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Histomorphorlogical and biochemical evaluation of oral administration of datura metel stramonium on the kidneys of adult male wistar rats

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Abstract---Datura metel stramonium (leaves) extract has traditionally been used to treat swellings, burns, ulcers, asthma and sinus infections. However, report indicate that this plant is a strong poison and has been linked to delirium and acute poisoning, which may result in death. Aim: Histomorphological potentials and biochemical effects of Datura metel stramonium on the kidneys of adult male Wistar rats. Fresh Datura metel leaves were harvested, cleaned, air-dried and crushed into fine powder and cold macerated in 0.5 L of 80% v/v methanol in water for 72 hours and the resultant mixture was filtered using Whatman filter paper (No.1). The filtrate was condensed to dryness in vapour at 40^0C using water bath, yielding 9g (18% w/w) of a semi-solid extract and stored in the refrigerator at 4^0C until use. *Twenty-four*

(24) adult male Wistar rats were divided into four (4) groups of six (6) animals each. Groups 1 (0.2ml of distilled water), 2 (200 mg/kg), 3 (400 mg/kg), and 4 (600 mg/kg) body weight/day had oral administration for twenty-eight (28) days. The Wistar rats were sacrificed by cervical dislocation and kidney tissues were excised for histomorphological and biochemical examinations. Generated data were analyzed using GraphPad Prism version 7 and expressed as Mean ± SEM. Results from the study show haemorrhagic renal cortex, aggregation of inflammatory cells and grossly dilated and degenerated convoluted tubules which may lead to renal failure. Also, the decreased level of bound sialic acid is an indication of increased sialidase activity exposing the kidneys to damage.

Keywords---Datura Metel Stramonium, Nephrotoxicity, Wistar rats.

Introduction

According to World Health Organization, traditional medicine is the sum of all knowledge, skills, and practices based on theories, beliefs, and experiences indigenous to various cultures, whether explicable or not, that are used in the maintenance of health as well as the prevention, diagnosis, improvement, or treatment of physical and mental illness, whether explicable or not (WHO, 2003). Due to rising awareness of natural products, demand for medicinal plants is increasing in both developed and developing nations (Ossai et al., 2021), and herbal medicine is an important aspect of both traditional and modern medical systems (Kirtikar and Basu, 1994).

History has it that plants have widely been in use by the society as a major source of natural medications and its use predate human history (khaton et al., 2012). The medicinal plant "Datura Metel" is an herbaceous plant belonging to the family solanocaese (Damilare et al., 2010), a native to Asia and Africa widely cultivated and naturalised in the tropic and subtropical regions and is distributed worldwide (Imo et al., 2019). The flowers are violet on the outside but whitish on the inside, the fruit is a spiny capsule with a diameter of 1.25 inches, and the seeds contain the most alkaloids compared to the flowers, stem, immature fruits, and leaves (Wannang et al., 2009; Priyanka et al., 2012). There are about 10 species of Datura, the most important of which are Datura anoxia, Datura stramonium, and Dautura metel (Parashuram, 2011).

In Nigeria, Datura metel is found to be growing as a weed in abandoned farmland or in dump-sites. They are commonly called Thorns apple, Devil's weed, Jimson weed or Angels trumpet and it's indigenous names are Myaromuo in Igbo, Zakami in Hausa, Apikan or gegemu in Yoruba, Ukwuani, Okpe, Urhobo and jegemi by the Ogoni people of Rivers State in Nigeria (Imo et al., 2019; Wannang et al., 2009).This plant is one of the most important medicinal herbs used world-wide due to its anti-inflammatory property (Tahiya et al., 2013).The leaves and the seed of datura metel are used for several purpose and several ways ,especially for its phytoactive activities (Arowora et al., 2017). Leaves are used as sedative for patients with mental disorder, hemorrhoid, sore-skin diseases and also for

relieving of asthma, cough, tuberculosis, bronchitis as well as anaesthetics when smoking the dried leaves, root and flowers (Nuga et al, 2008). It has also been investigated that Datural metel seed has hypoglycaemic properties (khaton et al., 2012). Globally, datura metel is considered as a poisonous plant when taken in large doses which can cause delirium, coma, and even death due to its high percentage of alkaloids (Tahiya et al., 2013).

Figure 1: Datura metel leaves in its natural habitat in Obinomba, Ukwuani Local Government Area of Delta State, Nigeria

Datura metel has been utilized for religious visionary reasons all over the world from ancient civilization, and it was also used by witchcraft in medieval Europe (Parashuram, 2011; Priyanka et al., 2012). Shiva, the Hindu god, was known to consume Cannabis and Datura. People still bring the little thorn apple as an offering in Shiva statues at temples during festivals and special days. The leaves are used to make an extract that is taken orally to treat asthma and sinus infections, while the stripped bark is used to treat swellings, burns, and ulcers (Priyanka et al., 2012). The spiny fruit is used to card cotton, among other uses for the fruits and seeds. The base of the calyx is utilized to massage teeth. Fulani youths in Nigeria are given an intoxicant prepared from the seeds to encourage them to participate in the "Sharo contest," or agony of manhood (Wannang et al., 2009).

The aim of this study was to evaluate the histomorphological architecture of the kidneys in adult Wistar rats administered with Datura metel leaves extract

Materials And Methods

Collection of Plant

Fresh leaves of the Datura metel plant were collected from its growing habitat at Obinomba in Ukwuani LGA of Delta State, and scientifically identified by Dr. Ekeke Chimezie of the Department of Plant Science and Biotechnology, University of Port-Harcourt with Herbarium Number: UPH/P/281 and then taken for extraction at the Department of Human Anatomy and Cell Biology, Delta State University, Abraka. Nigeria.

Preparation of Crude Methanolic Extract

The leaves of Datura metel were cleaned, air-dried and crushed into fine powder using a blender. 50 grams of the powdered leaves was weighed (using Mettler weighing balance instrument S/N 754550, Zurich, Switzerland) and dissolved in 500mL of 80 percent v/v methanol for 72 hours. The resulting mixture was then filtered with Whitman filter paper (No.1) and the filtrate concentrated to dryness in vacuo at 40^0C using water bath to give 9 g (18 % w/w) of a dark green semi-solid extract. The semi-solid mixture extract was stored in a refrigerator at 4^0C until use. (Tijani et al., 2015; Ekam et al., 2013; Ojieh et al., 2013).

Experimental Animal

Twenty (20) adult male Wistar rats weighing between 150 and 200 g were procured at the Delta State University's College of Health Sciences Animal House in Abraka, Nigeria. The animals were housed in metabolic cages. Top Feed Food Production in Sapele, Delta State, provided animal feed. They were fed a daily mash diet of animal feed growers, which included protein 17.0%, minimum fat 4.5 percent, minimum calcium 0.96 percent, minimum phosphorus 3.92 percent usable, 2450kcal capacity, and water ad libitum.

Experimental Design

Group 1 (n-5) – Wistar Rats received distilled water within the period of the experiment.

Group 2 (n-5) – Wistar Rats received 200 mg/kg body weight of Datura metel leaves extract

Group 3 (n-5) – Wistar Rats received 400 mg/kg body weight of Datura metel leaves extract

Group 4 (n-5) – Wistar Rats received 600 mg/kg body weight of Datura metel leaves extract.

Sample Collection

After 28 days of oral administration of extract, rats were placed on their dorsal surfaces, a laparotomy was performed to reveal internal organs and the kidneys were harvested for histomorphological and biochemical evaluations.

Histomorphological Study

Preparation of Tissues for Microscopy

Methodology:

The process of preparation of the kidney for histological examination was carried out in stages: fixation, tissue processing, sectioning, mounting and staining (Fischer et al, 2008).

Materials:

10 % formal saline, kidney tissue, absolute alcohol, 95% alcohol, 70% alcohol, xylene, paraffin wax, oven, microtome, slides, borosilicate cover glass, microscope, digital microscope eyepiece.

Methodology:

The process of preparation of the kidneys for histological examination was carried out in stages.

Fixation:

The kidney was carefully removed whole and fixed in 10 % formal saline for 72 hours.

Tissue Processing:

The kidney was cut along the coronal plane and processed using the automated tissue processor.

Sectioning and Mounting:

Sections were cut using the Rotary microtome with size 10 micron. The cut sections were floated on hot water bath, picked and mounted on clean slides for staining.

Staining:

The routine staining technique employed in this preparation was the Haematoxylin and Eosin (H & E).

Photomicrography:

The stained tissue images were captured using Digital Microscope Eyepiece "SCOPETEK" DCM 500, 5.0 megapixel connected to USB 2.0 computer.

Biochemical Analysis: Determination of the Free and Bound sialic acid cleaved.

0.1g of kidney tissue was homogenized with 1 ml of deionized water for determination of both kidney free and bound acid cleaved using the thiobarbituric (TBA) assay according to Aminoff (1961).

Determination of the Free sialic acid levels (cleaved) in Kidneys of Wistar rats

Briefly: 200µl (0.2ml) of homogenized brain tissue was dispensed into each test tube, then 250µl of sodium Periodate was added to each test tube and incubated for 20mins at 37C in water bath. 100µl of Sodium Arsenite solution was added to destroy excess periodate. Then 1 ml of thiobarbituric acid was added to each test

tube and placed in boiling water for 71/2-10 minutes to produce a pink colour. In order to extract sialic acid at the colour face for measurement with Colorimeter, 2ml of acid butanol (concentration of 1: 19, i.e. 1 part conc. HCl and 19 parts of butanol) was added. The test tubes were centrifuged for 5 minutes at 1000 RPM and colorimeter measurement of absorbance was obtained at 549nm.

Determination of the Bound sialic acid levels (cleaved) in kidneys of Wistar rats

Briefly: 200µL (0.2ml) of homogenized brain tissue was dispensed in each test tube, then 200µL (0.2ml) of 0.1NH2SO4 was added and incubated at 80C for 1hr in water bath. 250µL (0.25ml) of Sodium Periodate was then added and incubated for 20 minutes in a water bath at 37^0C, after which 1ml of Thiobabituric Acid was added to each test tube and placed in boiling water for 7½ -10 minutes with subsequent pink color growth. 2ml of acid butanol (concentration of 1: 19, i.e. 1 part conc. HCl and 19 parts of butanol) was added. The test tubes were centrifuged for 5 minutes at 1000 RPM and colorimeter measurement of absorbance was obtained at 549nm

Statistical Analysis

After comparing the values for individual controls for different treatment groups, the results were expressed as mean values with standard error of mean (Mean±SEM). Using Graphpad Prism version 7 software, significant differences between control and experimental groups were examined using the One-way analysis of variance (ANOVA), with p-values of less than 0.05 ($p \leq 0.05$) were considered significant.

Results

Microscopic Examination of Kidney tissues

In group I (control), the renal cortex shows normal histological features. The Bowman's capsule is intact. The glomerulus contains cells with tuft capillaries. The distal and proximal convoluted tubules show normal outline. The proximal convoluted tubules (P) show single cuboidal epithelial cells (circles), with normal cellular structure.

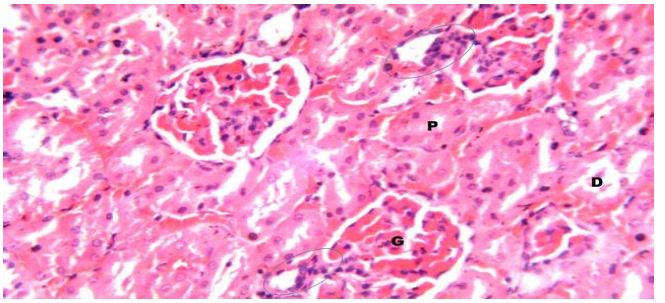

Plate 1: Photomicrograph of coronal section of kidneys of adult Wistar rats. Group I (control) (H & E x250)

In group II that received 200mg of Datura Metel extract orally, the renal cortex shows haemorrhagic areas (H), moderately degenerated glomerular tuft (G) with infiltration of inflammatory cells (circles). The Bowman's spaces are moderately dilated. Both the distal and proximal convoluted tubules are dilated.

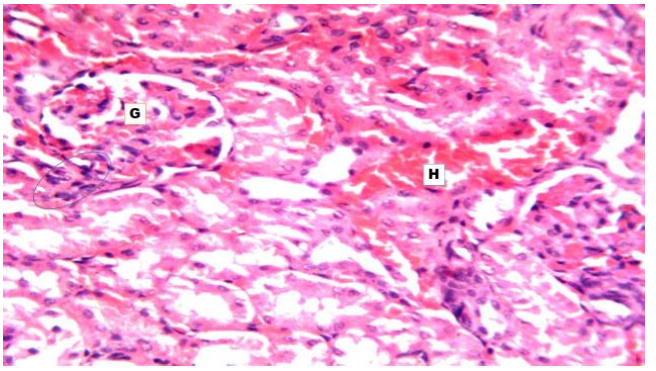

Plate 2: Photomicrograph of coronal section of kidneys of adult Wistar rats. Group II received 200 mg/kgbwt/day of Datura Metel orally. (H & E x250)

Note: G-Glomerulus, H-Haemorrhagic area

Group III, that received 400 mg/kgbwt/day of Datura Metel orally, the renal cortex shows the aggregation of inflammatory cells (circle). The proximal (P) and distal convoluted (C) tubules appear dilated.

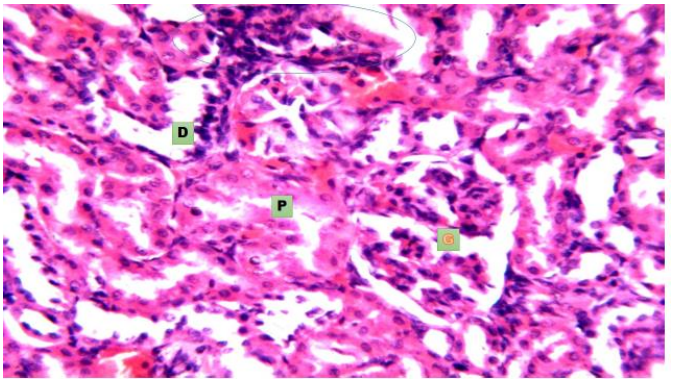

Plate 3: Photomicrograph of coronal section of kidneys of adult Wistar rats. Group III received 400 mg/kgbwt/day of Datura Metel leaves extract orally for 28 days). (H & E x250)

Note: G – Glomerulus, D – Distal convoluted tubule, P – Proximal convoluted tubule, Circle – Inflammatory cells

Group IV that received 600 mg/kgbwt/day of Datura metel leaves extract orally for 28 days show haemorrhagic renal cortex (H). There are aggregation of inflammatory cells surrounding the blood vessels (BV) and grossly dilated and degenerated distal and proximal convoluted tubules (circle).

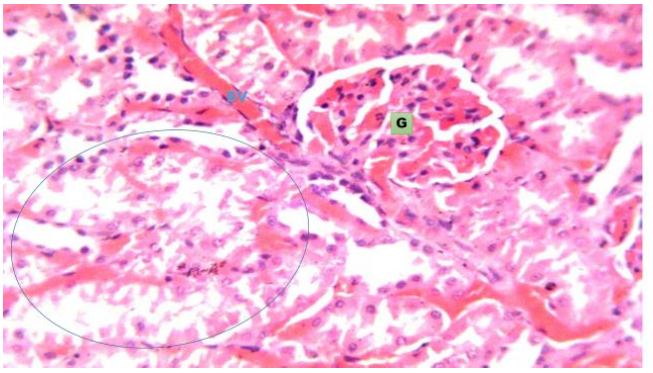

Plate 4: Photomicrograph of coronal section of kidneys of adult Wistar rats. Group IV received 600 mg/kgbwt/day of Datura Metel leaves extract orally for 28 days (H & E x250).

Note: G–Glomerulus, BV–Blood vessel, Circle–Grossly dilated distal and proximal convoluted tubules.

Biochemical Analyses:

Free Sialic Acid level of Kidneys of Wistar rats:

There were significant differences between the experimental groups when compared with the control group. There was a decrease in sialic acid level in group II when compared with the control group I. Thereafter, the levels of sialic acid cleaved steadily increased in groups III and IV.

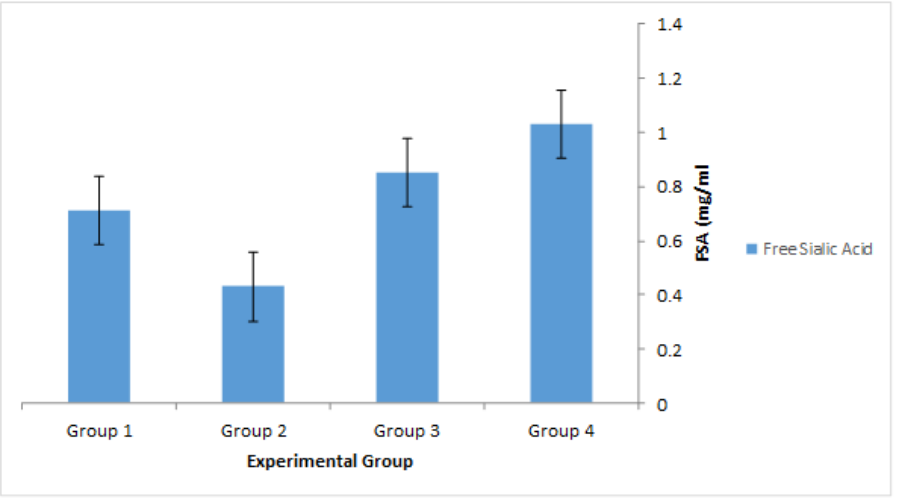

Figure 2: Free Sialic Acid level (cleaved) of Kidneys of Wistar rats post oral administration of Datura Metel leaves extract.

Data are expressed in Mean ± SEM. (n=5). One-way Analysis of Variance (ANOVA) was used followed by Post Hoc (LSD) multiple range tests. P-values of less than 0.05 (P<0.05) are considered statistically significant. **p = 0.019**

KEY: Group 1: Normal Control Untreated rats, Group 2: Wistar rats received

Datura Metel leaves extract (200mg/kg/day), Group 3: Wistar rats received

Datura Metel leaves extract (400mg/kg/day), and Group 4: Wistar rats received

Datura Metel leaves extract (600mg/kg /day).

Bound Sialic Acid levels of Kidneys of Wistar rats:

There were significant differences between the experimental groups and when compared with the control group. There was an increase in bound sialic acid cleaved in group II when compared with the control group I. Thereafter, the levels of sialic acid cleaved steadily decreased in groups III and IV.

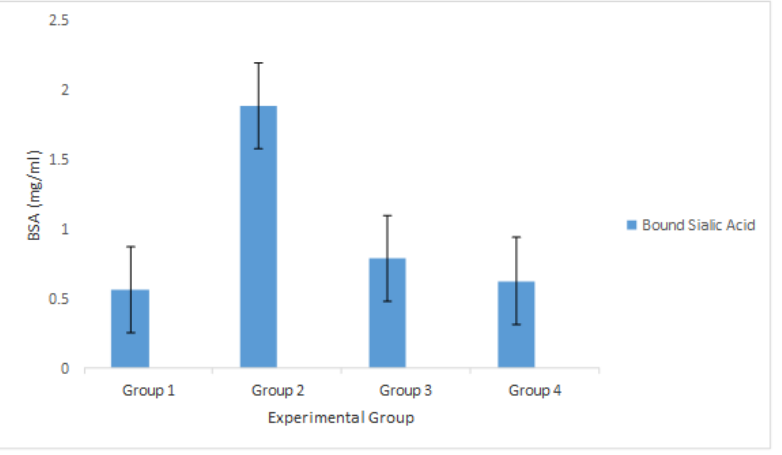

Figure 3: Bound Sialic Acid levels (cleaved) of Kidneys of Wistar rats post oral administration of Datura Metel leaves extract.

Data are expressed in Mean ± SEM. (n=5). One-way Analysis of Variance (ANOVA) was used followed by PostHoc (LSD) multiple range tests. P-values of less than 0.05 (P<0.05) are considered statistically significant. **p = 0.008**

KEY: Group 1: Normal Control Untreated rats, Group 2: Wistar rats received

Datura Metel leaves extract (200mg/kg/day), Group 3: Wistar rats received

Datura Metel leaves extract (400mg/kg/day), and Group 4: Wistar rats received
Datura Metel leaves extract (600mg/kg /day).

Discussion

Many problems in primary health care are caused by a lack of understanding and sensitivity to local health behaviours, as well as the economic and cultural variables that influence these practices (Asif, 2012). However, there is no clear statement of substance or medically relevant information on the package labels of available herbal products, and they have not been validated or certified by any recognized agency. This is concerning for both consumers and medical professionals who may unintentionally prescribe these natural products. These principles underpin the study of ethno-medicinal plants because not all plants considered to be beneficial are harmless (Lans, 2006; Asif, 2012). Herbal remedies for dialysis and chronic renal failure problems, as well as any usage of medicinal herbs, may be inappropriate for renal patients (Zhang, 1989; Wei et al., 1999; Asif, 2012). Because of their pyrrolizidine alkaloid content and hence hepatotoxic potential, various medicinal plants such as borage (Borago officinalis), comfrey (Symphytum spp), coltsfoot (Tussilago farfara), life root (Senecio aureus), and others are therefore adviced to be avoided by dialysis patients (Foote and Cohen, 1998; Asif, 2012). Some therapeutic herbs have been linked to nephrotoxicity and due to abuse of the drug or ignorance of the herb's recommended administration, unfavourable unadulterated herb reactions resulting in noteworthy renal symptoms have been observed (Asif, 2012).

Homeostasis and acid-base balance, management of electrolyte balance in the blood, elimination of metabolic waste products, production of certain enzymes and hormones, metabolism, and osmoregulation are all functions performed by the kidneys (Sembulingam and Sembulingam, 2010). Any change or anomaly in the kidneys could result in the kidney's inability to execute or inefficiency in performing these activities. The values of some kidney function parameters, as well as a histological examination of the organ, can be used to determine problems associated with renal function.

Histomorphological results of this study show that in the group I control rats, the renal cortex shows normal histological features. The Bowman’s capsule is intact. The glomerulus contains cells with tuft capillaries. The distal and proximal convoluted tubules show normal outline. The proximal convoluted tubules (P) show single cuboidal epithelial cells (circles), with normal cellular structure (Plate 1). The group II that received 200mg of Datura Metel orally showed haemorrhagic areas in the renal cortex (H), moderately degenerated glomerular tuft (G) with infiltration of inflammatory cells (circles) and the Bowman’s spaces (Both the distal and proximal convoluted tubules) are moderately dilated.

In group III, that received 400 mg/kgbwt/day of Datura Metel orally, the renal cortex shows aggregation of inflammatory cells (circle). The proximal (P) and distal convoluted (C) tubules appear dilated (Plate 3), whereas, group IV that received 600 mg/kgbwt/day of Datura metel orally shows haemorrhagic renal cortex (H) with aggregation of inflammatory cells surrounding the blood vessels (BV) and grossly dilated and degenerated distal and proximal convoluted tubules (Plate 4). This is consistent with Catteli et al. (1998) findings, which suggest crystal deposition, extension from the lower urinary tract infections (pylonephritis), chronic progressive nephropathy, previous infarction, or direct

chemical administration, all of which are characterized by the presence of inflammatory cells in the tubule lumen, epithelium, or both.

In comparison to the normal control, Datura metel extracts were found to cause glomerular extrusion and glomerular collapse, resulting in increased urinary space, dilated tubules, vacuolations in some epithelial lining of most tubules in the medulla, and inflammatory cellular infiltration at some peritubular regions in histology of the animals which is in agreement with the report of Chukwuma et al. (2019). Some portions of Datura metel have been reported to have modest negative effects, while others have been shown to have nephroprotective potential in male albino rats through modulating kidney function (Chukwuma et al., 2019). In rats, aqueous seed extract and ethanol extract of Datura stramonium, a member of the Datura metel family, were found to produce nephrotoxicity and hepatotoxicity (Gidado et al., 2007; Dubey and Sanjeev, 2017). Accidental poisoning of horses with Datura Metel stramonium resulted in toxic liver dystrophy, dystrophic and necrotic changes in the renal parenchyma and myocardium on necropsy (Binev et al., 2006; Dubey and Sanjeev, 2017), and nephrotoxicity in domestic animals (Oladosu and Case, 1979), but renal failure has not been reported in humans.

Datura metel extract has been recognized as a strong poison, and its indiscriminate use has been linked to delirium and acute poisoning, which can lead to death (Chinedu et al., 2019), and could be as a result of Alkaloids occurring in large amounts, making plants poisonous despite its medicinal effects (Chukwuma et al., 2019).

Sialic acid is a monosaccharide with a nine-carbon backbone and a wide structural variation that is found at the end of numerous glycoprotein and glycolipid oligosaccharide chains (Zhang et al., 2019). They are common monosaccharides that are widely expressed as outer terminal units on cell surfaces and play a key role in all cell-cell and cell-microenvironment interactions (Samraj et al., 2014). In mammalian tissue, the most common sialic acids are N-glycolylacetylneuraminic acid (Neu5Gc) and N-acetylneuraminic acid (Neu5Ac). Due to their terminal location (Stencel-Baerenwald et al., 2014) sialic acid functions as ligands or receptors for cell-cell or host-parasite interaction, enhancing tumor proliferation, metastasis, and promoting tumor angiogenesis (formation of blood vessels from preexisting ones) (Xiaoman et al., 2020), as well as influencing the structure and function of glycoconjugates and as ligands for lectins, antibodies, and enzymes (Bauer et al., 2015).

When compared to the normal control group 1 that received distilled water, in figure 2, there was a significant decrease in the level of free Sialic Acid cleved in the kidneys of group II, thereafter there were increases in the levels of sialic acid in groups III and IV that oral administration of 400mg/kg and 600mg/kg respectively. The decrease in the level of free sialic acid is an indication of activation of sialidase activity. Whereas, the increased levels are an indication of inhibition of sialidase activity. There was a significant increase in bound Sialic Acid level in the kidneys of group 2 that had oral administration of 200mg/kg body weight per day when compared with the control group I. There were statistically significant decreases in the level of sialic acid in groups III and IV

when compared with group II. The observed levels of the decrease of sialic acid levels in groups III and IV are an indication of significant activation of sialidase activity. This is the first report to the best of our knowledge in connection with Datura Metel stramonium toxicity. The resulting effect is the damage observed histologically in the kidneys (haemorrhagic renal cortex, aggregation of inflammatory cells surrounding the blood vessels and grossly dilated and degenerated distal and proximal convoluted tubules which may lead to renal failure).

The use of herbs in conjunction with therapeutic medications increases the risk of herb-drug interactions. Herb-drug interactions are clinically significant depending on the herb, medicine, and patient profile (Nudrat and Naira, 2016). Herbs are potentially potent since they impact physiological functions; therefore, using herbal medicine and supplements without first consulting the Food and Drug Administrators can be dangerous.

Alkaloids found in large amounts in Datura Metel may be responsible for the plant's poisonous nature and negative effect on the kidney's histo-architecture despite its medicinal effects, according to a report that agrees with that of Allard et al. (2013). Toxic herbs contain large amounts of alkaloid and diterpenoid epoxide, which may induce apoptosis causing kidney damage (Nudrat and Naira, 2016; Chukwuma et al., 2019).

Conclusion

The findings of this study show that Datura metel leaves extract causes changes in the kidney tissues' histomorphological structure. Despite its therapeutic value, it causes aggregation of inflammatory cellular infiltration at some peritubular sites and renal cortex dilation (dilation of the tubules and Bowman's capsule). Datura metel is being abused most especially amongst youth, despite the fact that it has negative effects and that some parts (in specific concentrations) could regulate the kidney function of male Wistar rats; this calls for caution in the use of this plant parts and suggests that the use of this plant parts should be based strictly on pharmacological need.

Recommendations

The use of Datura metel parts should be based solely on pharmacological need, and we are in the process (second phase) of conducting a phytochemical screening to identify the constituents of the leaves and chemicals responsible for the negative effects on kidney functions and structures, as well as to educate the public about the issue in order to prevent further damage to the renal system.

Ethical Consideration

The protocol of the experiments in this study was examined and approved by the Research, Ethics Committee of the Department of Human Anatomy and Cell Biology, Delta State University, Abraka, Nigeria with reference number DELSU/CHS/ANA/2020/56. This research was performed in accordance with

the ethical standards on the care and use of animals as laid down (Helsinki, 1964).

Competing Interests Disclaimer:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was funded by personal efforts of the authors.

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