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THE EFFECT OF COMMONLY USED ANTIHYPERTENSIVE DRUGS ON SOME BIOCHEMICAL INDICES AND SEX HORMONES

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ABSTRACT

Thiazide, a diuretic medication, is often used to treat high blood pressure and fluid accumulation leading to edema visible in various parts of the body. Complications and severe adverse effects have been reported with some antihypertensive drugs. This research assessed the effects of hydrochlorothiazide (HCTz), a thiazide diuretic, on selected biochemical indices and sex hormones in Wistar albino rats. A reputable brand of HCTz tablets was purchased from Joez Pharmacy, Zik's Avenue, Awka, and used for the study. A total of ninety-four (94) male and female Wistar rats, purchased from Chris Animal Farm and Laboratories, Awka, were used. Twenty-four (24) Wistar rats were used for an acute toxicity test employing Lorke's method. The remaining seventy (70) animals were divided into three major groups (A, B, and C). Groups B and C were further subdivided into B1, B2, B3, and C1, C2, C3. Each subgroup and group A (control) contained ten (10) animals, paired males and females housed in different cages for group A, B, and C. All animals in group B received a diet with ten percent (10%) fructose for twenty-one days to induce hypertension before administering HCTz. HCTz was administered at graded doses of 25 mg/kg, 50 mg/kg, and 100 mg/kg body weight to the subgroups of groups B and C for 60 days. Liver and kidney functions were evaluated, and testosterone, estrogen, and progesterone levels were monitored to assess the effects of the drug on reproductive hormones. All analyses were conducted using standard methods. The results showed no significant changes in the mean AST and ALT activities of the test rats compared to the control. The mean alkaline phosphatase activity in subgroups C1 (54.33 ± 1.75 IU/L), C2 (54.17 ± 2.79 IU/L), and C3 (53.17 ± 2.48 IU/L) was significantly higher than the control (46.50 ± 5.44 IU/L). The mean urea and creatinine levels in all subgroups were significantly higher than in the control (group A), with group C showing higher values than group B. Electrolyte analysis revealed significant increases in the mean sodium, potassium, and chloride levels in subgroups B1, B2, C1, C2, and C3 compared to the control. The study observed an insignificant increase ($p > 0.05$) in testosterone levels across the groups and subgroups compared to the control. Female hormone analysis indicated an insignificant decrease in progesterone levels. Based on these findings, it can be inferred that HCTz may have some negative effects on the organs of hypertensive subjects; alterations in sex hormone levels could potentially impact normal fertility in men and women.

KEYWORDS: Antihypertensive Drugs, biochemical indices, Sex Hormones, Thiazide, Wistar albino rats,

1.0.INTRODUCTION

Hydrochlorothiazide (HCTz) is the most widely used thiazide in clinical practice (Reungjui *et al.,* 2008). Other uses of HCTz include treating diabetes insipidus, renal tubular acidosis, and reducing the risk of kidney stones in individuals with elevated calcium levels in the urine (Oyedeji *et al.,* 2018).

Being a thiazide, HCTz is frequently suggested as a first-line treatment for hypertension, either as the sole therapeutic substance or in combination with other antihypertensive agents (Chobanian *et al.,* 2003). The European Medicines Agency recommends hydrochlorothiazide for the treatment of hypertension. It is a recommended antihypertensive drug in Europe (Mansia *et al.,* 2009). Thiazides, including hydrochlorothiazide, are among the most commonly used antihypertensive drugs in the United States and Western Europe, accounting for around 30% of prescribed antihypertensive medications for patients with hypertension (Wang *et al.,* 2007). Hydrochlorothiazide has been reported to have photosensitizing properties, increasing skin sensitivity to sunlight, which has been associated with skin and lip conditions (Friedman *et al.,* 2009). Sensitivities to HCTz have been reported to be more common in individuals with hypersensitivities to sulfa-containing drugs; however, this association is not widely confirmed (The American Society of Health-System Pharmacists, 2016).

It has been documented that HCTz initiates formative toxicity in mice and rats (George *et al.,* 1995). The association of HCTz with green tea removal on diuretic activity in animal models has been noted by Chakraborty *et al.,* (2014).

Hydrochlorothiazide has also been recorded to increase the contractile action of mouse cavernosal smooth muscle (Gagliano-Juca *et al.,* 2016). Lijinsky and Reuber (1987) reported a proconvulsive effect in an in vitro rodent seizure model. Pathological effects of its constant administration to rats have also been documented (Kellinghaus and Gorji, 2016).

The extensive organization of HCTz has also been shown to increase the focus of H+ATPase B1 subunit in rodent kidneys (Na *et al.,* 2007). According to archived reports, it is well established that thiazide diuretics reduce mortality in people with hypertension; however, thiazide use can also cause various metabolic irregularities that raise cardiovascular risk, including hypokalemia, hyperlipidemia, new-onset diabetes mellitus, hyperuricemia, insulin resistance, and activation of the renin-angiotensin-aldosterone system (RAAS) (Houston, 2004; Morganti, 2005; Salvetti and Ghiadoni, 2006; Hebert *et al.,* 2007). Although these issues can be minimized by using low doses of thiazides, they still may occur at a concerning frequency (Lindholm *et al.,* 2003; Verdecchia *et al.,* 2004). Population-based and clinical studies on diuretics report a non-renal protective effect and are associated with accelerated renal decline in the population (Reungjui *et al.,* 2008).

Ozougwu (2011) detailed drug-induced liver injury as the primary reason for drug withdrawal. Arizon *et al.,* (2004) documented a case of severe hepatotoxicity associated with hydrochlorothiazide use. Reports of adverse effects affecting male sexual function, ranging from 3% to 32%, include decreased libido, difficulty ejaculating, and erectile dysfunction (Bansal,

1988; Wassertheil-Smoller *et al.,* 1991; The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, 2002). A typical example is shown in the MRC trial, where 15,000 hypertensive patients were treated with either placebo, thiazide (bendrofluazide), or a β-blocker (propranolol) for a long period. Fatigue was recorded at 22 times and four times higher in those treated with bendrofluazide compared to placebo or a β-blocker, respectively (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, 2002). Fatigue was the most common reason for discontinuing antihypertensive therapy in this study. Another smaller study reported an increased frequency of decreased sexual desire, impotence, and delayed ejaculation in patients treated with thiazides (Chang *et al.,* 1991).

2.0. MATERIALS AND METHODS

Hydrochlorothiazide tablets (25mg) were obtained from Joez Pharmacy in Awka, Anambra State, Nigeria. The drugs were dissolved in distilled water, and the various doses were administered in milliliters using the following control formula, which was calculated based on the weight and size of the rats.

$$Dose\ (ml) = \frac{Dose\frac{mg}{Kg} \times Weight\ of\ Rat}{1000 \quad Concentration\ (\frac{mg}{Kg})}$$

Chemicals/kits

Chemicals and kits used for the biochemical assays were of analytical quality and bought from a reliable company (Sigma Aldrich Chemicals).

Experimental animal

Altogether, ninety-four (94) male and female wistar albino rats measuring 120kg – 180kg/ body weight, with no signs of ill-health were purchased from a Dr. Chris animal farm, Mgbakwu, Awka.

Irrespective of the established gain of effective long-term antihypertensive medication therapy in the reduction of blood pressure and treatment of edema, complications induced by these medications are poorly accepted side/adverse effects reflecting on the patient's willingness to continue with medication. Many healthcare givers and patients are ignorant of possible adverse effects of these medications, primarily associated complications, thus predisposing the patients to serious health challenges. Therefore, this study is tailored to investigate the impact of Hydrochlorothiazide drug on liver and kidney function, and reproductive parameters using wistar albino rats.

Study design

A total of seventy (70) wistar albino rats (35 males and 35 females) were grouped into three(3) major groups. Two of the three major groups were further grouped into three subgroups. Each of the sub-groups and one major group contained ten (10) animals per group (5males and 5 females) and were housed in different cages, with one male and one female in each cage. They were maintained and kept in cages, allowed to get accustomed to the study site for one week before the experiment, with constant access to water and food.

The subgroups were administered different doses of hydrochlorothiazide (HCTZ), while the main group served as a control.

The groups are as detailed below;

Major groups

Group A: Control
Group B: 10% fructose + HCTz
Group C: HCTz

Sub-groups

Group B1: 10% fructose + 25mg/kg of HCTz
Group B2: 10% fructose + 50mg/kg of HCTz]
Group B3: 10% fructose + 100mg/kg of HCTz
Group C1: 25mg/kg of HCTz
Group C2: 50mg/kg of HCTz
Group C3: 100mg/kg of HCTz

All the animals in group B were given ten percent (10%) fructose in diet for twenty-one days to induce hypertension as reported by Virupaksha (2017) before the commencement of the administration of HCTz.

Duration of the study

The study lasted for sixty (60) days, with body weight taken daily and the dosage of HCTz administered orally using a 22-gauge oral feeding needle, as reported by the manufacturer.

Collection of blood samples

Twenty-four hours after the last dosage/ overnight fast (Day 61), the animals were anesthetized with chloroform and immolated. Blood samples were obtained via cardiac puncture into plain tubes for biochemical analysis.

Acute Toxicity Study (LD_{50})

The LD_{50} of HCTz was determined using a modified Lorke (1983) method. Twenty-four (24) wistar albino rats were randomized in six (6) groups of four rats in a group. Group A – Control, Group B- 1000mg/kg, Group C- 2000mg/kg, Group D– 3000mg/kg, Group E– 4000mg/kg and Group F – 5000mg/kg. Hydrochlorothiazide was administered to the rats orally via a 22-gauge feeding needle. The animals were observed for 2 hours after drug administration for behavioral changes. They were further checked for mortality after 24 hours. The surviving animals were also observed for a further 14 days for signs of delayed toxicity.

Evaluation of Alanine Aminotransferase (ALT)

The ALT activity was determined using the method outlined by Reitman and Frankel (1957) as detailed in Randox Kit.

$$Principle: \alpha - oxoglutarate + L - Alanine \xrightarrow{GPT} L - Glutmate + Pyruvate$$

ALT activity is measured by checking the level of pyruvate hydrazone formed with 2, 4-dinitrophenylhydrazine. The colour intensity was determined against the blank at 546nm.

Evaluation of Aspartate Aminotransferase (AST)

The AST activity was determined using the method outlined by Reitman and Frankel (1957) as detailed in Randox Kit.

$$Principle: \alpha - oxoglutarate + L\,aspertate \xrightarrow{GOT} L - glutamate + oxoloacetate$$

AST or SGOT activity is determined by checking the level of oxaloacetate hydrazone formed with 2, 4-dinitrophenylhydrazine. The colour intensity was evaluated against the blank at the wavelength of 546nm.

Determination of Alkaline Phosphatase (ALP)

Alkaline phosphatase (ALP) activity was measured using IFCC method kit as recommended by Tietz *et al.,* (1983).

$$Principle: P - nitrophenylphosphate + H_2O \xrightarrow{ALP} Phosphate + P = nitrophenol\ (pH = 9.8)$$

This method relied on the interaction between serum alkaline phosphatase and the substrate P-nitrophenylphosphate. The ALP hydrolyses P-nitrophenylphosphate, resulting in phosphoric acid and P-

nitrophenol, which in alkaline pH can be determined spectrophotometrically at 405nm.

Measurement of Urea Level

Berthelot method was used.

Principle: Urea in the serum is hydrolysed to ammonia by the enzyme urease. The ammonia interacts with phenol and hypochlorite in an alkaline environment to form indophenol. The intensity of the colour shows the level of urea in the sample. The reaction was catalysed using Nitroprusside. The indophenol formed was then determined photometrically.

Determination of Creatinine

The Jaffe Slot Method was used.

Principle: Creatinine reacts with picric acid to produce a yellow-red picrate in an alkaline medium. The intensity of this color indicates the level of creatinine in the sample. The absorbance of the yellow–red color was measured spectrophotometrically at 520nm.

Determination of electrolytes (Na^+, K^+, Cl^- and HCO_3^-)

Martin and Frank's method using the ISE machine was used.

Principle: The machine converts the activity of a specific ion (Na^+, K^+, Cl^- and HCO_3^{-}) dissolved in a solution into an electric potential, which can be determined using a pH meter or voltmeter. The result was obtained from the potentials of the sample and two standard solutions.

Determination of Sex Hormone

Testosterone, Estrogen (Estradiol) and progesterone concentration were determined using ELISA method (Accu – Bind ELISA micro wells by Mono bind Inc).

Principle: This is based on Competitive Enzyme Immunoassay: The important reagents needed for an enzyme immunoassay include enzyme-antigen conjugate, antibody, and native antigen. With the mixing of enzyme-antigen conjugate, biotinylated antibody, and a serum containing the native antigen, a competition reaction occurs between the native antigen and the enzyme-antigen conjugate for a small number of antibody binding sites.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software version 23 (SPSS Inc., Chicago, Illinois, USA) was used for the data analyses. Comparisons were made via one-way analysis of variance (ANOVA) followed by the post hoc test (least square deviation). All data are expressed as mean ± standard deviation, and $P<0.05$ is considered significant.

3.0. RESULTS AND DISCUSSIONS

Table 1: The mean AST activity value of sub-group B1 (5.83 ± 1.72) increased insignificantly when compared with group A (5.10 ± 1.73). Other subgroups have lower AST mean values than A.

Table 1: Mean value of Aspartate aminotransferase (AST) levels of the different groups of rats

Groups N= 10 rats per group	AST Concentration (mmol/l)	Control N= 10	p-value
B1	5.83 ± 1.72	5.10 ± 1.73	0.36
B2	4.83 ± 1.17	5.10 ± 1.73	0.74
B3	4.17 ± 0.75	5.10 ± 1.73	0.24
C1	4.00 ± 1.09	5.10 ± 1.73	0.17
C2	4.00 ± 2.09	5.10 ± 1.73	0.17
C3	4.17 ± 1.47	5.10 ± 1.73	0.24

Table 2: The result of ALT activity of the sub-groups B1 (7.50 ± 1.52), B2 (7.67 ± 1.03), B3 (7.00 ± 1.79) and C2 (6.67 ± 1.63) are insignificantly higher than the control; group A (6.60 ± 1.71). Subgroups of group B have higher ALT levels than subgroups of group C.

Table 2: Mean value of Alanine transaminase (ALT) levels of the different group of rats

Groups N= 10 rats per group	ALT Concentration (mmol/l)	Control N= 10	p-value
B1	7.50 ± 1.52	6.60 ± 1.71	0.31
B2	7.67 ± 1.03	6.60 ± 1.71	0.23
B3	7.00 ± 1.79	6.60 ± 1.71	0.65
C1	5.83 ± 2.31	6.60 ± 1.71	0.38
C2	6.67 ± 1.63	6.60 ± 1.71	0.94
C3	6.50 ± 1.52	6.60 ± 1.71	0.91

Table 3: The mean concentration of alkaline phosphatase (ALP) of sub-groups C1 (54.33 ± 1.75), C2 (54.17 ± 2.79), and C3 (53.17 + 2.48) is significantly higher than the control (46.50 ± 5.44). Furthermore, the sub-groups of group C have higher ALP values when compared with the sub-groups of group B as shown in table 3 above.

Table 3: Mean value of Alkaline phosphatase (ALP) levels of the different group of rats

Groups N= 10 rats per group	ALP Concentration (mmol/l)	Control N= 10	p-value
B1	42.83 ± 6.79	46.50 ± 5.44	0.10
B2	50.67 ± 4.32	46.50 ± 5.44	0.06
B3	46.50 ± 2.66	46.50 ± 5.44	1.00
C1	54.33 ± 1.75**	46.50 ± 5.44	0.001
C2	54.17 ± 2.79**	46.50 ± 5.44	0.001
C3	53.17 ± 2.48**	46.50 ± 5.44	0.004

** considered significant

The increment in the result of the mean Urea concentration (mEq/l) was significant (p=0.00) in all the sub-groups; B1 (6.28 ± 0.18), B2 (6.53 ± 0.05), B3 (6.27 ± 0.10), C1 (7.37 ± 0.15), C2 (7.48 ± 0.15) and C3 (7.63 ± 0.19) in contrast with the control; group A (5.68 ± 0.10). Group C has a higher urea concentration than group B, and this appears to be progressive within the subgroups, as shown in Figure 1.

All the sub-groups; B1 (91.00 ± 1.54), B2 (112.17 ± 3.48), B3 (109.33 ± 4.50), C1 (190.83 ± 1.33), C2 (181.83 ± 2.40) and C3 (184.33 ± 1.97) have significantly higher mean creatinine (mEq/l) level when compared with the control; group A (71.00 ± 1.05). The sub-groups of group C showed higher creatinine level compared with the sub-groups of group B as shown in figure 2.

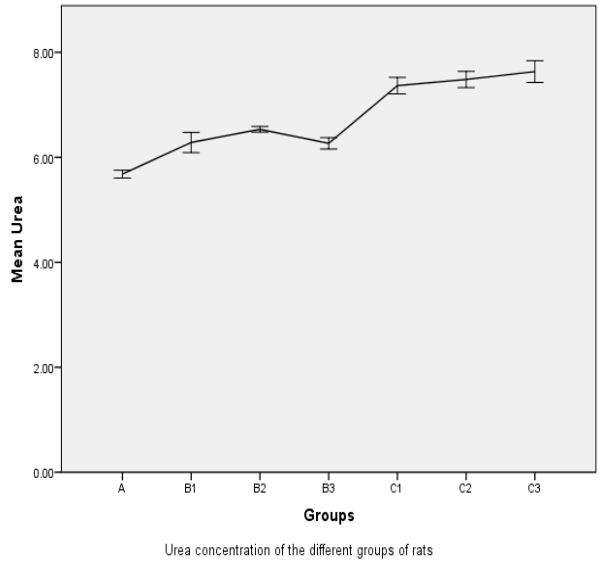

Fig. 1: Showing the mean urea concentration of the different groups of rats

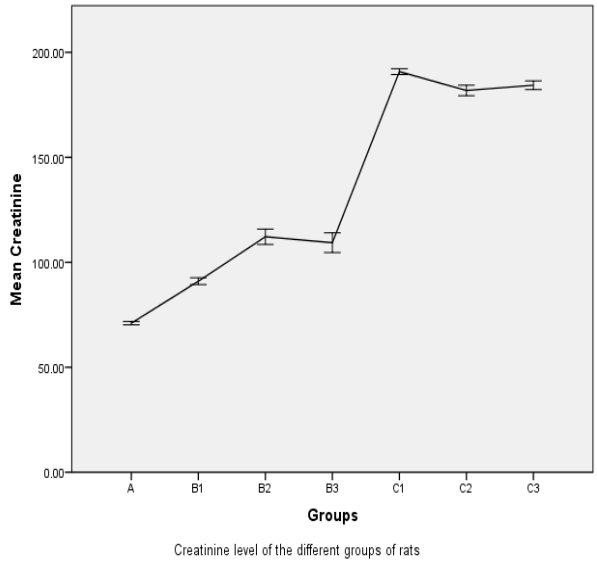

Fig. 2: Showing the mean creatinine concentration of the different groups of rats

The mean result of sodium concentration (mEq/l) of B1 (153.50 ± 2.74), B2 (161.83 ± 0.98), C1 (154.00 ± 1.26), C2 (154.83 ± 1.33), and C3 (154.00 ± 1.26) increased significantly when the values are compared with the control group A (145.60 ± 0.84). Figure 4.6 also shows a significant elevation in chloride levels across all subgroups (B1, B2, B3, C1, C2, and C3) compared with the control group A (100.30 ± 0.48). Furthermore, subgroup C has a higher chloride level than subgroup B, as shown in Figure 3.

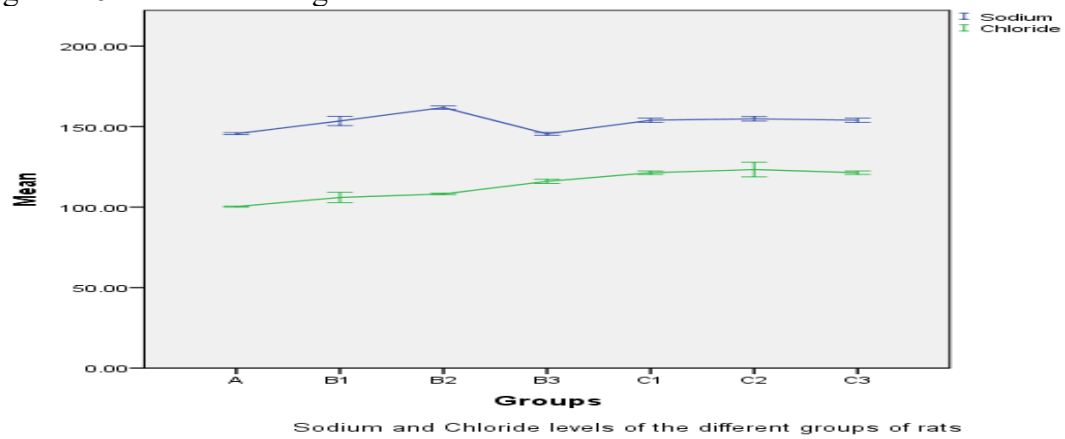

Figure 3: Mean sodium and chloride concentration of the different groups of rats.

In Table 4, the sub-groups of B1 (4.93 ± 0.98), B2 (5.28 ± 0.13), C1 (4.88 ± 0.04), C2 (4.88 ± 0.04), and C3 (4.88 ± 0.04) showed a significant increment in the level of potassium when compared with the control group, group A (4.24 ± 0.09). The mean bicarbonate concentration of sub-groups B1 (25.00 ± 0.63), B2 (24.83 ± 0.75), C1 (25.50 ± 0.55), and C2 (25.60 + 0.52) is insignificantly higher than the control group A (24.80 + 0.63), as shown in Table 5.

Table 4: Mean value of potassium concentration of the different group of rats

Groups **N= 10 rats per group**	**K^+ Concentration** **(mEq/l)**	**Control** **N= 10**	**p-value**
B1	4.93 ± 0.98	4.24 ± 0.09	0.00
B2	5.28 ± 0.13	4.24 ± 0.09	0.00
B3	4.20 ± 0.11	4.24 ± 0.09	0.83
C1	4.88 ± 0.04	4.24 ± 0.09	0.00
C2	4.88 ± 0.04	4.24 ± 0.09	0.00
C3	4.88 ± 0.04	4.24 ± 0.09	0.00

Table 5: Mean concentration of bicarbonate levels of the various groups of rat

Groups N= 10 rats per group	CO_3^- Concentration (mEq/l)	Control N= 10	p-value
B1	25.00 ± 0.63	24.80 ± 0.63	0.57
B2	24.83 ± 0.75	4.24 ± 0.09	0.92
B3	24.17 ± 0.98	4.24 ± 0.09	0.08
C1	25.50 ± 0.55	4.24 ± 0.09	0.05
C2	25.60 ± 0.52	4.24 ± 0.09	0.06
C3	24.67 ± 0.92	4.24 ± 0.09	0.70

Table 6 shows that the mean result of testosterone level of sub-groups B1 (0.60 ± 0.10), B2 (0.63 ± 25), B3 (0.63 ± 0.12), C2 (0.60 ± 0.10), and C3 (0.60 ± 0.17) increased insignificantly ($p>0.05$) when compared with control; group A (0.57 ± 0.15). The difference between the subgroups B and C was not significant.

There was an insignificant increase in the mean estrogen concentration of sub-groups B1 (72.33 + 10.01), B2 (76.33 + 1.15), B3 (83.00 + 21.17), and C1 (87.67 + 2.52) when compared with the control group; group A (72.00 + 4.00) as shown in Table 7.

The mean result of progesterone level of sub-groups B1 (4.67 ± 0.56), B2 (5.70 ± 0.67), C1 (6.93 ± 2.75), C2 (4.30 ± 4.25) and C3 (5.80 ± 5.03) decreased insignificantly when compared with the control; group A (6.53 ± 1.06).The progesterone levels across the subgroups did not differ significantly, as shown in Table 8.

Table 6: Mean testosterone levels of the different group of rats

Groups N= 10 rats per group	Testosterone Concentration (mmol/l)	Control N= 10	p-value
B1	0.60 ± 0.10	0.57 ± 0.15	0.86
B2	0.63 ± 25	0.57 ± 0.15	0.73
B3	0.63 ± 0.12	0.57 ± 0.15	0.73
C1	0.53 ± 0.47	0.57 ± 0.15	0.86
C2	0.60 ± 0.10	0.57 ± 0.15	0.86
C3	0.60 ± 0.17	0.57 ± 0.15	0.86

Table 7: Mean estrogen level of the various groups of rat

Groups N= 10 rats per group	Estrogen Concentration (mmol/l)	Control N= 10	p-value
B1	72.33 ± 10.01	72.00 ± 4.00	0.99
B2	76.33 ± 1.15	72.00 ± 4.00	0.81
B3	83.00 ± 21.17	72.00 ± 4.00	0.55
C1	87.67 ± 2.52	72.00 ± 4.00	0.39
C2	58.00 ± 51.88	72.00 ± 4.00	0.44
C3	66.67 ± 5.86	72.00 ± 4.00	0.77

Table 8: Mean progesterone concentration of the different group of rats

Groups N= 10 rats per group	Progesterone Concentration (mmol/l)	Control N= 10	p-value
B1	4.67 ± 0.56	6.53 ± 1.06	0.44
B2	5.70 ± 0.67	6.53 ± 1.06	0.73
B3	6.93 ± 2.75	6.53 ± 1.06	0.87
C1	6.33 ± 1.81	6.53 ± 1.06	0.93
C2	4.30 ± 4.25	6.53 ± 1.06	0.36
C3	5.80 ± 5.03	6.53 ± 1.06	0.76

It has been long known that drugs can be transformed in the body into various metabolites that elicit therapeutic and toxicological responses. All drugs have been associated with hepatotoxicity due to the vital role of the liver in drug biotransformation (Tolman, 1998). Liver disease is a major cause of increased transaminase activity in the serum (Awotunde *et al.,* 2019). The insignificant changes in AST and ALT suggest that the drug did not affect the integrity of the liver cells. This observation is similar to the report of Kale *et al.,* (2019) on the sub-acute and sub-chronic oral toxicity of the hydroethanolic extract of the root of *Acridocarpus smeathmannii* in Wistar rats. Onochie *et al.,* (2018) also reported normal liver function due to insignificant changes in the liver function test indices of male Wistar albino rats exposed to Dichlorvos and aluminum phosphide insecticides.

The serum alkaline phosphatase level increased significantly in sub-groups C in contrast with the control group following the administration of HCTz, although this was observed not to be dose-dependent. No

observable significant changes were recorded in the ALP levels sub-groups of group B, when compared with control. This may be as a result of the induction of hypertension using fructose. Pollak *et al.,* (1983) reported that amino sugars and glucose clearly inhibited ALP enzyme activity. High serum concentration of ALP is indicative of liver damage. ALP is secreted into the bile duct and is often used to evaluate the integrity of the liver plasma membrane (Ahangarpour *et al.,* 2016). Elevation of total ALP levels in plasma is associated with increased osteoplastic activity and is explained by a degree of cholestasis (Ahangarpour *et al.,* 2016). The ALP result of this work agrees with a study by Ahangarpour *et al.,* (2016). This trend of increased serum ALP was also reported by Awotunde *et al.,* (2019) for the aqueous extract of Terminalia schimperiana root in male rats.

Blood creatinine and urea concentrations are standard biochemical indices used to assess renal function (Owoade *et al.,* 2019). Plasma creatinine level is used to determined glomerular filtration rate (GFR) while urea is used to investigate the nephrotoxic effects of chemicals (El-Wessemy, 2008). In this study, a significant increment in the urea and creatinine levels of all the sub-groups of rats when compared with control (group A) is indicative of renal impairment (Fig. 1 and 2), which results in a reduction of glomerular filtration rate, giving rise to the build-up of urea and creatinine in the blood. The higher urea and creatinine concentrations in subgroups of group C compared with group B could be due to fructose-induced hypertension and subsequent HCT treatment. This study is similar to the report by Owoade *et al.,* (2019), on the defect of the renal functions in rats administered with tramadol, as shown by a significant elevation in urea and creatinine levels in the plasma, compared to the control group. The result also concurred with previous studies (El-Gaafarawi, 2006; Noori and Mahboobe, 2010). Conversely, Oyedeji *et al.,* (2019) reported no significant changes in urea and creatinine levels in rats treated with hydrochlorothiazide. Renal function can also be determined through assessment of electrolyte status. These electrolytes are usually assessed to know the normal functioning capacity of different parts of the nephron (Panda *et al.,* 1989). The study showed a significant increase in sodium, chloride, and potassium ion concentrations, with an insignificant increase in bicarbonate concentrations in the test groups compared with the control group (Fig. 3, Table 4 and 5). This controversial imbalance in electrolyte concentrations about HCT might be attributed to the composition of the rat's diet or water supply.

Sexual dysfunction is a problem experienced by an individual or a couple during any stage of a regular sexual activity. This consists of a variety of conditions that are characterized by disorganisation in the various stages of the sexual response cycle of arousal, desire, orgasm, and resolution, as well as sex-related pain disturbances (Birnbaum, 2009). The causes of sexual dysfunction vary considerably, but include a possible reduction in the sex hormones of males and females (Eden and Wylie, 2009).

This study revealed an insignificant increase ($p > 0.05$) in testosterone concentration in the groups compared with the control and among the subgroups (Table 6). Testosterone is the major male sex hormone synthesized by the interstitial cells of the Leydig in the testis and is the primary index of androgenicity. It's established that elevated testosterone level enhances sexual behavior in humans, and sexual desire may be stimulated directly by elevating serum testosterone levels or by inducing testosterone-like effects (Ndukui *et al.,* 2014). The findings of this research on testosterone agreed with a study by Oyedeji

et al., (2018) and were similar to a work by Woode *et al.,* (2011) on the effects of the ethanolic fruit extract of *Xylopia aethiopica* on the reproductive function of male rats. Ndukui *et al.,* (2014) also reported an elevation in testosterone levels in rats administered Leaf Extracts of *Citropsis Articulata* and *Mystroxylon Aethiopicum*. In contrast, Nwabufo and Olusanya (2017) reported reduced testosterone levels in male Wistar rats administered *Hibiscus sabdariffa* calyx extract. Salah *et al.,* (2019) also reported a decrease in testosterone levels in animals treated with tramadol. The results of the female hormonal assessment showed minor fluctuations in estrogen and progesterone levels.

In females, estrogen and progesterone are primarily produced in the ovaries under the influence of gonadotropins (Amah-Taria *et al.,* 2016). An imbalance in these sex hormones can lead to irregularities in ovarian and uterine functions. Elevated estrogen levels are crucial for the luteinizing hormone surge that triggers ovulation (Adewale *et al.,* 2014). Subsequently, the corpus luteum produces progesterone, which supports implantation and maintains pregnancy (Sheeja *et al.,* 2012). A direct toxic effect of HCTz on the corpus luteum may be responsible for the decrease in progesterone levels. Adewale *et al.,* (2014) reported that water extracts of M. charantia significantly reduced plasma levels of progesterone and estrogen in female Wistar rats in a dose-dependent manner. Obi *et al.,* (2018) observed a significant increase in these two sex hormones following treatment with *Chrysophyllum albidum.*

4.0. CONCLUSION

Based on the findings of this work, it may be concluded that HCT may have adverse effects on the organs of hypertensive subjects. Chronic administration of HCT may result in some possible nephrotoxic effects and excess secretion of testosterone, which could adversely affect the functionality of the male reproductive organ. Observably, low levels of progesterone were secreted, and this could affect the normal fertility status in women.

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