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A Comparative Study of the Effect of Phase I Enzymes in Rat Kidney Tissue Treated with *Psidium Guajava* Leaf Extract in Paracetamol Induced Toxicity.

Dr. (Mrs.) Chinyere P. Obidiegwu
Mrs. Ogbe Augustina Chukwude
Mrs. Ogochukwu-Isiekwene Mercy
Mrs. Erukpe Bolanle

School of Science Education, Biology Department, Federal College of (Technical), Asaba, Delta State, Nigeria.

Abstract:

This study evaluated the effect of phase I enzymes on rat kidney tissue with guava leaf extract (*Psidiumguajava*Linn.) on Paracetamol-induced toxicity, which were investigated in male albino rat by monitoring the activities of tissue enzyme. The phytochemical screening of *Psidiumguajava* leaf extract was carried out. Twenty-five albino rats were divided into five groups: Group1 and Group 2, served as normal and intoxicated control respectively, Group 3 as treated with Curcumin (100mg/kg for 6 days) as standard, Group 4 and 5 received extract (250 and 500mg/kg) respectively for six days. On the fourth day, after two hour's treatment, Group 2 and 5 received Paracetamol (400mg/kg) respectively. After the treatments the animals were scarified 48 hours after with acute dose of Paracetamol.

Pretreatment with guava extract before the administration of Paracetamol significantly prevented the increase in tissue Alanine Aminotransferase (ALF), Alkaline Phosphate (ALP) activities. This results provided showed that guava extract significantly inhibits the kidney damage toxicity induced by high dosage of Paracetamol in rats, as shown by a reduction of kidney enzymes activities in Aspartate Transferase (AST), Gamma Glutamyl Trans peptidase (GGT) and Lactate dehydrogenase (LDH). The use of guava extract alone on the other hand showed nephron-protective properties of guava leaf extract, in that the above parameters were significantly lower than those of the untreated control. The protective effect of the extract against Paracetamol toxicity was however limited to the kidney, effects which may be due to this anti-oxidant and free radicals scavenging properties of some of the components of the extract. Also, the phytochemical investigation of the extract of *Psidiumguajava* leaf extract showed the absence of Alkaloids and the presence of Flavonoid, Saponins, Phenols, Terpenes, Sesquiterpenes and Tannins. Finally, the treatment with Acetaminophen (APAP) as shown in the study had an acute devastated effect on the kidney, as exemplified by the increases in kidney enzymes, creatinine, urea and total protein release into the blood stream as a result of damages on the kidney cells by presence of APAP.

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1. INTRODUCTION

Medicinal plants or herbs are plants with medical or curative properties. The usage of alternative medicine is as old as the practice of alchemy; due to the enormous natural healing potential of some plants, disease prevalence has reduced. For example, recent research revealed the anti-cancer properties of soursops plant. It is believed that many modern drugs are products of herbalism, hence, the abuse of some "over the counter" drugs such as Paracetamol, vitamin C, etc.

According to National Health Portal (2016) medicinal plants include various types of plants used in herbalism ("herbology or herbal medicine). It is the use of plants for medicinal purposes and the study of such uses.

Paracetamol (Acetaminophen) is one of the common and most frequently used drugs used in treatment of analgesic and antipyretic disorder such as mild fever. Aches and cold; globally in Nigeria it is available without prescription note from doctor (over the counter) hence, the abuse or intake of high doses which can harm internal organs like the liver, kidney in some severe cases (MHS. UK, 2016). Chronic use of Paracetamol is nephrotoxic and older age fasting and dehydration are associated with increase toxicity (Bell, 2014).

Paracetamol overdose is knownto cause hepatotoxicity and significant Paracetamolinduced hepatotoxicity usually triggers nephrotoxicity (Dogukan, *et al*, 2016). In paracetamol over dosing cases glutathione stores are depleted and rapid increase in the concentrationof N-Acetyl-p-benzoquinone (NAPQI) causes necrosiscondition which produces massive metabolites causing large amounts of unbound reaction which is one of the main causes of acute failure of the kidney.

Kidney have many clearly defined physiologic function, they serve as organ of excretion of drugs and chemicals in the body, kidney is metabolically very active in effecting the bio-transformation of varieties of chemicals and drugs, it receives a substantial portion of the cardiac output, it makes significant contribution to the total metabolic alteration of drugs in the body.

Plant remedies are increasingly being recognized by scientist as a very important low cost alternative to industrially produced drugs, the guava plant, *Psidiumguajava Linn,* which belong to the family of myrtaceae is one of the medicinal plant which the leaf and back parts is used in treatment of various diseases. This tropical fruit have medicinal and therapeutic properties leaves are medically useful as the nutrimental powerhouse fruit, it also has antioxidant

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potentials which can be used in the treatment of chronic diseases and wounds. (Medicaldaily.com 2018). Studies have revealsthat guava leaves can aid weight loss, reduce blood glucose level, treat digestion issues, sore throat and prostate cancer.

According to Barbalho, *et al*, (2012), guava leaves, seeds and peels of fruits have significant proportion bioactive compounds with beneficial physiological and metabolic properties.

Statement of the Problem

Abuse of Paracetamol is a common practice in Nigeria, because it is easily purchased and can be administered without Doctors' prescription and medical supervision. Unfortunately, some individual do not know the medical implication of abusing Paracetamol. Recently, the pharmaceutical society of Nigeria warned against indiscriminate or misuse of Paracetamol, saying such practice damages the liver and kidney (Premium Times, 23 July, 2018).

Paracetamol abuse has been associated with renal and liver issues; in severe cases, it may result to death.

Aims and Objectives

The aims and objective of this research work is slated below

1. To analyze the medical potential of *Psidium guajava* leaf extract on rat's damaged tissues.
2. To optimize phytochemical screening of *Psidium guajava* leaf extract.
3. To ascertain damages, caused by high Paracetamol intake.
4. To ascertain the effects of *Psidium guajava* leaf extract on total serum protein, creatinine and urea levels in APAP toxicity in albino rat.
5. To investigate the effect of phase 1 enzymes in rat kidney tissues induce by overdose of Acetaminophen and the extent *Psidium guajava* extract treat toxicity.
6. To contribute to health life style choices, through alternative medicines.

2.0. MATERIALS AND METHOD

2.1. Chemicals: Randox and Teco diagnostic kit, Ethylene diamine-tetra-acetic acid bottle (EDTA).

2.2. Laboratory Apparatus

Test tube, micropipette, Beakers dissecting kit, buffer solution, Lithium heparin bottle, (anticoagulant) Serological Water bath, Spectrophotometer (Jenway 6505UV/VIS) film bottle fluoride oxalate bottles, needle syringe, cotton wool, surgical hand gloves, blades, test tube, ranks, hematocrit centrifuge refrigerator, dissecting board, cuvette NaOH, Laboratory mortal & pestle (homogenizer).

2.3. Collection of Plant Materials

Guava leaves (*Psidium guajava*) were collected from F. C. E., Asaba, compound, dried for 7 days under room temperature and blended into dried powder. The leave was soaked in methanol solution 100ml and filtered, the filtrate was collected using Whatman, No. 2 filter paper.

2.4. Experiential Animals:

Thirty -five (35) Rats (Rattus norvegicus) weighing 55kg – 130g were obtained from Onitsha market in Anambra State, Nigeria. The rats were housed in plastic animal cages and fed with standard feeds from animal care Agro allied limited, Asaba, water and libilum was given.

2.5. Experimental procedure:

Twenty-five albino rats were divided into five groups: Group1 and Group 2, served as normal and intoxicated control respectively, Group 3 as treated with Curcumin (100mg/kg for 6 days) as standard, Group 4 and 5 received extract (250 and 500mg/kg) respectively for six days. On the fourth day, after two hour's treatment, Group 2 and 5 received Paracetamol (400mg/kg) respectively. After the treatments the animals were scarified 48 hours after with acute dose of Paracetamol.The treatment lasted for 7 days and their blood samples were collected for biochemical analysis.

2.6. Determination of Aspartate Transaminase Activity

The glutamate Oxaloacetate transaminase was analyzed according to Reitman and Frankel (1957) method.

2.7. Lactate Dehydrogenase Activities.

In order to ascertain the rule of (LDH) in experimental animal, LDH is distributed in the heart, liver, muscle, and kidney and is made up of 5 isoenzymes base on their mobility in patient with liver, renal and cardiac disease the enzyme, LDH is usually elevated.

L – Lactate + NAD LDH Pyruvate + NADH + H+

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This enzyme LDH can be measured in both directions at catalyzes the oxidation of lactate to pyruvate in the presence of NAD, which is reduced to NADH, and is measured at 340nm which is proportional to the serum LDH.

2.8. ALKALINE PHOSPHATASE ACTIVITY DETERMINATION

For the direct determination of alkaline phosphatase in human serum and tissues of experimental animals as described by Kaplan and Rightetti (1955), modified by Demetrious, et al. (1974). ALP is distributed in almost every tissues of the body. Serum alkaline phosphatase levels are of interest in the diagnosis of hepatobiliary disorder bone disease. Most of the ALP in normal adult serum is from the liver of biliary tract. Normal ALP levels are age dependent levels are elevated during periods of active periods of active bone growth. Moderate elevation of ALP (noting involve the liver or bone) may be attributed to Hodgins disease, congestive heart failure, and abnormal bacterial infections.

2.9. GAMMA GLUTAMYL TRANSPEPTIDASE ACTIVITY DETERMINATION

For quantitative in-vitro determination of Gamma-glutamyl-trans-peptidase (GGT) in serum and tissues of experimental animals as described by Teitz (1987), modified by (Scasz and Scasz, 1974).

2.9.1. Anesthetization of Animals and Isolation of Tissues.

The experimental animals were placed in a jar containing cotton wool soaked with chloroform.

The Lives, Kidney, Brian& Intestines were removed and placed in a beaker containing ice of 0.25m phosphate buffer solution. The blood obtained was preserved in lithium 3,500 rpm for 15mins using refrigerated centrifugal RC65^{0}s.

2.9.2. Preparation of Homogenate

The tissues kept the beaker were chopped into pieces and homogenized, then diluted with phosphate buffer solution and stored at 4^{0}C for centrifugation.The supernatant (centrifuged tissue) was used for the test using phase 1 enzymes kit, lives enzymes kit ofAST, LDH, GGT and ALP.

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3. RESULTS:

The results of the phytochemical screening of the leaf extract of *Psidium guajava* is presented in table 1. The phytochemical investigation revealed that presence of the Flavonoids, Saponins, Phenols, Terpenes, Sesquiterpenes, Tannin and absence of Alkaloids.

Table 1: Phytochemical Screening of *P. guajava* leaf extract.

S/N.	CONSTITUENTS	OBSERVATION
1	Alkaloids	-ve
2	Flavonoids	++ve
3	Saponins	+ve
4	Phenols	+ve
5	Terpenes	+ +ve
6	Sesquiterpenes	+ve
7	Tannins	+ve

(+ve) = Present, (++ve) = Abundant, (-ve) = Absent

As shown in the Table 2 below, the kidney enzymes, ALT and ALP and GGT values were considerably brought down in those rats given both APAP 400mg/kg and 250 and 500mg/kg guava leaf extract ($p>0.05$) when compared to the untreated

control (Group A) and even those treated with APAP only (Group B) and 100mg/kg. Curcumin (Group C) respectively. However, AST and LDH, did not show any considerably difference across the groups treated with Paracetamol (APAP) and guava extract when compared with the untreated control and those rats that were given APAP or guava leaf extract only.

Table 2: Effect of guava (*Psidium guajava*) leaf extract on Kidney enzymes, levels Acetaminophen (APAP) in Albino Rats.

Parameters	**Group A Control**	**Group B Acetaminophen (APAP)**	**Group C Curcumin (100mg/kg)**	**Group D Guava Extract (250mg/kg)**	**Group E Guava Extract + APAP (500mg/kg)**
ALT	97.12± 5.501^{a}	113.4±13.89^{ab}	110.5± 4.329^{abc}	79.12±2.66^{bd}	98.04± 5.979^{abc}
ALP	73.49±3.840^{a}	44.44± 7.950^{b}	75.22± 8.078^{bd}	45.34± 1.801^{bd}	12.32± 2.574^{bc}
LDH	1156.4±335.47^{a}	1718.9±139.4^{ab}	110.1± 189.8^{abc}	126.6±83.22^{ad}	93.06±59.32^{ad}
GGT	45.67± 3.953^{a}	141.51±45.09^{ab}	90.85±21.41^{ab}	42.39± 8.048^{bcd}	73.3±3.190^{abc}
AST	423.9±3.995^{a}	443.0±8.899a^{b}	442,9±10.03^{abc}	419.6±3.881^{abcd}	403.4±14.30^{abcd}

Values with the same superscript alphabet are significantly different. *= p<0.05 **= p< 0.01, *** = p<0. 001.Values are expressed as means ±SD.

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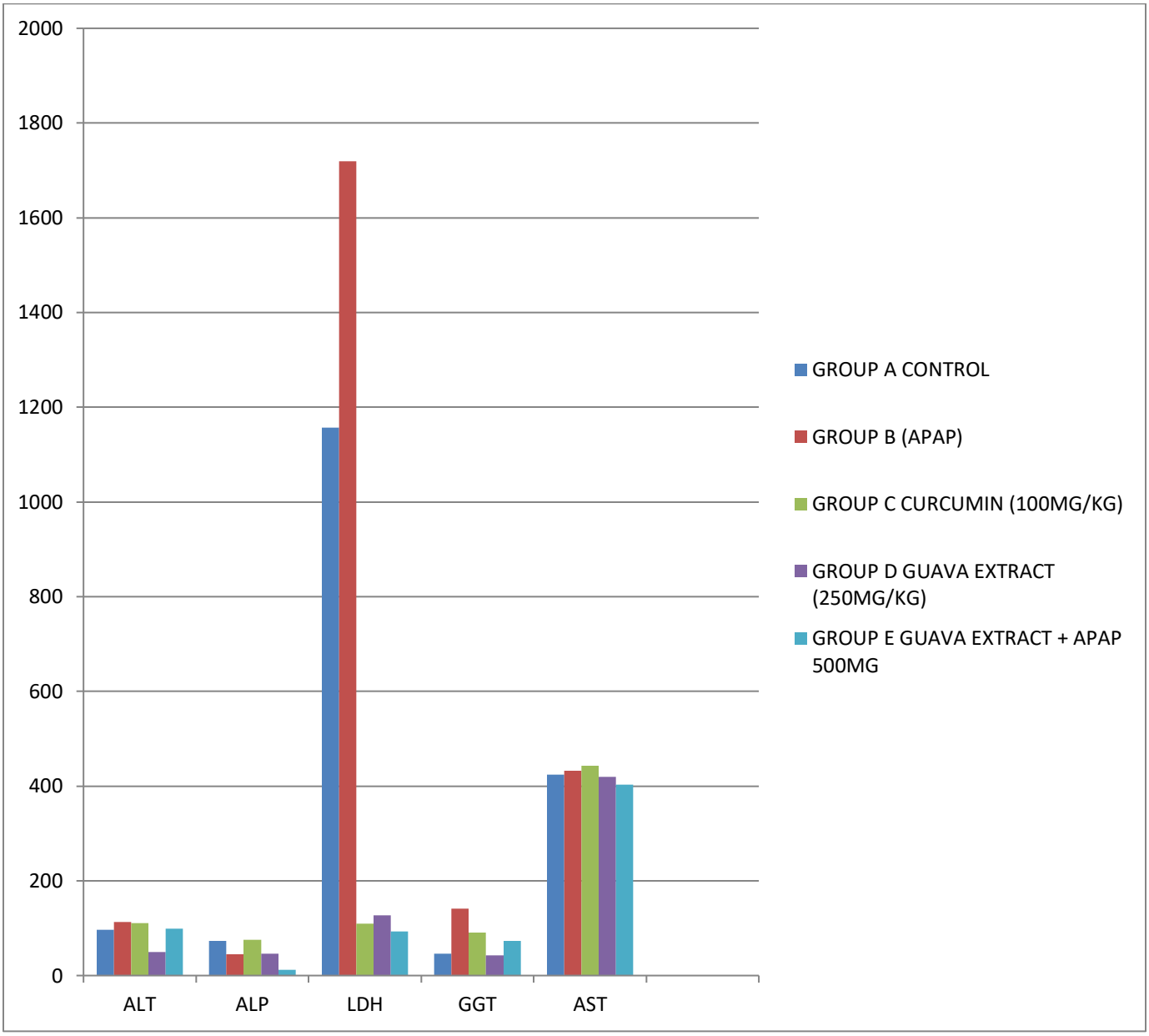

FIG 1: Showed the effect of guava (*Psidium guajava* Linn.) leaf extract in kidney enzymes, levels on Acetaminophen (APAP) in Albino Rat.

Table 3: Effects of guava *(Psidium guajava Linn.*). Leaf extract on total Serum Protein, Creatinine and Urea levels in APAP toxicity in albino Rats.

Parameters	**Group A Control**	**Group B Acetaminophen (APAP)**	**Group C Curcumin (100mg/kg)**	**Group D Guava Extract (250mg/kg)**	**Group E Guava Extract + APAP (500mg/kg)**
TP	5.57 ± 0.27^{abcd}	$6.42\pm0.05^{*}$	5.24 ± 0.12^{abcd}	$6.4\pm0.01^{c***}$	$6.44\pm 0.02^{d***}$
ALB	$3,54\pm0.13$	3.50 ± 0.03	3.68 ± 0.10	3.38 ± 0.05	3.56 ± 0.02
GLOB	2.04 ± 0.38	$2.92\pm0.089^{*}$	1.56 ± 0.18^{ab}	2.66 ± 0.33	$2.88\pm0.09^{b*}$
CREAT	0.30 ± 0.00^{abcde}	$0.58\pm0.04^{a***}$	$0.28\pm0.0^{abcde***}$	$0.54\pm0.02^{c***}$	$0.54\pm0.02^{d***}$
UREA	41.60 ± 4.86	37.60 ± 1.28	33.20 ± 4.07	35.80 ± 1.72	43.00 ± 0.02

Values with the same superscript alphabets are significantly different. *= $p< 0.05$, ** = $p <0.01$,***= $p< 0.001$.

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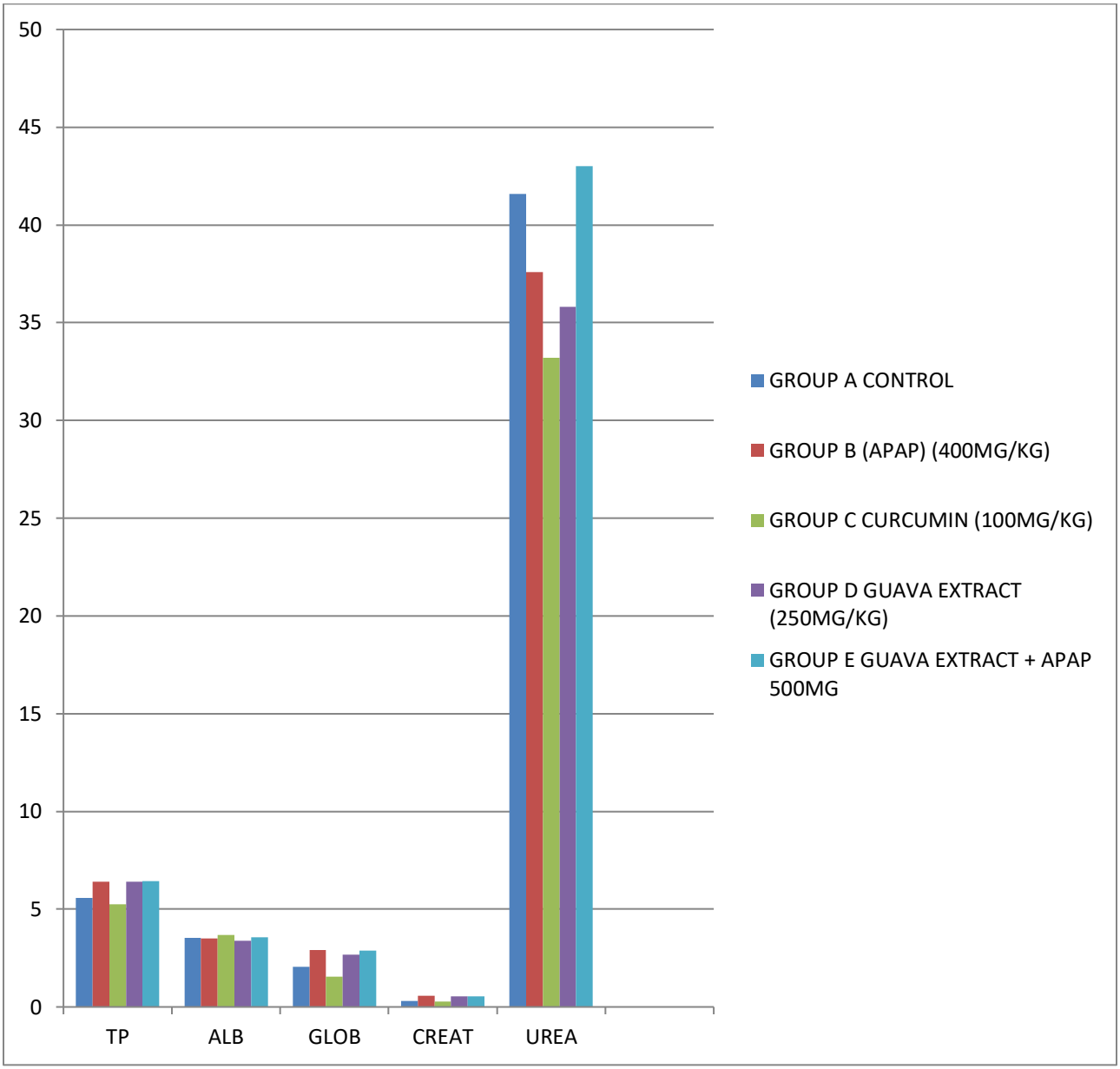

Fig 2: Showed the effect of Guava (*Psidium guajava* Linn.) Leaf extract on total serum Protein, Creatinine, Albumin, Globulin and Urea Levels in APAP toxicity in Albino Rat.

The total protein value was also significantly lower in Group C than were those treated with APAP 250mg/kg and 500mg/kg guava leaf extract ($p>0.01$), respectively. It was also lower than those of the untreated control and those treated with APAP only ($p>0.05$).

In the like manner, the globulin value was significantly lower in Group C than those treated with APAP only (Group B) and ADR +500mg/kg guava leaf extract Group E.

4. DISCUSSION:

Thephytochemical investigation of the extract of *P. guajava* leaf showed that absence of alkaloids and the presence of flavonoid, saponins, phenols, terpenes, sesquiterpenes and tannins. This result partially corroborates those of Biswas *et al*, (2013), which showed the presence of phenols, flavonoids, tannins, saponins, terpenoids and glycosides in the extract of the plant. The anti-bacterial activity of *P. guajava* extract may be due to the different groups of secondary metabolites found present in this extract. Indeed, the antimicrobial activity of medicinal plants is correlated with the presence in their extracts of one or more classes of bio-active secondary metabolites (Reuben, *et al*, 2008).

According to Tamokou, *et al*., (2017), a plant extract is considered to be highly active if the MIC < 100ug/ml, significantly active when 100≤MIC≤512-ug/ml, modetately active when 512< MIC ≤2048ug/ml; weakly active if MIC>2048ug/ml and not active when MIC>10mg/ml.

The flavonoid and tannins found in *P. guajava* extract have been shown to be important for wound healing due to their anti-oxidant, anti-inflammatory and antibacterial activities (Mulisa, *et al*., 2015). Many previous studies have shown that antimicrobial activity of wound can seriously delay the healing process by causing the formation of poor-quality granulation tissue, causing reduction of the tensile strength of the connective tissue as well as epithelization and the appearance of Odor (OECD, 1987 Annan and Houghton, 2008). Therefore, a high rate of wound contraction and a decrease in epithelization period in the animals treated with the extract in the excisional injury model are also attributed to the antibacterial properties of *P. guajava*.

Treatment with Acetaminophen (APAP) as demonstrated in the present study had an acute devastating effect on the kidney, as exemplified by the increases in the kidney enzymes creatinine, urea and total protein release into the body steam as a

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result of damages on the kidney cells by the presence of APAP. This obviously exacerbates the grave situation being experienced by cancer patients that are being treated by the drugs. This is not farfetched, as APAH and other anthracyclines, despite being the drugs of choice in cancer therapy because of their efficacy and efficiency of Granados-principal *et al*, (2010) produces considerable and debilitating acute and chronic side effects, some of which are irreversible especially in the heart, in the form of cardiomyopathy such as hypertension, cardiac dilatation, tachycardia and congestive heart failure. There could also be complementary loss of cardiomyopathy (Chen, *et al*., 2017).

Therefore, to prevent as much as possible side effect of APAP therapy in cancer patients, thus the use of dietary antioxidants and natural products, as shown in the present study, there was reduction of the kidney damage by APAP in the presence of guava leaf extract as observed by the reduced levels of ALT, ALP and GGT in the rats that were treated with the APAP and the extract. It might not be unconnected with the presence of Flavonoids, carotenoids and phenolic compounds as well as the free radical scavengers including terpenes, tannins and essential oil (Thaipong, *et al*, 2005).

The mechanism involved in the chemotherapeutic elucidated by previous studies. It is believed that APAP destroys cancer cells by inhibiting DNA synthesis via the blockage of topoisomerase II (Top2), the enzyme responsible for modification of DNA typology without altering the structure and sequence of deoxynucleotide (Granados-Principal, *et al*, 2010).

APAP also facilitates apoptosis of cancer cells via activation of p53. The most important mechanism of APAP employed in cancer therapy and conversely in the associated side effects is the generation of free radicals and other reactive oxygen species (Takemura and Fujiwara, 2007).
As stated by Granados-principal *et al*. (2010), Dox is transformed into a semi-Quinone free radical through election reduction by various NADPH – dependent reductases in the complex 1 of the electron transport chain (Cytochrome P-450 reductase). This Semi-quinine reacts with molecular oxygen to produce the super oxide radical (O_2) and it converts Dox into quinine. This quinine-semi quinine cycle generates large amount of O_2 which subsequently give rise to ROS and RNS

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species such as hydrogen peroxide (H_2O), hydroxyl radical (HO^-) or per oxy-nitrate (Quiles, *et al*, 2006).

APAP also has the ability to modify the chemical composition, structure and function of biological membranes, mainly at the mitochondrial level, fundamentally due to the peroxidation of membrane lipids, leading to the release of protein and cholesterol from the cytosol into the blood stream (Huertas, *et al*, 1992).

The extract of *Psidium guajava* could not ameliorate the kidney damage associated with APAP therapy as there was no improvement in the values of creatinine and urea in those rats that were treated with APAP and the extract, despite the fact that animals treated with 500mg/kg of the extract alone had value of creatinine and urea that were lower than the untreated control. We can deduce from this study that guava leaf extract has nephron protective activities.

It also demonstrated the capacity to lower blood triglyceride and cholesterol levels, although, it could only protect the kidney against APAP associated nephritic damages.

The nephritic-protective activity of guava leaf extract has been previously reported at 500mg.kg body weight against CCL_4, Paracetamol and Thioacetamide induced kidney damage in the rats as used in our current study. The nephrotic protective activity was attributed to the presence of antioxidants in the guava leaf extract (Roy, e*t al*, 2006).

In another study by Roy and Das (2010), evaluating the nephron-protective effects of different guava leaf extracts (petroleum ether, chloroform, ethyl-acetate, methanol and aqueous) against CCL_4 and Paracetamol induced nephrotoxicity in rats, nephron-protective activity of various leaf extract was also reported with methanol extract showing better protection against liver damage than the other forms of extract.

Apart from antioxidant activities, anti-bacterial, anti-diarrheal, anti-viral, anti-tussive and anti-inflammatory as well as anti-diabetes activities of *Psidium guajava* has been reported.

In conclusion, the present study demonstrated the nephron-protective properties of methanol guava leaf extract (*Psidium guajava* Linn.) as well as its ability to lower blood cholesterol and triglycerides when used alone. However, its use in the amelioration of APAP toxicity was limited to the protection of kidney in this study.

Our result showed that the selected dose of Paracetamol-induced nephrotoxicity in biochemistry aspects. The administration of *Psidium guajava* significantly reduced the toxic effect of APAP on the kidneys in a dose-dependent manner. The nephron-protective properties of *Psidium guajava* may be related to its positive effects on the antioxidant system. It is concluded that *Psidium guajava* can protect kidney from the damage caused by APAP over dose and might be a potential therapeutic candidate against Paracetamol- induced acute nephrotoxicity.

Conclusion

In light of this observation, we found out that therapeutic administration of *Psidium guajava* prevented APAP- induced oxidative stress changes. It can be speculated that the role of the *Psidium guajava* extract in preventing the formation of APAP-induced nephrotoxicity as seen in the present study, is in part due to the anti- inflammatory and anti-oxidant effects of the different enzymes. These Enzymes may interfere with anti-oxidant and anti-inflammatory mechanism, which may be crucial to reducing APAP-induced nephrotoxicity,

The use of *Psidium guajava* seeds for centuries as a condiment without side effects, and the desirable amount of effective substances present in the seeds encourage natural medicinal source.

RECOMMENDATION:

The world Health Organization (WHO, 2010) estimated that more than half of the world's population does not have access to sufficient health care services. This may be due to the fact that compliance to present health care service is very expensive in a country like Nigeria, where about 50% individuals live below the poverty line, getting prompt and proper medical attention/services becomes difficult for these individuals, hence, the need to encourage the use of alternative medicine in order to safe live and reduce mortality rates of preventable deaths.

Several researches have also replicated the antimicrobial, anti-inflammatory activities of plants (Bojo, *et al*, 1994).

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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