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(RESEARCH ARTICLE)

Ameliorating effect of ethanolic leaf extract of *Carica papaya* (PAWPAW) on the histology of the kidney of methamphetamine-induced rats

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Abstract

Objective: This research study was carried out to investigate the effect of ethanolic leaf extract of *Carica papaya* on the histology of kidney of methamphetamine-induced rats.

Methodology: Twenty-five (25) male wistar rats weighing 120 g to 150 g were procured and acclimatized for two weeks, after which, they were divided into five (5) groups of five (5) rats each, and were housed in cages. The groups were designated as groups A - E. Group A served as the control group and was not induced with methamphetamine, while Groups B – E were induced. Group A received distilled water only, Groups B - E received Methamphetamine only, 100 mg/kg of body weight of ethanolic leaf extract of *Carica papaya*, 200 mg/kg of body weight of ethanolic leaf extract of *Carica papaya*, and 300 mg/kg of body weight of ethanolic extract of *Carica papaya* respectively for 14 days through oral route with the aid of oral gastric tube. On the 15th day, the animals were weighed and sacrificed via chloroform inhalation, and kidneys were harvested from the rats for histological study.

Results: Histopathological findings showed renal tissue with mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and tubular atrophy (TA) for animals in group A, moderate degeneration with moderate fatty changes (FC), moderate intra renal hemorrhage (IRH), and moderate renal inflammation (IRI) for animals in group B, mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and tubular atrophy (TA) for animals in group C, mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and infiltration of inflammatory cell (IIC) for animals in group D, and moderate healing with mild fatty changes (FC) and infiltration of inflammatory cell (IIC) for animals in group E.

Conclusion: Ethanolic leaf extracts of *Carica papaya* have ameliorating effect on the histology on the kidney of methamphetamine-induced rats, and the ameliorating effect improves with increase in the dosages of the extract.

Keywords: Kidney disease; Methamphetamine; Kidney; *Carica papaya*

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1. Introduction

Kidney disease affects approximately 37 million American adults [1]. It occurs when kidneys become damaged and cannot perform their function. Damage may be caused by diabetes, high blood pressure, and various other long-term (chronic) conditions, and may lead to other health problems, including weak bones, nerve damage, and malnutrition [1]. Kidney disease or renal disease technically referred to as nephropathy, is damage to or disease of a kidney which usually causes a loss of kidney function to some degree and can result in kidney failure or the complete loss of kidney function [1]. Chronic kidney disease is as prolonged kidney abnormalities (functional and/or structural in nature) that last for more than three months [2], while acute kidney disease (acute kidney injury) is marked by the sudden reduction in kidney function over seven days [1]. Kidney failure is the end-stage of kidney disease, where dialysis or a kidney transplant is the only treatment option.

According to the World Health Organization, kidney diseases have risen from the world's nineteenth leading cause of death to the ninth, with the number of deaths increasing by 95% between 2000 and 2021 [3]. In the United States, prevalence has risen from about one in eight in 2007 [4], to one in seven in 2021 [5]. Its causes include deposition of the Immunoglobulin A antibodies in the glomerulus, administration of analgesics, xanthine oxidase deficiency, toxicity of chemotherapy agents, and a long-term exposure to lead or its salts [6]. Chronic conditions that can produce nephropathy include systemic lupus erythematosus, diabetes mellitus and high blood pressure (hypertension), which lead to diabetic nephropathy and hypertensive nephropathy, respectively [1].

Methamphetamine (contracted from N-methylamphetamine) [7] is a potent central nervous system (CNS) stimulant that is mainly used as a recreational or performance-enhancing drug and less commonly as a second-line treatment for attention deficit hyperactivity disorder (ADHD) [8]. Research has shown it to be a potential drug for the treatment of traumatic brain injury [9]. It was discovered in 1893 and exists as two enantiomers: levo-methamphetamine and dextro-methamphetamine [7]. Methamphetamine is rarely prescribed over concerns involving its potential for recreational use as an aphrodisiac and euphoriant, among other concerns, as well as the availability of safer substitute drugs with comparable treatment efficacy such as Adderall and Vyvanse [8]. In low to moderate doses, methamphetamine can elevate mood, increase alertness, concentration and energy in fatigued individuals, reduce appetite, and promote weight loss [7]. At very high doses, it can induce psychosis, breakdown of skeletal muscle, seizures, and bleeding in the brain [7]. Chronic high-dose use can precipitate unpredictable and rapid mood swings, stimulant psychosis (e.g., paranoia, hallucinations, delirium, and delusions), and violent behavior [7]. Recreationally, methamphetamine's ability to increase energy has been reported to lift mood and increase sexual desire to such an extent that users are able to engage in sexual activity continuously for several days while binging the drug [9, 7].

It is known to possess a high addiction liability (i.e., a high likelihood that long-term or high dose use will lead to compulsive drug use) and high dependence liability (i.e., a high likelihood that withdrawal symptoms will occur when methamphetamine use ceases) [7]. Discontinuing methamphetamine after heavy use may lead to a post-acute-withdrawal syndrome, which can persist for months beyond the typical withdrawal period [7]. At high doses, methamphetamine is neurotoxic to human midbrain dopaminergic neurons and, to a lesser extent, serotonergic neurons [10, 11]. Its neurotoxicity causes adverse changes in brain structure and function, such as reductions in grey matter volume in several brain regions, as well as adverse changes in markers of metabolic integrity [11]. Also, its use may results to immediate negative health effects such as paranoia, anxiety, rapid heart rate, irregular heartbeat, stroke, increased blood pressure, kidney damage, nonfatal overdose (also called "overamping"), or fatal overdose [12, 13, 14, 15, 16]. According to Mooney et al, [17], medical effects methamphetamine use include cerebral stroke, hemorrhage, psychoses, seizures; in heart these include myocardial infarction, arrhythmias, cardiomyopathy and ventricular hypertrophy; in lung these include pulmonary edema and hypertension; and in kidneys it includes acute renal failure.

The kidneys are bilateral bean-shaped organs, reddish-brown in colour and located in the posterior abdomen [18]. Their main functions are to filter and excrete waste products from the blood, and are also responsible for water and electrolyte balance in the body. Metabolic waste and excess electrolytes are excreted by the kidneys to form urine which is transported from the kidneys to the bladder by the ureters and leaves the body via the urethra, which opens out into the perineum in the female and passes through the penis in the male. Kidneys lie retroperitoneally in the abdomen, and on either side of the vertebral column [18]. They typically extend from T12 to L3, although the right kidney is often situated slightly lower due to the presence of the liver. Each kidney is approximately three vertebrae in length. The kidneys are encased in complex layers of fascia and fat, and are arranged as follows (deep to superficial): - renal capsule, perirenal fat, renal fascia and pararenal fat. Internally, the kidneys have an intricate and unique structure. The renal parenchyma can be divided into two main areas – the outer cortex and inner medulla [18]. The cortex extends into the medulla, dividing it into triangular shapes known as renal pyramids. The apex of a renal pyramid is called a renal papilla. Each renal papilla is associated with a structure known as the minor calyx, which collects urine from the pyramids.

Several minor calices merge to form a major calyx. Urine passes through the major calices into the renal pelvis, a flattened and funnel-shaped structure. From the renal pelvis, urine drains into the ureter, which transports it to the bladder for storage.

The medial margin of each kidney is marked by a deep fissure, known as the renal hilum which acts as a gateway to the kidney – normally the renal vessels and ureter enter/exit the kidney via this structure. The kidneys are supplied with blood via the renal arteries, which arise directly from the abdominal aorta, immediately distal to the origin of the superior mesenteric artery. The renal artery enters the kidney via the renal hilum. At the hilum level, the renal artery forms an anterior and a posterior division, which carry 75% and 25% of the blood supply to the kidney, respectively [18]. The kidneys are drained of venous blood by the left and right renal veins which leave the renal hilum anteriorly to the renal arteries, and empty directly into the inferior vena cava [18]. Lymph from the kidney drains into the lateral aortic (or para-aortic) lymph nodes, which are located at the origin of the renal arteries [18]. The nephron is the functional unit of the kidney [19]. Each nephron consists of one renal corpuscle and its associated tubule. The kidney as a whole consists of many nephrons (millions) with their associated blood vessels. The renal corpuscles are the sites where the process of urine formation begins with a filtrate of blood plasma. Each renal corpuscle consists of an epithelial cup called Bowman's capsule enclosing a knot of capillaries called the glomerulus [19].

Carica papaya (pawpaw) is one the plant species of the 21 accepted species in the genus *Carica* of the family *Caricaceae* [20]. It is a small, sparsely branched tree, usually with a single stem growing from 5 to 10 m (16 to 33 ft) tall, with spirally arranged leaves confined to the top of the trunk [21]. Its lower trunk is conspicuously scarred where leaves and fruit were borne [21], while, its leaves are large, 50–70 cm (20–28 in) in diameter, deeply palmately lobed, with seven lobes. Its fruit is known as pawpaw. It was first domesticated in Mesoamerica, within modern-day southern Mexico and Central America [22, 23] and is grown in several countries in regions with a tropical climate. In 2022, India produced 38% of the world's supply of papayas [21].

C. papaya is a powerhouse of nutrients that is rich in threes source of powerful antioxidant vitamin C, vitamin A and vitamin E; the minerals, magnesium and potassium; the B vitamin pantothenic acid and folate and fiber and is available all through the year [24]. In addition to all this, it contains digestive enzyme-papaintha which effectively treats causes of trauma, allergies and sports injuries [24]. According to Aravind *et al*, [24], all the nutrients of papaya as a whole improve cardiovascular system, protect against heart diseases, heart attacks, strokes and prevent colon cancer. Its fruit is an excellent source of beta carotene that prevents damage caused by free radicals that may cause some forms of cancer, and it has been reported that it helps in the prevention of diabetic heart disease [24]. *C. papaya* lowers high cholesterol levels as it is a good source of fiber [24].

Its leaf contains active components such as alkaloids, glycosides, tannins, saponins, and flavonoids, which are responsible for its medicinal activity and its leaf juice increases platelet counts in people suffering from dengue fever [25]. *C. papaya* represents a promising natural source of antiviral agents due to its rich reservoir of bioactive secondary metabolites, including flavonoids, phenolic compounds, alkaloids, and proteolytic enzymes [26]. These secondary metabolites offer immense therapeutic potential, and the understanding of their dual roles in both healing and harm is critical for their effective utilization in medical science, leading to innovative treatments for some of the most challenging diseases as these compounds exhibit multifaceted antiviral mechanisms, such as inhibiting viral replication, blocking viral entry, modulating host immunity, mitigating inflammation, minimizing the risk of resistance development, and being used as adjunct therapies [26]. Its leaf extract possess potent antimicrobial, antiviral, anticancer, hypoglycaemic, and anti-inflammatory effects [27]. Also, the leaf extract mediates several benefits related to dengue prevention by boosting platelet count, lowering oxidative stress, and regulating immunological response [28]. Lastly, *C. papaya* leaf extract can been used to treat various illnesses such as dengue (a viral disease), fever, asthma, colic, beriberi, and jaundice [25]. In traditional medicine, it can also been used as a therapeutic agent due to its wound healing, anti-cancer, hypolipidemic and hypoglycemic properties [25]; and for the treatment of digestive disorders, arthritis, ringworm, and hypertension [29].

Because kidney disease can have serious consequences if it is not being controlled effectively, and its progression is from mild to serious, then later kidney failure, it therefore becomes necessary to investigate on medicinal plants that will be easily accessed in the developing world where most people do not have access to synthetic drugs for renal diseases due to lack or insufficient fund. Therefore, this study will help to educate the public on the ameliorating effect of ethanolic extract of *Carica papaya* on the histology of kidney of methamphetamine-induced rats thereby encourages its consumption especially by patients who are suffering from kidney diseases.

2. Material and methods

2.1. Animal procurement, care and treatment

Twenty-five (25) male wistar rats weighing between 120 g to150 g were procured and housed at the Animal house of Anatomy Department, Abia State University; Uturu with wire gauze cages in a well-ventilated area, were maintained under standard laboratory conditions of temperature (22+2 ℃), relative humidity (55-65 %) and 12 hours light/dark cycle. They were fed with standard commercial pellet diet and water *ad libitum* and were also acclimatized for two weeks before the experiment. Their health statuses were closely monitored before and during the experiment. All procedures were carried out in strict accordance with the Institutional guidelines on the care and use of experimental animals.

2.2. Collection, identification and preparation of plant material

Carica papaya leaves were purchased from a local market in Uturu in Abia State, and were authenticated at Herbarium unit, Botany Department, Abia State University, Uturu, Abia State with the Herbarium number ABSU/ANA/HERB/25/002. The *Carica papaya* leaves were washed peeled and crushed using laboratory blender to obtain fresh juice. Extractions were done using ethanol. The crude ethanol extracts were kept in an air-tight container and stored in a refrigerator at 4 0C until time of use. At the time of use, the ethanol extracts were filtered into a stainless basin with a white cloth and placed in a water bath so as to dry up the ethanol. 250 mg of these extracts /kg body weights were dissolved in 10 mls of distilled water and were administered to the animals.

2.3. Induction of Methamphetamine

Methamphetamine was purchased at pharmaceutical shop at Ariaria Market Aba, Abia State, Nigeria. The rats were administered with 0.5 mls of Methamphetamine dissolved in normal saline, at 10 mg/kg body weight, intraperitoneally for 14 days [30] since the lethal dose (LD_{50}) for methanmphetamine with intraperitoneal (ip) administration is calculated to be 55 and 57 mg/kg, in rat and mouse, respectively [31, 32].

2.4. Experimental protocol

The animals were grouped into five (5) groups of five (5) rats each. Different doses of the ethanolic leaf extracts of *C. papaya* were administered via oral route with the aid of oral gastric tube as shown below:

- Group A: The control group + distilled water.
- Group B: Methamphetamine only.
- Group C: Methamphetamine + 100 mg/kg of body weight of ethanolic leaf extract of *Carica papaya*.
- Group D: Methamphetamine + 200 mg/kg of body weight of ethanolic leaf extract of *Carica papaya*.
- Group E: Methamphetamine + 300 mg/kg of body weight of ethanolic extract of *Carica papaya*.

2.5. Sample collection and analysis

The extracts were administered for fourteen (14) days. On the 15th day, the animals were sacrificed by anaestethizing under chloroform vapour and dissected. Kidneys were harvested from the rats, weighed, and fixed in Bouin's fluid for histological analyses.

3. Results

3.1. Histopathological findings

The histopathological findings of this research work reveals as follows: -

Micrograph 1 is the result of is the result of the histology of the kidneys (x400) (H/E) of the animals of group A (GPA) control section showing normal renal architecture with glomeruli (G), bowman space (BS), renal tubules (RT) with distended tubular cell (TC).

Micrograph 2 is the result of the histology of the Kidneys (x400) (H/E) of the animals in group B (GPB) induced with methamphetamine and without treatment showing moderate degeneration with moderate fatty changes (FC), moderate intra renal hemorrhage (IRH) and moderate renal inflammation (IRI).

Micrograph 3 is a photomicrograph of group C (GPC) section of kidneys (x400) (H/E) induced with methamphetamine and treated with 100 mg/kg extract showing mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and tubular atrophy (TA).

Micrograph 4 is a photomicrograph of group D (GPD) section of kidneys (x400) (H/E) induced with methamphetamine and treated with 200 mg/kg extract showing mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and infiltration of inflammatory cell (IIC).

Micrograph 5 is a photomicrograph of group E (GPE) section of kidney (x400) (H/E) induced with methamphetamine and treated with 300 mg/kg extract showing moderate healing with mild fatty changes (FC) and infiltration of inflammatory cell (IIC).

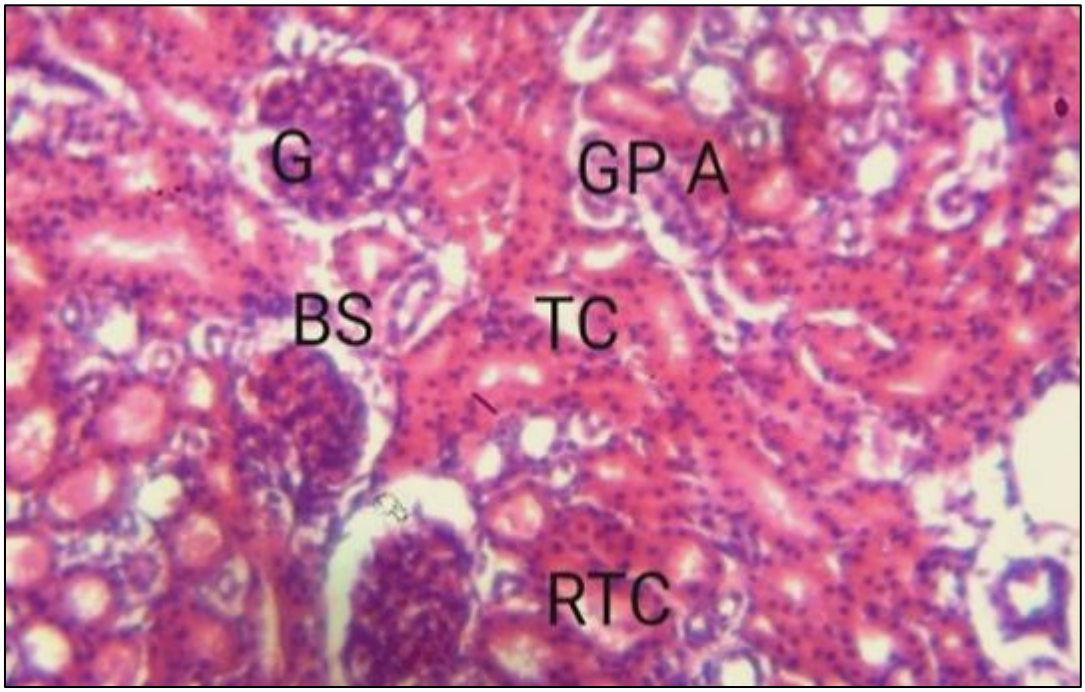

Figure 1 Micrograph 1 is showing normal renal architecture with glomeruli (G), bowman space (BS), and renal tubules (RT) with distended tubular cell (TC)

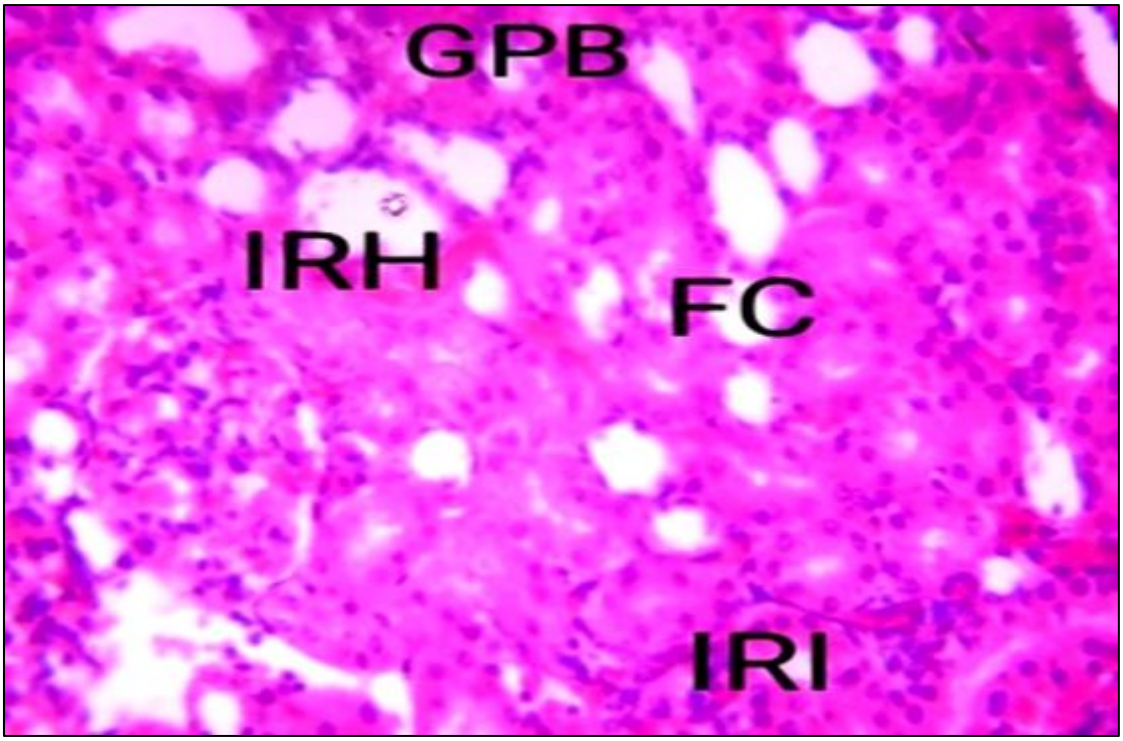

Figure 2 Micrograph 2 is showing moderate degeneration with moderate fatty changes (FC), moderate intra renal hemorrhage (IRH), and moderate renal inflammation (IRI)

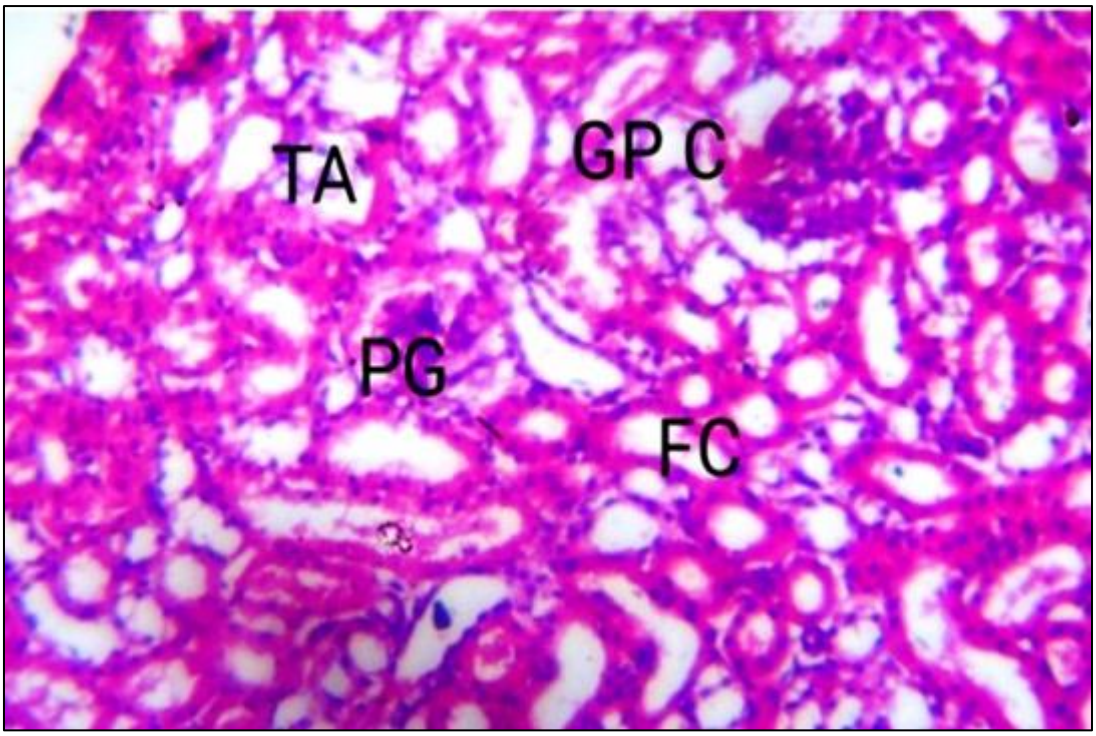

Figure 3 Micrograph 3 is showing mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and tubular atrophy (TA)

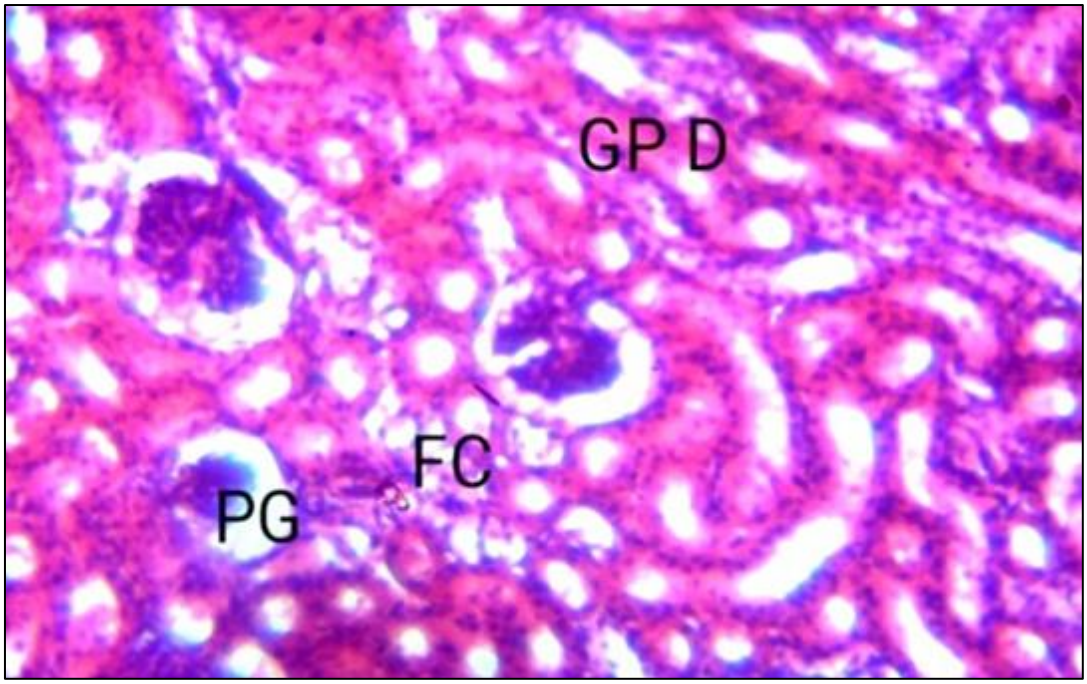

Figure 4 Micrograph 4 is showing mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and infiltration of inflammatory cell (IIC)

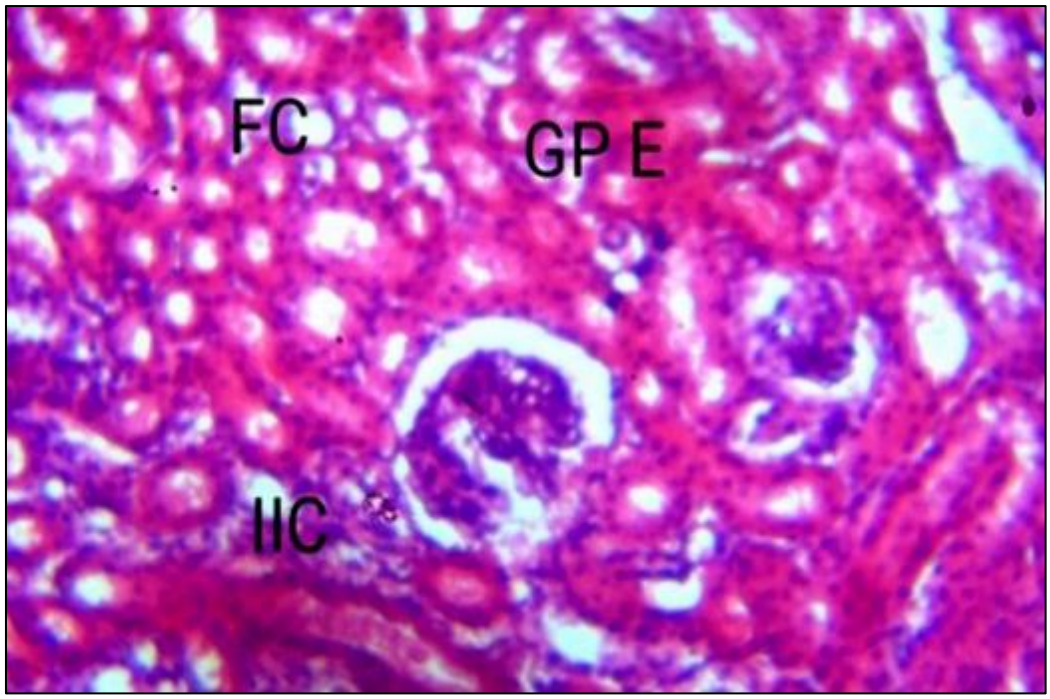

Figure 5 Micrograph 5 is showing moderate healing with mild fatty changes (FC) and infiltration of inflammatory cell (IIC)

4. Discussion

Methamphetamine is an extremely powerful stimulant, which can be smoked, injected, snorted, or eaten to produces a rapid and intense high that's brief enough to keep users coming back for more, thus, resulting to a strong addiction and days-long binges, thus, encouraging the development of tolerance that makes methamphetamine users require more

and more of the drug over time. This highly addictive drug also poses a heavy risk of damaging one's health in a variety of ways. Its effects can impact several crucial organ systems and cause long-term harm to the body as methamphetamine users face an elevated risk of heart disease, stroke, liver damage, immune suppression, and even Parkinson's disease [33]. Thus, the aim of this research study is to investigate the ameliorating effect of ethanolic leaf extract of *C. papaya* on the kidney of methamphetamine induced rats.

The histopathological finding of this present study of the kidney of the animals in group A (GPA) (x400) (H/E) of Micrograph 1 (figure 1) showed normal renal architecture with glomeruli (G), bowman space (BS), renal tubules (RT) with distended tubular cell (TC). This is in line with the normal structure of a nephron which is the functional unit of the kidney which consists of one renal corpuscle and its associated tubule [19].

While, the histopathological result of the histology of the kidneys of the animals in group B (GPB) induced with methamphetamine only (x400) (H/E) of Micrograph 2 (figure 2) showed moderate degeneration with moderate fatty changes (FC), moderate intra renal hemorrhage (IRH), and moderate renal inflammation (IRI). This could be due to the toxins present in methamphetamine, as study has shown that toxins in methamphetamine which are secreted throughout the body exacerbates the damage done to the brain, skin, internal organs and immune system [34]. Also it has been shown that blood vessel constriction caused by methamphetamine use can cut off blood flow to the bowel, potentially leading to the death [33].

The result of the histology of the kidneys of the animals in group C (GPC) induced with methamphetamine (x400) (H/E) and treated with 100 mg/kg of body weight of ethanolic leaf extract of *C. papaya* of micrograph 3 (figure 3) showed mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and tubular atrophy (TA); in micrograph 4 (figure 4) the result of the histology of the kidneys of the animals in group D (GPD) induced with methamphetamine (x400) (H/E) and treated with 200 mg/kg of body weight of ethanolic leaf extract of *C. papaya* showed mild healing with moderate fatty changes (FC), pyknotic glomeruli (PG) and infiltration of inflammatory cell (IIC); while that of micrograph 5 (figure 5) induced with methamphetamine (x400) (H/E) and treated with 300 mg/kg of body weight of ethanol leaf extract of *C. papaya* showed moderate healing with mild fatty changes (FC) and infiltration of inflammatory cell (IIC). These positive results could be due to the ameliorating effect of *C. papaya* which increases with the increase in the leaf extract dosages. This could be due to the ability of the ethanolic leaf extract of *C. papaya* to detoxify the toxins present in methamphetamine thereby reducing markers of oxidative stress that could have caused the damages in micrograph 2 (figure 2) that received not the leaf extract at all.

5. Conclusion

Therefore, the ethanolic leaf extracts of *Carica papaya* have ameliorating effect on the histology of methamphetamine-induced kidneys of male wistar rats, and the ameliorating effect is dose-dependent, and improves better with increase in dosages of the extract.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

Statement of ethical approval

This research work was approved by the Ethical Approval Committee, Faculty of Basic Medical Sciences, Abia State University, Uturu, Abia State, Nigeria.

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