Amitriptyline induced alterations in liver and kidney functions and structures in male rats

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ABSTRACT

Aims: Depression is a mental health issue that starts most often in early adulthood and it is a common and recurrent disorder causing significant morbidity and mortality worldwide. Amitriptyline is a tricyclic antidepressant that is known to inhibit the presynaptic reuptake of serotonin, norepinephrine, and inhibitor of mitochondrial functions and induces apoptosis in several tissues. This study aims to identify the changes in liver and kidney structure and functions after treatment of male rats with Amitriptyline drugs.

Materials and Methods: A total of 20 male albino rats were randomly and equally divided into 2 groups (G1, control group that included animals that did not receive any treatment during the experimental period. G2, Amitriptyline (Tryptizol; El Kahira Pharm And Chem Ind Co) group in which rats were injected intraperitoneally with Amitriptyline (100 mg/kg body weight/daily) for four weeks).

Results: The current results revealed that; Amitriptyline treatments significantly (P <0.05) increased the levels of serum ALT, AST, ALP, urea, creatinine, sodium ions, chloride ions and liver and kidney damages as compared to control. In contrast; a significant (P <0.05) decrease in albumin, and total protein, potassium ions and calcium ions in Amitriptyline group was reported when compared with control group.

Conclusion: Amitriptyline has many side effects on rat liver and kidney, it induced liver and kidney toxicity and tissue injury were it metabolized to nortriptyline which inhibits the reuptake of norepinephrine and serotonin almost equally. Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons.

Key words: Amitriptyline**,** Antidepression**,** liver and kidney, Rats.

1. INTRODUCTION

Depression is a mental health issue that starts most often in early adulthood and is a common and recurrent disorder causing significant morbidity and mortality worldwide [1]. Antidepressant drugs are used to treat depression by balancing certain chemicals in brain called neurotransmitters [2-4].

Tricyclic antidepressants (TCAs) are a class of antidepressant drugs associated with sedation, dry mouth, blurred vision, constipation, urinary retention, and increased pressure in the eye. They are also associated with hypertension, abnormal heart rhythms, anxiety,

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insomnia, seizures, headache, rash, nausea, and vomiting, abdominal cramps, weight loss, and sexual dysfunction [5-7]. Amtriptyline is a tricyclic antidepressant (TCA) that is known to inhibit the presynaptic reuptake of serotonin (5-HT) and norepinephrine (NE) and thus increase the concentrations of both neurotransmitters at the synaptic cleft used to treat a number of mental illnesses including major depressive and anxiety disoders, and less commonly deficit hyperactivity disorder [8,9]. Amitriptyline was found to be an inhibitor of mitochondrial functions and it induced oxidative stress and apoptosis in several tissues, including brain, in a dose-dependent manner [10]. Therefore; the current study aimed to study the effect of treatment with amitriptyline on liver and kidney structure and functions in male rats.

2. MATERIAL AND METHODS

The animal house of the College of Sciences at Tanta University in Tanta, Egypt, provided 6 albino rats for the experiments, with a weight of 110-130 g and age of 9-10 weeks. The rats were kept in cages in suitable environmental conditions (22-24°C, 12-hour light/dark cycle) and were put on a diet of commercial pellet, without water restrictions. Animal maintenance and treatments were conducted in accordance with the Faculty of Science, Tanta University guide for animal, as approved by Institutional Animal Care and Use Committee (IACUC-SCI-TU-0050).

The experiments were initiated 14 days after the animals were procured acclimatized to allow them to become accustomed to the laboratory setting.

2.1. Experimental design and animal groups:

A total of 20 male rats were equally divided into 2 groups.

G1, Control group included animals that received no treatment.

G2, Amitriptyline group included animals that received Amitriptyline orally by Stomach tube with a dose of 100 mg/Kg body weight daily for four weeks according to Tousson et al. [9].

At the end of the experimental period, rats were euthanized with intraperitoneal injection of sodium pentobarbital and subjected to a complete necropsy. Blood samples were individually collected from the inferior vena cava of each rat in non-heparinized glass tubes for estimation of liver and kidney functions biomarkers [11]. Blood samples were incubated at room temperature for 10 minutes and left to clot then centrifuged at 3000 r.p.m for 15 min and the sera was separated and kept in clean stopper plastic vial at –80°C for analysis of serum parameters.

2.2. Liver function Biomarkers:

Serum aspartate transaminase (AST) and alanine transaminase (ALT) were estimated in the rat sera according to Moustafa et al. [12] and Al-Rasheed et al. [13] respectively while alkaline phosphatase (ALP) was estimated according to El-Moghazy et al. [14]. Serum albumin was estimated according to Basuony et al. [15] while serum total proteins level was estimated according to Tousson et al. [16].

2.3. Electrolytes and kidney functions Biomarkers:

Serum urea and creatinine were determined in the rat sera according to Oyouni et al. [17] and Eldaim et al. [18] respectively. The approach proposed by El-Masry et al. [19] was followed to measure the levels of serum electrolytes (Potassium, sodium, calcium and chloride ion) using commercial kits (Sensa core electrolyte, India) according to El-Masry et al. [19] or Tousson et al. [20].

2.4. Histological preparation

After necropsy the liver and kidney were immediately removed and fixed by immersion in 10% neutral buffered formalin solution for 24-48 hours. The specimens were then dehydrated, cleared and embedded in paraffin. Serial sections of 5 µm thick were cut by mean of rotary microtome (Litz, Wetzlar; Germany) and stained with haematoxylin and eosin [21,22].

2.5. Statistical Analysis

Data were expressed as mean values±SD and statistical analysis was performed using one-way analysis of variance (ANOVA) followed by the Least Significant Difference (LSD) tests to assess significant differences among treatment groups. The criterion for statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS statistical version 16 software package (SPSS® Inc., USA).

3. RESULTS

3.1. Effects of Amitriptyline on liver functions

Alanine amino transferase (ALT), Aspartate amino transferase) and alkaline phosphatase (ALP) activities were significantly increased in Amitriptyline treated group as compared to control group (Figures 1). On the other hand; a significant decrease in serum albumin and total proteins were detected in Amitriptyline treated group as compared to control group (Figure 1).

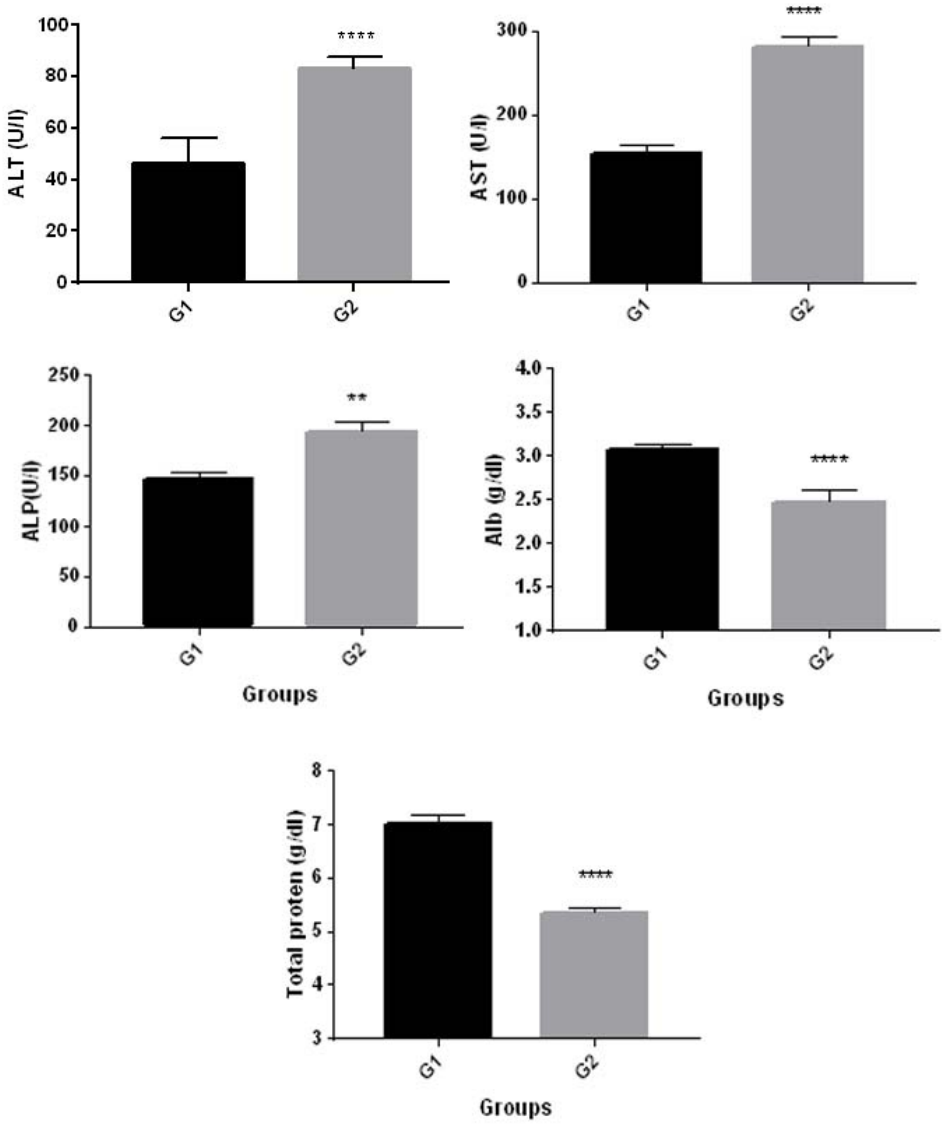


Figure 1: Changes in ALT (U/L), AST (U/L), alkaline phosphatase (ALP; U/L), albumin (g/dl) and total proteins (g/dl) levels in different groups under study. The significant difference was analyzed by T-test unpaired. Values are expressed as mean± SEM. T-test was significant at p<0.05. T-test unpaired was significant from corresponding amitriptyline at NSP=0.1234; *P=0.0332; **P=0.0021; ***P=0.0002; ****P<0.0001. G1, control group; G2, Amitriptyline group.

3.2. Effects of Amitriptyline on kidney functions and electrolytes

Serum urea, creatinine, sodium and chloride ions levels were significantly increased in Amitriptyline treated group as compared to control group (Figures 2&3). On the other hand; a significant decrease in serum potassium and calcium ions were detected in Amitriptyline treated group as compared to control group (Figures 2&3).

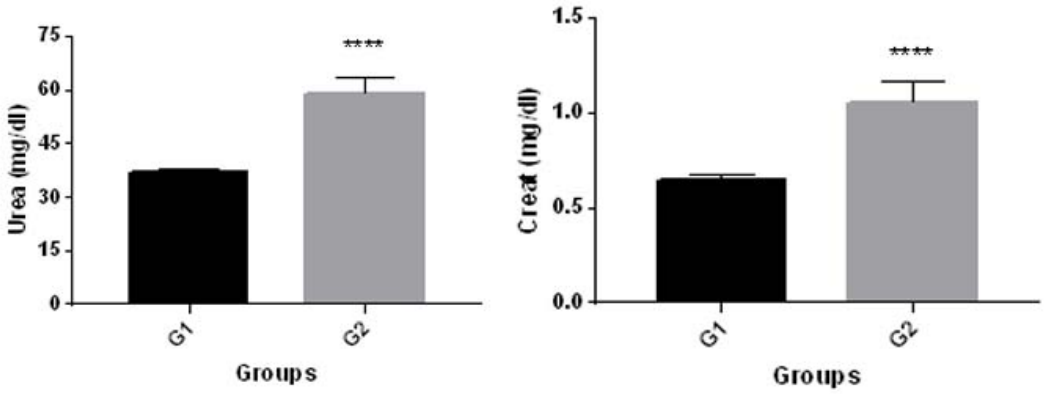


Figure 2: Changes in serum urea (mg/dl) and creatinine (mg/dl) levels in different groups under study. The significant difference was analyzed by T-test unpaired. Values are expressed as mean± SEM. T-test was significant at p<0.05. T-test unpaired was significant from corresponding amitriptyline at NSP=0.1234; *P=0.0332; **P=0.0021; ***P=0.0002; ****P<0.0001. G1, control group; G2, Amitriptyline group.

3.3. Effects of Amitriptyline on liver structure

Histological examination of haematoxylin and eosin stained on liver sections in control (G1) group showed that the structural unit of the liver is the hepatic lobule which is made up of radiating plates, cords, or strands of hepatocytes forming a network around central vein (Figure 4A&4B). The hepatocytes are polygonal in shape with prominent round nuclei, eosinophilic cytoplasm, and few spaced hepatic sinusoids arranged in-between the hepatic cords with fine arrangement of Kupffer cells (Figure 4A&4B).

Liver section in treated rats with Amitriptyline (G2) showed lose of liver architecture as disturbance of the hepatocytes radially arranged cords, marked degenerated and vacuolated hepatocytes, congestion in central veins and portal vein, surrounded by leucocytoc infiltrations, cytoplasmic vaculation and the nuclei are pyknotic indicating apoptosis, moderate fibrosis, and marked diffuse necrosis of hepatic tissue (Figures 4C&4D).

3.4. Effects of Amitriptyline on kidney structure

Rat kidney is differentiated into two regions; an outer cortex and an inner medulla (Figures 5A&5B). The cortex consists of Malpighian corpuscles that consist of tuft of blood capillaries, the glomerulus and Bowman's capsule and both proximal and distal convoluted tubules while the medulla consists mainly of the descending and ascending limbs of Henle's loop. However, the collection tubules are

located in both the cortical and medullary regions (Figures 5A&5B). Kidney sections of treated rat with Amitriptyline showed some histopathological lesions such as variable pathological changes in glomeruli and some parts of the urinary tubules (Figures 5C&5D). The most severe changes were in the Malpighian corpuscles lost their characteristic configuration and the renal tubules appeared with wide lumen, marked cortical and medullar tubular epithelial degeneration, focal tubular epithelial necrosis, moderate hemorrhage, mild to moderate atrophic glomerulus and degenerated epithelium and marked congestion in the renal blood vessels (Figures 5C&5D).

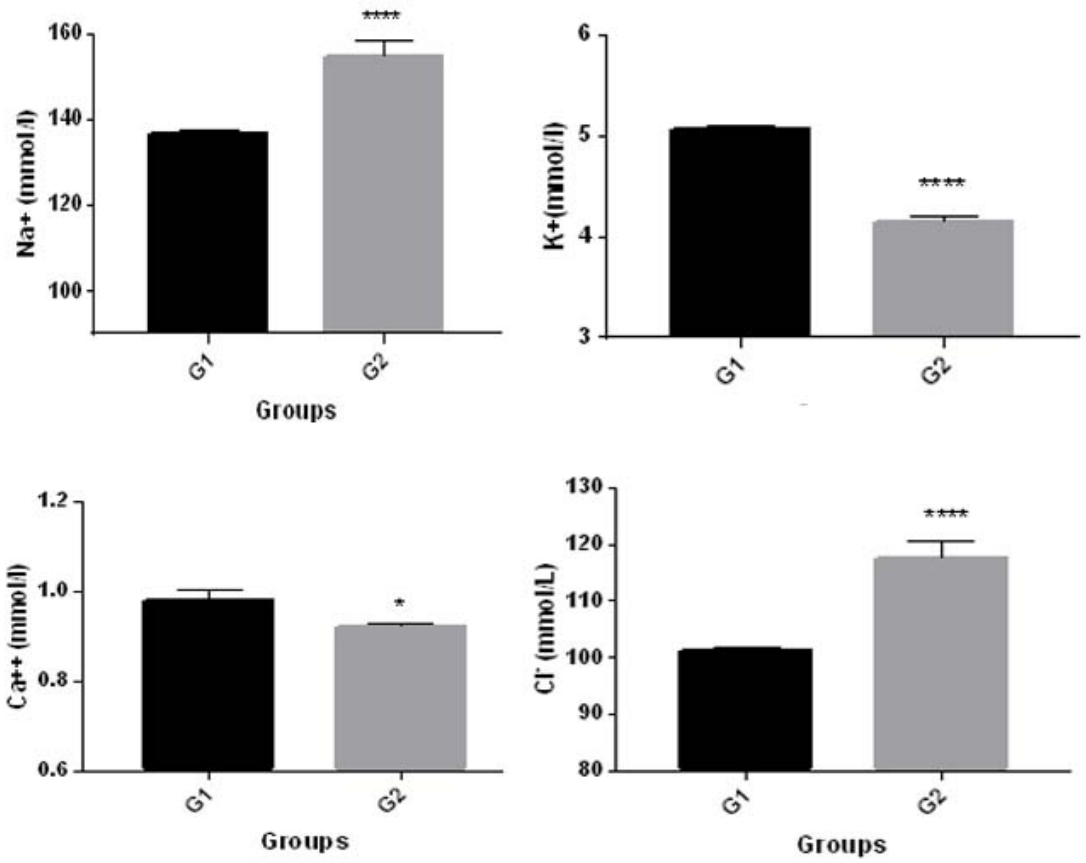
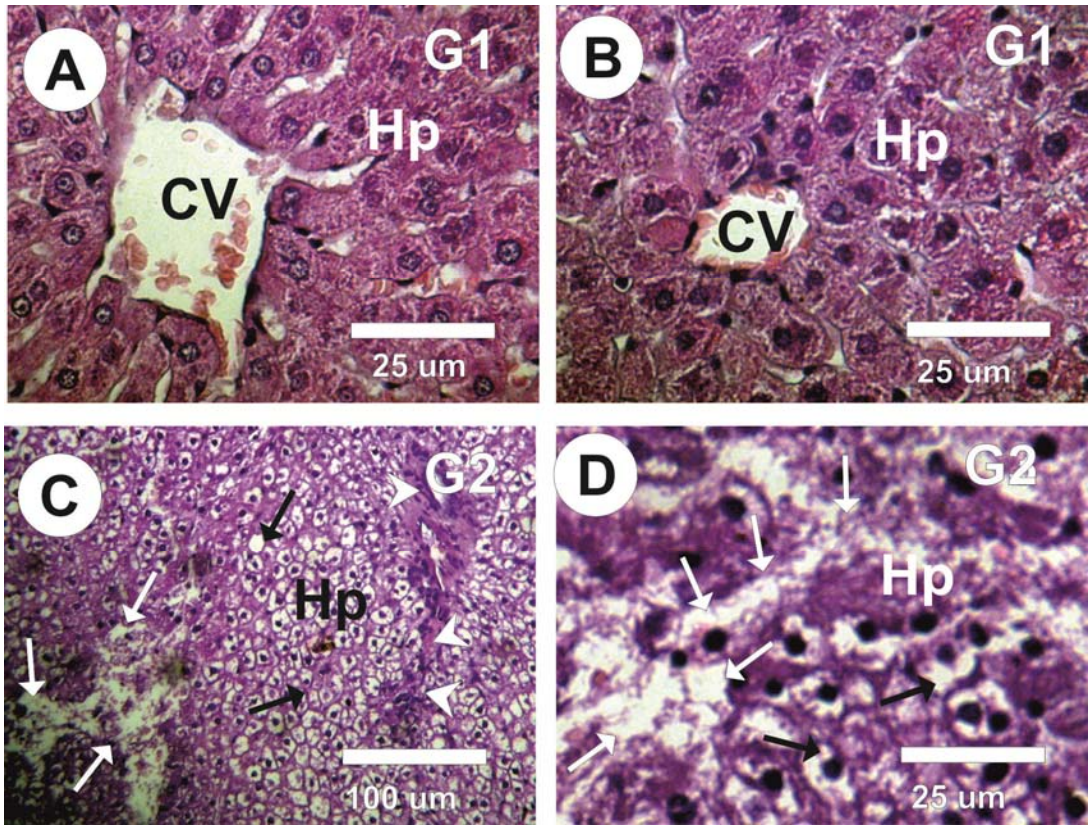
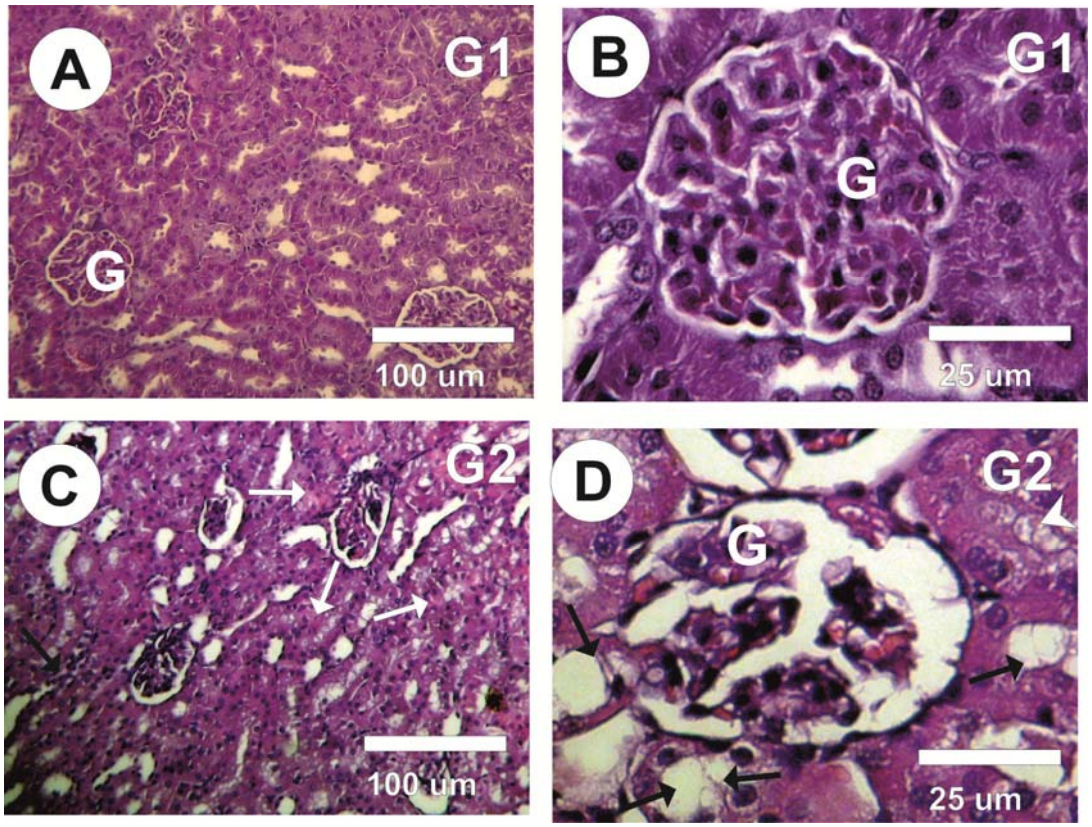


Figure 3: Changes in serum sodium ions (mmol/l), potassium ions (mmol/l), calcium ions (mmol/l) and chloride ions (mmol/l) levels in different groups under study. The significant difference was analyzed by T-test unpaired. Values are expressed as mean± SEM. T-test was significant at $p<0.05$. T-test unpaired was significant from corresponding amitriptyline at NSP=0.1234; *P=0.0332; **P=0.0021; ***P=0.0002; ****P<0.0001. G1, control group; G2, Amitriptyline group.



Figures 4: Photomicrographs of rat liver sections stained with Haematoxylin & Eosin. **A&B:** Liver sections in control group (G1) revealed normal structure of hepatocytes (Hp) with normal central veins (CV). **C&D:** Liver sections in Amitriptyline treated group (G2) revealed a disturbance of the hepatocytes radially arranged cords, marked vacuolated hepatocytes, cytoplasmic vaculation and the nuclei are pyknotic (Black arrows), moderate fibrosis (arrow heads), and marked diffuse necrosis of hepatic tissue (White arrows)**.**



Figures 5: Photomicrographs of rat kidney sections stained with Haematoxylin & Eosin. **A&B:** Kidney sections in control group (G1) revealed normal structure of glomerulus (G) and renal tubules**. C&D:** Kidney sections in treated rat with Amitriptyline (G2) showed severe changes were in the Malpighian corpuscles (G) lost their characteristic configuration and the renal tubules appeared with wide lumen, mild atrophy (arrows), tubular epithelial degeneration with focal tubular epithelial necrosis (arrow heads).

4. DISCUSSION

Antidepressants are psychiatric drugs which are available on receipt and are authorized to treat depression by altering chemical imbalances of neurotransmitters in the brain. Antidepressants have been in use for a long period of time. Although it has been used effectively to treat depression, its side effects are also known. The current study is aimed to determine the effects of antidepressants on vital organs such as liver and kidney.

The liver is the largest and very important organ in the body. It assists the body in breaking down drugs, including antidepressants. The liver has enzymes to help with its functions. AST and ALT are enzymes that are normally found within liver cells. Some drugs cause liver enzymes to leak from liver cells into the blood, causing the counts of liver enzymes in the blood to rise [14,16,23].

Liver is the most important organ, which plays a pivotal role in regulating various physiological processes in the body. It is involved in several vital functions, such as metabolism, secretion and storage. It is also an organ of excretion, essential in the removal of the wastes and the toxic products from the blood [24]. It has great capacity to detoxifycate toxic substances and synthesize useful principles [25]. Hepatocytes, which make up the majority of the liver structure, are very active in the metabolism of exogenous chemicals, and this is one of the major reasons why the liver is a target by toxic substances. The liver is necessary for survival; there is currently no way to compensate for the absence of liver function over long term, although liver dialysis can be used short term.

Some drugs can cause these enzymes to leak from the cells and into the blood, thus elevating the blood levels of the enzymes [11,26,27]. Antidepressants are medications used to treat major depression, dysthymia or chronic low-grade depression, and anxiety disorders such as obsessive compulsive disorder and social anxiety disorder [4].

Chronic exposure to stress contributes to the etiology of mood disorders, and the liver as a target organ of antidepressant and antipsychotic drug metabolism is vulnerable to drug-induced toxicity.

In the current study; significant increase in ALT, AST and ALP activates in treated rat with Amitriptyline when compared with control group were observed. On the other hand; a significant decrease in serum albumin and total proteins were observed in Amitriptyline group when compared with control group. The histopathological changes in the liver structure occur either during the hepato-cellular failure or the parenchymal damage caused due to various physiological and pathological conditions [27]. Antidepressant-induced liver injury is generally considered to be dose independent. DeSanty and Amabile [28] reported that; antidepressant-induced liver injury.

Cunningham [29] who reported that treatment with amitriptyline and diazepam induced acute hepatic necrosis. The results were consistent with Ebuehi and Asonye [30] who reported that; a significant increase in alkaline phosphatase, aspartate transaminase (AST) and alanine transaminase (ALT) activities in rabbits administered sertraline, clozapine, Amitriptyline. Anttila et al. [31] reported that; selegiline induced marked effect of liver and kidney function. Antidepressant-induced liver injury includes various biological and clinical presentations, ranging from isolated increases in liver enzyme levels to nonspecific symptoms such as fatigue, asthenia, anorexia, nausea, vomiting, and upper right abdominal pain, and also to more specific symptoms such as jaundice, dark urine or pale stool, progressive or even fulminant liver failure with hepatic encephalopathy, loss of hepatocellular functions, acute liver failure, and death [27].

The kidney is a compound tubular gland concerned with the important function of excretion [32]. It excretes urea and other nitrogenous waste products, eliminates substances foreign to the body and it maintains homeostasis by controlling the composition, volume and pressure of blood [33]. Approximately one and a half quarters of blood per minute are circulated through the kidneys, where waste chemicals are filtered out and eliminated from the body (along with excess water) in the form of urine. Medications are a common cause of kidney damage, also known as nephrotoxicity or, when severe, renal failure. This suggests a renal dysfunction and plasma creatinine were found to be high in correlation with the histological observation. The study concludes that any treatment with antidepressants may have negative effect on the vital organs. Thus these effects have to be considered while administering dose of the antidepressants the depression patients.

In the current study; a significant increase in the serum urea, creatinine, sodium and chloride ions levels was detected in the treated rats with Amitriptyline when compared with control. In contrast; a significant decrease in serum potassium and calcium ions were detected in Amitriptyline group when compared with control group. Our results were consistent with Tousson et al. [9,34] who reported that; amitriptyline induced an increase in sodium ions levels and decrease in potassium ions level.

creatine is primarily synthesized in the liver from the methylation of glycocyamine (guanidino acetate, synthesized in the kidney from the amino acids arginine, glycine, and methionine) by S-Adenosyl-L-Methionine [32,33]. It is then transported through blood to the other organs, muscle, and brain where, through phosphorylation, it becomes the high energy compound phosphocreatine. Enzyme evaluation of changes in the activity of lysosomal enzymes in rat kidneys could be useful indicator of kidney damage as well as kidney failure [35-37]. Hence a biochemical assay of creatinine was carried out to ascertain the effects of Amitriptyline on kidney.

5. CONCLUSION

Amitriptyline has many side effects on rat liver and kidney, it induced liver and kidney toxicity and tissue injury were it metabolized to nortriptyline which inhibits the reuptake of norepinephrine and serotonin almost equally. Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons.

Ethical Approval:

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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Conflict of interests

The authors declare no conflict of interest.

Authors' Contributions

Ehab Tousson designed the study, performed the statistical analysis, and wrote the protocol, Ahmed Massoud, Fathy Atta and Noha Dabour wrote the first draft of the manuscript. All author managed the analyses of the study. Ahmed hasan managed the literature searches and experimental studies. All authors read and approved the final manuscript.

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