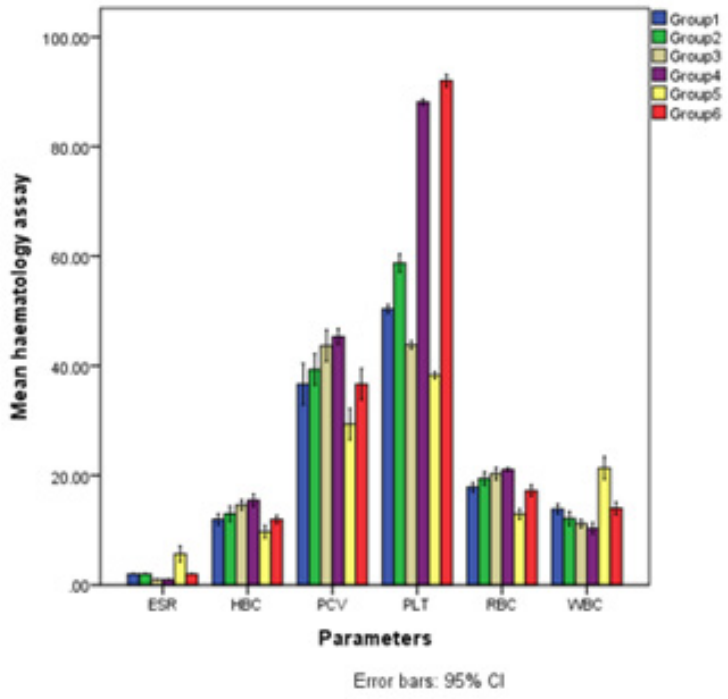

Figure 1: Effect of induced diabetes and treatment with plant extracts on the experimental rats
Key: a= Group induced and treated with A. conizoides extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both A. conizoides and T. procubens extracts; d= Group induced and treated with drug; e= Group induced and not treated with anything;f= Group not induced and not treated at all.

The effect of the induced diabetes and treatment with plants extracts on the gross morphology and histopathology of the brain tissues are shown on Plates 1 (a-f). The resultant effects of the induced diabetes caused trigeminal nucleus with striated cortex and severe hypostatic central congestion. Neocortex with central mesencephalic nuclei infiltrations and abnormal cell architecture with negative pathology due nuclei gatherings. The plant extract caused these pathologies to be reduced into intact cortical sheath with dilated neocortex of the meninges having an increased nucleus number and intact locus coeruleus. The control group had well-formed cortex with dispersed infiltrated vesicular nuclei with their normal cell architecture without negative pathology but nearly amphophilic.

Furthermore, the effect of the induced diabetes and treatment with plants extracts on the gross morphology and histopathology

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of the heart tissues are depicted in Plate 2. It caused heart cardiac striata with profuse haemorrhage and inflammatory cells and congested intra-dilated capillaries causing the heart cardiac tissues to be stressed and over-dilated heart striata having central wobbling with few inflammatory cell infiltrations. The extracts caused these effects to be corrected but lack proper aorta opening network of systolic transport system. These features were significantly different from the control that showed well-formed heart striata revealing few inflammatory cells. Fibrous tissues have long nucleic cell infiltrations without any form of haemorrhage or necrosis. The induced diabetes caused pathological features that include complete washing away and haemorrhagic unformed kidney nephrons with calcium crystal deposits. Administration of the extracts caused recuperative effects that include nephrons with infiltrated cells and gobble structures. There is the presence of visible calcium crystals, long karyolitic intra-nephrotic drainage, inflammatory cells infiltration and immature nephrons. The result is shown in Plate 2 (a-f) & Plate 3 (a-f).

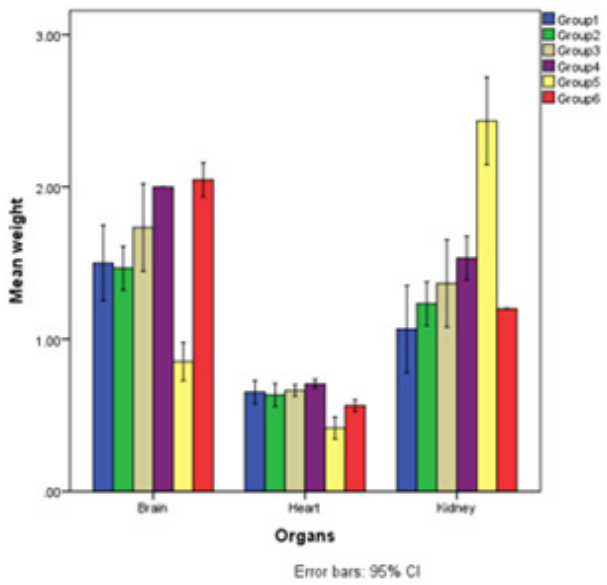

Figure 2: Effect of induced diabetes and treatment with plant extracts on the affected organs weight of experimental rats
Key: a= Group induced and treated with A. conizoides extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both A. conizoides and T. procubens extracts; d= Group induced and treated with drug; e= Group induced and not treated with anything;f= Group not induced and not treated at all.

Discussion

The effect of the induced diabetes on the glucose level of the rats' blood showed that the streptozotocin induced the diabetes in the rats for the period of the three weeks of treatment with the plant extracts. The highest therapeutic effect on the induced diabetes was induced by the standard drug administered (0.5mL of reference drugs for diabetes -Melanov), reducing the sugar level of the rats from 222±4 mg/dL to 102±4 mg/dL within the three weeks of treatment. This was closely followed by the effect of the synergistic effect of the two plants' extracts which reduced the sugar level from 223±6 mg/dL to 182±6 mg/dL within the period of treatment. In accordance with Omoya and Momoh, (2019), extracts that exert this effect has high anti-diabetes properties and is a potential therapy for the disease. Moreover, the effect of the induced diabetes on the weight of the experimental rats within the time of the experiment also showed that the disease causes reduction in weight. The plants extracts were able to cause an increase in the weight of the animal after an initial loss of weight immediately after the induction of the diabetes in the experimental rats which is part of the evidence of its therapeutic properties. This result is similar to the result obtained comparatively with all the other groups which recorded significant increase between the initial weight and final weight. The group induced and not treated with anything had the most significant loss of weight starting at the beginning with an initial weight of 110.18±5.42g and ended with a weight of 96.41±2.94g. The effect of the induced diabetes on the rats caused a significant increase of the erythrocyte sedimentation rate and white blood cell counts. Conversely, it caused significant decrease in haemoglobin concentration, packed cell volume, platelets and red blood cell count. The highest significant effect by all the plants extracts was exerted by synergistic combination of both the *T. procumbens* and *A. conizoides*. This result agrees with the result obtained by Okoye et al., (2014) when they examine the immunomodulatory effects of certain leaf extract. Also, the weight of organs directly affected by the induced diabetes (the brain, heart and the kidney) were deeply affected. The shrinking or reduction in size of the brain and the heart as well as a significant increase in the size of the kidneys of man and animals have been noted to be common according to Gary and David (2014).

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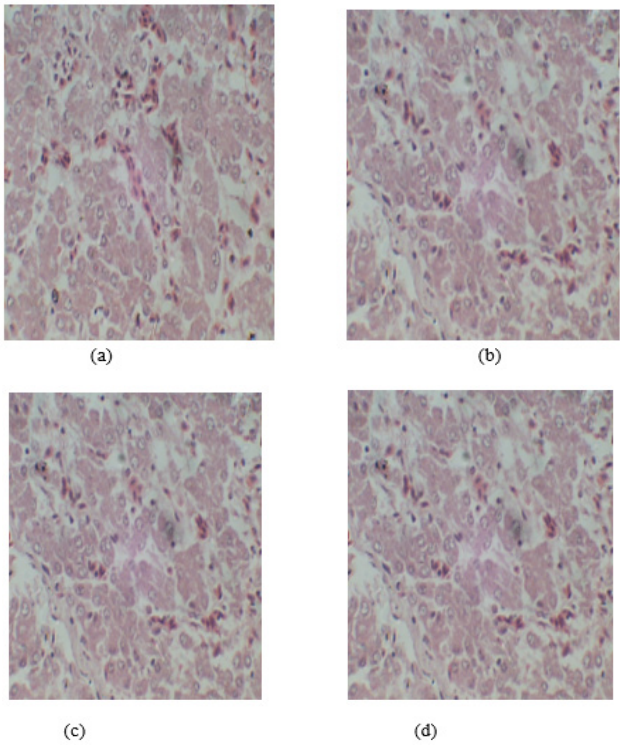
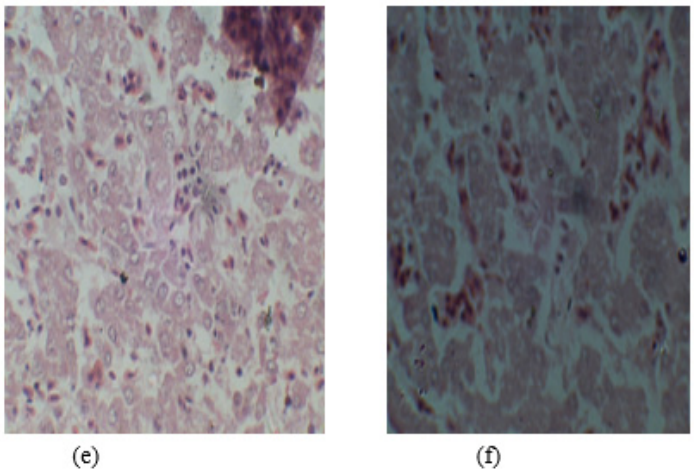


Plate 1:
A- Cortical sheath are intact and neocortex dilated a bit, but with increased nucleus number.
B- Cortical sheath are intact and neocortex are well-formed with intact locus coeruleus.
C- Cortex are well-formed with visible neocortex and nucleus are well-formed in large number.
D- well-formed with visible neocortex and nucleus are well-formed in large number. Normal cell architecture without negative pathology.



E= Trigeminal nucleus with striated cortex and severe hypostatic central congestion. Neocortex with central mesencephalic nuclei infiltrations, Abnormal cell architecture with negative pathology due nuclei gatherings
F= Well-formed cortex with dispersed infiltrated vesicular nuclei. *Normal cell architecture without negative pathology but nearly amphophilic.
Plate 9: Photomicrograph of the brain of rats induced with diabetes.
Key: a= Group induced and treated with A. conizoides extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both A. conizoides and T. procubens extracts; d= Group induced and treated with drug; e= Group induced and not treated with anything;f= Group not induced and not treated at all.

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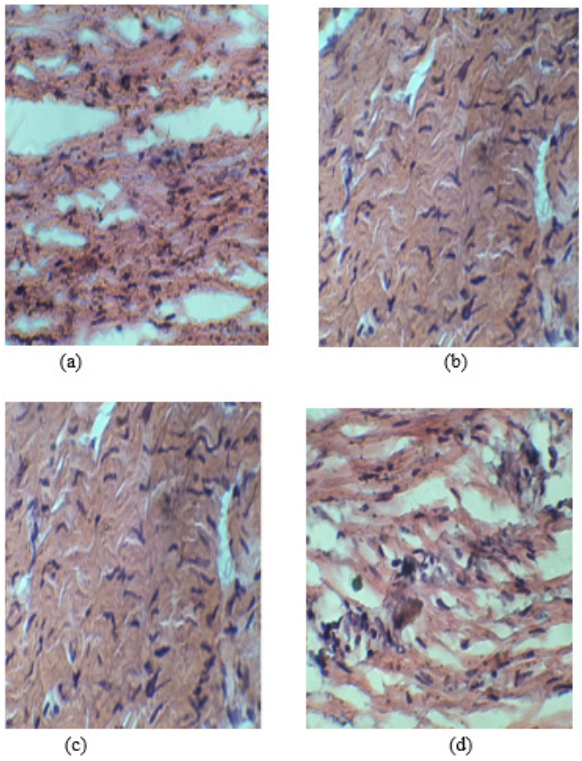
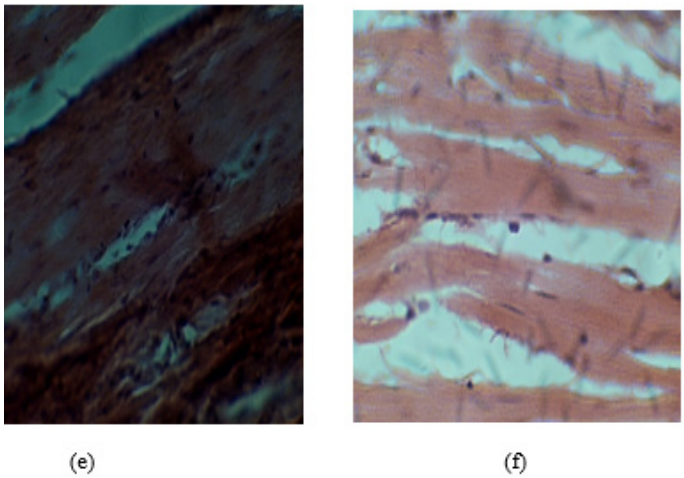


Plate 2:
A= Stressed and over-dilated heart striata having central wobbling with few inflammatory cells infiltrations. There is no haemorrhage or necrosis seen
B= heart cardiac fibres are not over stretched with few anterior and posterior striata. Although, heart is well-formed, striata are not well formed with visible connection for systolic movement of the heart.
C=Well-formed heart cardiac striata but lack proper aorta opening network of systolic transport system.
D= Recuperating heart striata with high cell infiltrations. There is no necrosis or haemorrhage, but shows inflammatory cells infiltration



E= Heart cardiac striata with profuse haemorrhage and inflammatory cells and congested intra-dilated capillaries.
F= Well-formed heart striata showing few inflammatory cells. Fibrous tissues have long nucleic cell infiltrations. There is no haemorrhage or necrosis.
Plate 10: Photomicrograph of the heart of rats induced with diabetes
Key: a= Group induced and treated with A. conizoides extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both A. conizoides and T. procubens extracts; d= Group induced and treated with drug; e= Group induced and not treated with anything; f= Group not induced and not treated at all.

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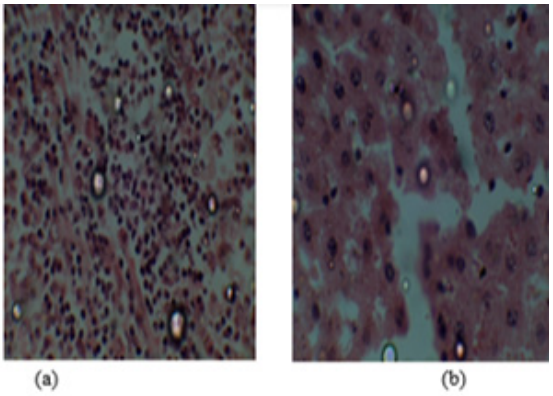
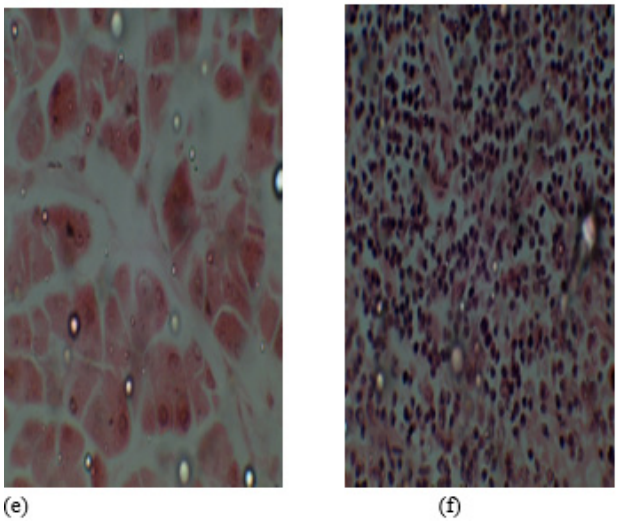


Plate 3: A= Kidney nephrons with infiltrated cells and gobble structures. There is the presence of visible calcium crystals.
(h) B= Kidney nephrons show long karyolitic intra-nephrotic drainage, inflammatory cells infiltration and deposits of calcium crystals.
(i) C= Kidney nephrons are immature with few inflammatory cells and presence of calcium crystals.
(j) D= Kidney nephrons are well-formed with infiltrated cell and few calcium crystals are seen.



(m) E= Completely washed and haemorrhagic unformed kidney nephrons with calcium crystal deposits.
(n) F= Kidney nephrons are well-formed without necrosis or haemorrhage seen. There are few centrally forming calcium deposits.
(o) Plate 11: Photomicrograph of the kidneys of rats induced with diabetes
(p) Key: a= Group induced and treated with A. conizoides extract; b= Group induced and treated with *T. procumbens* extract; c= Group induced and treated with both A. conizoides and T. procubens extracts; d= Group induced and treated with drug; e= Group induced and not treated with anything;f= Group not induced and not treated at all.

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However, the effect of the induced diabetes and treatment with plants extracts on the gross morphology and histopathology of the brain tissues that previously caused trigeminal nucleus with striated cortex and severe hypostatic central congestion as well as neocortex with central mesencephalic nuclei infiltrations leading to abnormal cell architecture with negative pathology due nuclei gatherings was corrected to about 80% by the extracts. The plant extract caused these pathologies to be reduced into intact cortical sheath with dilated neocortex of the meninges having an increased nucleus number and intact locus coeruleus indicating that the extracts, especially the synergistic combination of both plant extracts have a high therapeutic property on the vital organs (Gary and David, 2014). The same effect of the induced diabetes and treatment with plants extracts on the gross morphology and histopathology of the heart tissues was observed and this is similar to the results obtained by Kazemi et al. [12] causing heart cardiac striata with profuse haemorrhage and inflammatory cells and congested intra-dilated capillaries of the heart cardiac tissues to be stressed and over-dilated heart striata having central wobbling with few inflammatory cell infiltrations. The extracts caused these effects to be corrected but lack proper aorta opening network of systolic transport system. These features have also been observed by Yu et al. [13] in a diabetic retinopathy study. These features were significantly different from the control that showed well-formed heart striata showing few inflammatory cells. Fibrous tissues have long nucleic cell infiltrations without any form of haemorrhage or necrosis. Moreover, the induced diabetes caused pathological features that include complete washing away and haemorrhagic unformed kidney nephrons with calcium crystal deposits. Administration of the extracts caused recuperative effects that include nephrons with infiltrated cells and gobble structures. There is the presence of visible calcium crystals, long karyolitic intra-nephrotic drainage, inflammatory cells infiltration and immature nephrons. Generally, the extract was also active on the heart and kidneys based on the definition provided by Stedman Medical Dictionary [14]. Conclusively, the results obtained revealed the synergistic potentials of the two plant extracts providing the best therapeutic efficacy against diabetes. As a result, we hereby recommend further purification of both extracts for managing diabetes, especially in the recuperation of vital organs usually affected by diabetes.

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