CODEINESUBSTITUTE CHALLENGES DRUG AND SUBSTANCE ABUSE CONTROLS IN NIGERIA: HISTOPATHOLOGY EVALUATIONS OF *NORVEGICUS RATTUS* ON LACATOMTOM

ABSTRACT

Codeine substitute challenges to drug and substance abuse controls in Nigeria: Histopathology evaluations of *NorvegicusRattus*on lacatomtom is novel research that aimed to evaluate the Codeine substitute challenges to drugs and substance abuse; histopathology perspective and oxidative biomarkers evaluation of the tissues cum chemical pathology analysis of the serum of the control and intervened subjects. The experimental subjects were grouped into control, acute and chronic (T1, T2, and T3) respectively; the acute groups of the oral administration of lacatomtom mixture were given 0.01mg/g of lacatomtom for 14 days while the chronic were given for 42 days and periodically weighed and recorded; The Animals were sacrificed and the organs harvested following ethical procedures for animal killing. The blood and tissues of the harvested organs (blood, lungs, liver, and kidney) under investigation were subjected to chemical pathology analysis to assess the liver and kidney functions, then proceeded to histopathological examination using formalin fixed paraffin processed methods with both routine and special stains, liver, lungs and kidney homogenate were subjected to oxidative stress biomarkers test (MDA, SOD, Gpx, GSH and Catalase). Histopathology results first revealed a severe cellular injury in all the organs under study compare to the normal control; significance ($p<0.5$) elevation found among some enzymes AST, ALP ALT are also an indication of damaged liver, increase MDA and reduced SOD, Gpx,GSH and catalase correlate the histology results and biochemistry.

***Keywords**: codeine substitute, drug, substance abuse, histopathology, Novegiusrattus, lacatomtom*

INTRODUCTION

La casera soft drink is non-alcoholic, flavoured, carbonated beverage commercially prepared and sold in Nigerian markets, shops, fast food joints and hawks cold on major road to the desires

of travelers among millions of its consumers, usually it is commercially prepared and sold in plastic bottles. Examples of such soft drinks include Coca-cola products: Coke, Fanta, Sprite; Mountain Dew, La Casera among others. It was launched in 2009 and is a flagship brand of the La Casera Company Plc. (Van Eygen*et al*., 2019).

In Southwest Nigeria, Olley (2020) found that 47% of the respondents (University students) smoked dried pawpaw leaf to get high. In Southeast Nigeria, Dumbili*et al*. (2020) reported that young adult interviewees (University undergraduates and graduates) used Gutter-Water (a cocktail of tramadol, cannabis, codeine, and vodka) and Monkey-Tail (a cocktail of locally-produced gin, cannabis seeds, leaves, stems, and roots). The study also revealed the use of a mixture of 'La Casera Apple Drink (carbonated soft drink) and 'Tom-Tom' (menthol-flavoured candy) to get high (Lacatomtom) (Dumbili*et al*., 2020). According to Dumbili*et al*. (2020), the motivations for taking these substances include heightening and prolonging intoxication and pleasure. In the North, Danjuma *et al*. (2015) examined the awareness of nonconventional use of substances among 204 youth. They found that 87% were aware that Northern youth smoke lizard waste, dry pawpaw leaf and seeds, Zakami (Daturametel) seeds, Moringa (Zogale) leaf, mandrakes, and also inhale/sniff hydrogen sulphide gas (sewer gas), nail polish, gun powder, amongst others as psychoactive substances. Furthermore, 40.5% stated that their friends or acquaintances use these substances (Danjuma *et al*., 2015). Aside from the BBC report on the codeine/dextromethorphancontaining cough syrup epidemic in the Northern Nigeria, other local and international media outlets have reported the use of plant-based and non-classical substances among young Nigerians and the associated poor mental health. For instance, some young people sniff/snort pit toilets or sewages and smoke the white part of lizard faeces and cobwebs, searching for 'chemical' or 'pharmacological' bodily effects (Kazeem and Chutel, 2018). BBC News Pidgin reportage of the National Drug Law Enforcement Agency's (NDLEA) media chat shows that aside from dry pawpaw leaf, people also smoke cassava and plantain leaf, spirogyra, and dry human faeces (Kazeem and Chutel, 2018). The report also highlighted that some inhale burnt tyres, while others drink a mixture of bleach (sodium hypochlorite solution) and carbonated soft drinks and 10-day-old urine for psychoactive effects. Both media reports (Kazeem and Chutel, 2018) and empirical research (Dumbili, 2020) have revealed the harm associated with the use of these non-classical substances in the country, in that some users of Gutter-Water have died from drug overdoses.

MATERIALS AND MATHODS

Study Area

This research was carried out in Animal House of Ebonyi State University Abakaliki, Histopathology Department Federal Teaching Hospital Abakaliki, Nigeria.

Sample size estimation/ sample selection

Resource Equation method (E) was used for the sample size estimation; the formular:
E = (Total number of animals in a group multiply by number of groups) - Number of groups as reported by Nnaemeka et al, 2022.

Inclusion criteria: Eligibility of the subjects includes; healthy Rattus norvegicus, body weight between 150g to 200 g and must be male *Rattusnorvegicus*.

Exclusive criteria: Other species of rats except Rattus norvegicus, non-healthy *Rattus norvegicus*, and body weight below 150g or above 200 g were excluded in this study.

Experimental animal

Twenty-one (21) *Rattus norvegicus* with average weight of 275 g was procured from the central animal house of the College of Health Sciences of Ebonyi State University, Abakaliki, were all housed in Histopathology laboratory, allowed to acclimatize to the standard laboratory conditions (Nnaemeka et al, 2022).

Experimental Design

The experimental subjects were grouped into three (T1, T2 and T3) which are normal control (group without any intervention), Acute and chronic oral administration of lacatomtom ‘gigabyte’ solution respectively. Each of the groups contains seven replicate of the subjects and

each subjectin the intervention groups were given 0.01mg/g twice daily for 21 and 42 days for acute and chronic administration respectively with body weight obtained in each of the subjects in the group. The animals were all in their individual cages throughout the period of study till termination.

Sacrifice and Collection of Samples

The animals were anaesthetized using chloroform vapour in an enclosed transparent plastic jar, bloods were collected in plain container through cardiac puncture for chemical pathology analysis dissected to remove the Liver, kidney and lung; parts were fixed in 10% Buffered formal saline for histopathological evaluation, others then homogenized to demonstrate oxidative stress biomarkers using standard methods (Nnaemeka, 2022).

Laboratory Analysis

Liver, lungs and kidney specimens were grossed into triplicates, processing using conventional paraffin wax methods, using automatic Tissue Processor and embed using standard embedding Centre, sectioned and stained using both routine and special stained, oxidative stress biomarkers were done using standard method (Nnaemeka et al, 2022).

RESULTS

Plate 1a and b is a liver section of Norvegicus Rattus on acute administration of la caseratomtom mixture and its control

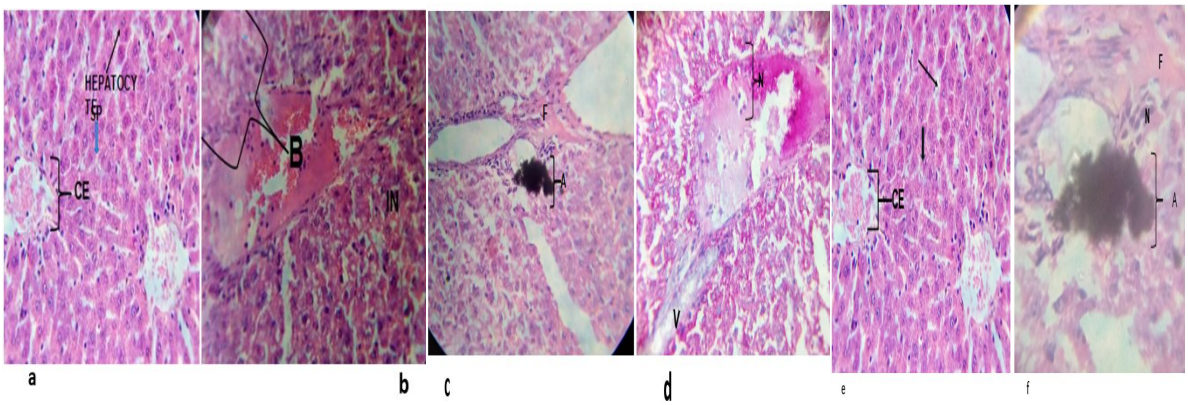

Plate 1 a Mag. X40 is a negative control liver section of *Norvegicusrattus* stained with H&E; The central vein **(CE).** Hepatocytes (black arrow) and the sinusoidal space **SP** (black arrow) are all well demonstrated and appeared normal. Plate 1b Mag. X40 is a liver section of same specie as in plate 1a on acute La caseratomtom mixture; section revealed ballooning **(B**) of hepatocyte as a manifestation of apoptosis (necrosis) and pink fibrin (**IN)** deposition occluding the sinusoidal space. The increase of serum AST and ALT observed also shown the level of hepatic necrosis seen

Plate 1c and 1d are liver sections of Norvegicus Rattus on chronic administration of la caseratomtom mixtures

Plate 1c Mag. X40 is a liver section of Norvegicus Rattus on chronic oral administration of la caseratomtom mixture stained with H&E; walls of the portal triad shown hemorrhagic with dark stained deposition (A) and fibrotic tissues shown a great level of cirrhosis (F) with infiltrating polymorphs. Plate 1d Mag. X40 is a liver section of Norvegicus Rattus on chronic La caseratomtom mixture stained with periodic acid Schiff. The section shown congested with vacuolated cells (V) (necrosis) and the central vein are filled with red cells deposition and infiltrating neutrophils (N)

Plate 1e and f are liver sections of Norvegicus Rattus on chronic administration of la caseratomtom mixture and its control

Plate 1 e Mag. X40 is a negative control liver section of Norvegicus Rattus stained with H&E, the central vein CE, sinusoidal space (Thin black arrow) and hepatocytes (Thick black arrow) are

all well demonstrated and appeared normal. Plate 1f Mag. X40 is a liver section of Norvegicus Rattus on oral chronic administration of la caseratomtom mixture; the section shown moderately cirrhosis or fibrosis (F) of tissues and heavy infiltrating neutrophils (N). Necrotic dark appearance of hemorrhagic vessels (A) and cellular vacuolation are seen

Plate 2a and b are lungs sections of Norvegicus Rattus on acute administration of la caseratomtom mixture and its control

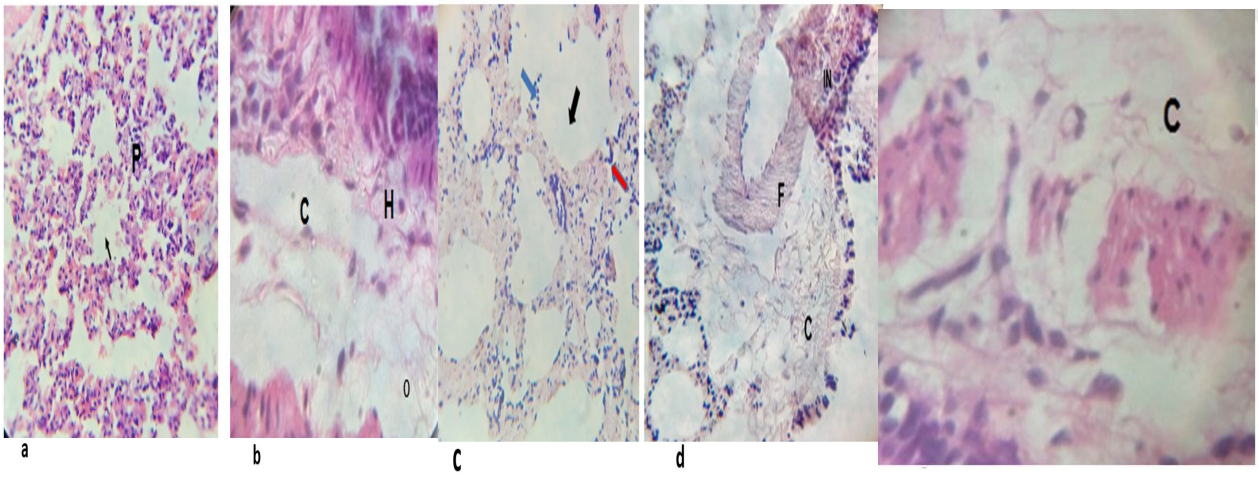

Plate 2a Mag.X10 is a negative control lung tissue section of *Norvegicus Rattus*; it shown the normal alveoli spaces and pneumocytes. Plate 2b Mag. X40 is lung section of Norvegicus Rattus on acute administration of la caseratomtom mixture; the section shown a collapsed congested alveoli wall (C), honeycombed appearance of distorted pneumocytes with edematous background (o)

Plate 2c and 2d are lungs sections of Norvegicus Rattus on chronic administration of la caseratomtom mixture and its control

Plate 2c Mag. X10 is a negative control lung tissue section of *Norvegicus Rattus* stained with phosphotungstic acid hematoxylin; section shown the normal alveoli air spaces (black arrow), Type I pneumocytes (blue arrow), and type II pneumocytes (red arrow) all the histological cellular pattern appeared normal. Plate 2d Mag. X10 is a lung tissue section of *Norvegicus Rattus*

on chronic administration of la caseratomtom mixture; the section shown a collapsed congested alveoli wall (C), honeycombed appearance of distorted pneumocytes with edematous background and fibrotic collagenous deposition **(F)** congesting the alveoli walls, seen also are inflammatory cells infiltrating the alveoli (**IN)**

Plate 2e are lungs sections of Norvegicus Rattus on chronic administration of la caseratomtom

Plate 2e Mag. X40 is a lung section of Norvegicus Rattus on chronic oral administration of la casera tom tom mixture the section shown; collapse congested alveoli wall (C), honeycombed appearance of distorted pneumocytes with edematous background consistence with atypical respiratory distress

Plate 3a and b are kidney sections of Norvegicus Rattus on acute administration of la caseratomtom mixture and its control

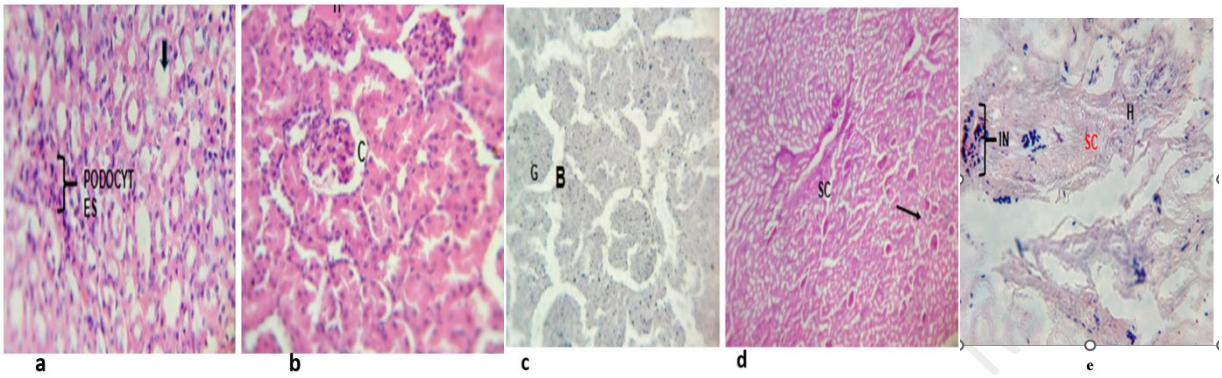

Plate 3a Mag. X40 is a negative control kidney section of a *Norvegicus Rattus* stained with H&E; section shown collecting ducts (black arrow) and podocytes and all appeared normal. Plate 3b is same specie as in plate 4.3a on acute oral administration of la casera tom tom mixture; section shown hyaline droplet in the glomerular tuft (**H**) with inflammatory cells, clear capsular spaces were seen

Plate 3c and 3d are kidney sections of Norvegicus Rattus on chronic administration of la caseratomtom mixture and its control

Plate 3c Mag. X40 is a negative control kidney tissue section stained with methenamine silver stain; section revealed glomerular contents and capsular spaces that appeared normal. Plate 3d is a kidney section of *Norvegicus Rattus* on chronic La caseratomtom mixture administration stained with periodic acid Schiff, section shown extensive glomerular hyalinization with

moderate renal sclerosis (**SC**), the numerous present of red blood cells (black arrow) is evidence of inflammatory lesion

The plate 3e Mag. X40 is a kidney section of Norvegicus Rattus on chronic oral administration of la caseratomtom mixture stained with phosphotungstic acid hematoxylins. The section shown hyalinization of glomerular tuft **(H),** thick sclerosis of the glomerular capillaries **(SC)** and infiltrating neutrophils **(IN)** inflammatory cells

Effects of Lacasara-Tomtom mixture on Oxidative Stress Markers in Norvegicusrattus Liver

Acute oral administration of La caseratomtom mixture on *norvegicusrattus* significantly ($p<0.05$) elevated the level of MDA and significantly($p<0.05$) reduced the activities of catalase, SOD, GPx and level of GSH in rat lung in time dependent manner.

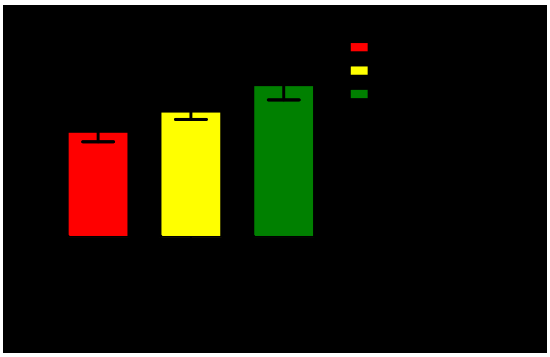

Figure 1a: Effects of Lacasara-Tomtom mixture on Liver Malondialdehyde Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-tomtom Liver (ACUTE LACATOM and Chronic Lacasara-tomtom liver (CHRONIC LACATOML)

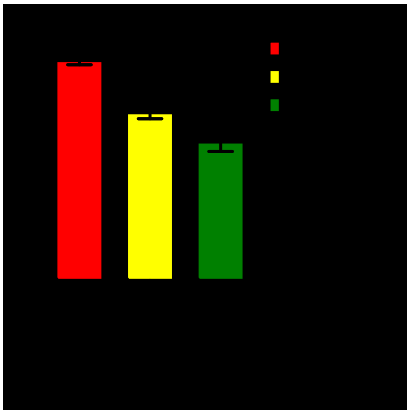

Figure 1b: Effects of Lacasara-Tomtom mixture on Liver Catalase Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-tomtom Liver (ACUTE LACATOML and Chronic Lacasara-tomtom liver (CHRONIC LACATOML)

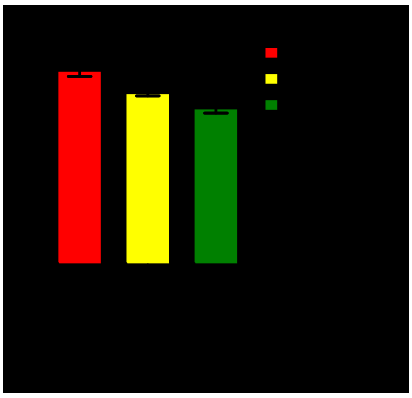

Figure 1c: Effects of Lacasara-Tomtom mixture on Liver Superoxidise dismutase Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-tomtom Liver (ACUTE LACATOML and Chronic Lacasara-tomtom liver (CHRONIC LACATOML)

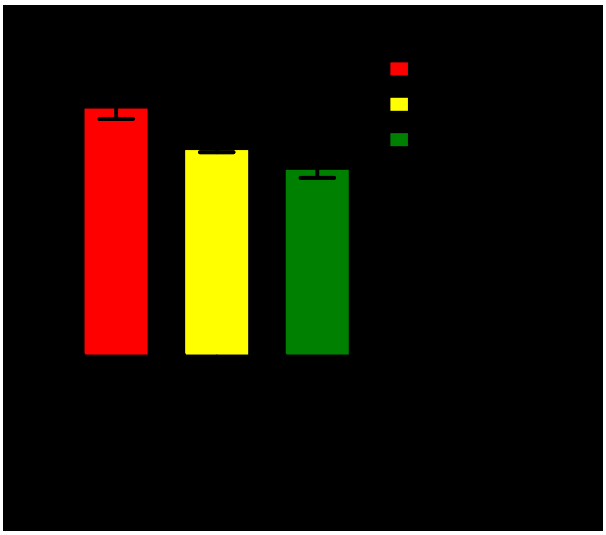

Figure 1d: Effects of Lacasara-Tomtom mixture on Liver Glutathione Peroxidase Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-tomtom Liver (ACUTE LACATOML and Chronic Lacasara-tomtom liver (CHRONIC LACATOML)

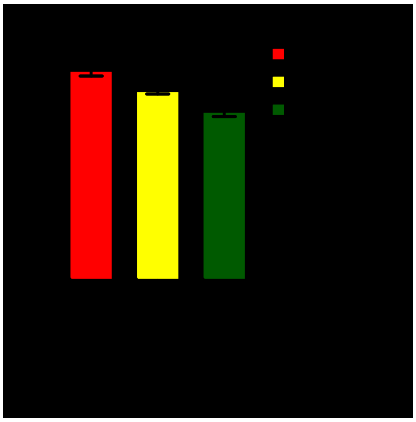

Figure 1e: Effects of Lacasara-Tomtom mixture on Liver Reduced Glutathione Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom Liver (ACUTE LACATOML and Chronic Lacasara-Tomtom liver (CHRONIC LACATOML)

Effects of Lacasara-Tomtom mixture on Oxidative Stress Markers in Rat Lung

Administration of Lacasara-Tomtom mixture in *Norvegicusrattus* significantly ($p<0.05$) elevated the level of MDA and significantly($p<0.05$) reduced the activities of catalase, SOD, GPx and level of GSH in rat lung in time dependent manner.

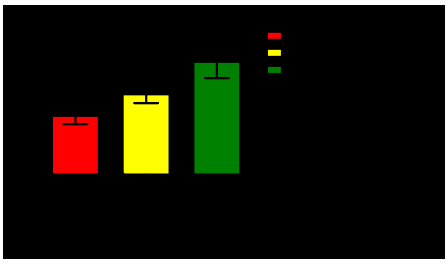

Figure 2a: Effects of Lacasara-Tomtom mixture on Lung MDA Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom Lung

(ACUTE LACATOM Lung and Chronic Lacasara-Tomtom lung (CHRONIC LACATOM Lung)

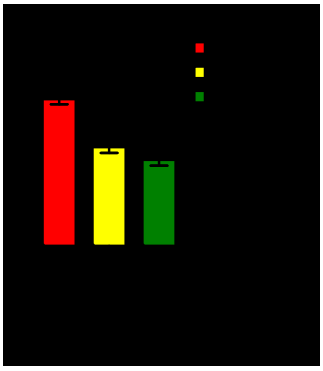

Figure 2b: Effects of Lacasara-Tomtom mixture on Lung Catalase Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom Lung (ACUTE LACATOM Lung and Chronic Lacasara-Tomtom lung (CHRONIC LACATOM Lung)

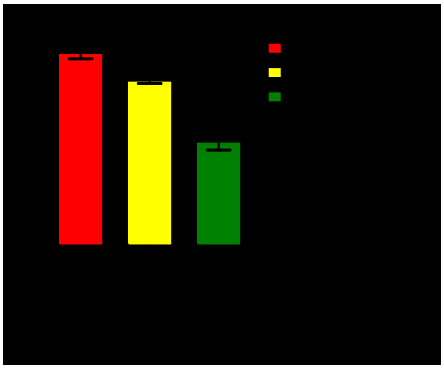

Figure 2c: Effects of Lacasara-Tomtom mixture on Lung SOD Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom Lung (ACUTE LACATOM Lung and Chronic Lacasara-Tomtom lung (CHRONIC LACATOM Lung)

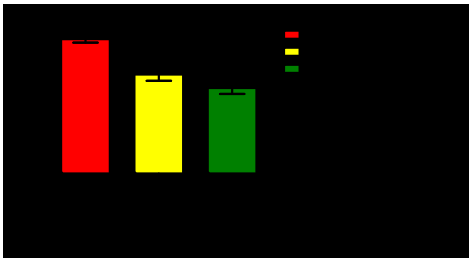

Figure 2d: Effects of Lacasara-Tomtom mixture on Lung GPx Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom Lung (ACUTE LACATOM Lung and Chronic Lacasara-Tomtom lung (CHRONIC LACATOM Lung)

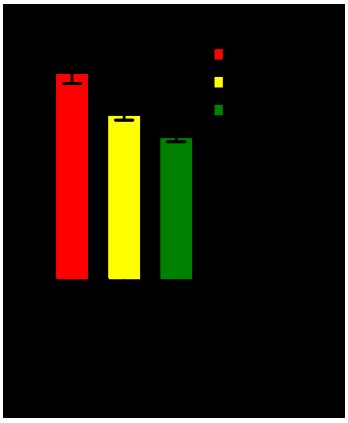

Figure 2e: Effects of Lacasara-Tomtom mixture on Lung GSH Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom Lung (ACUTE LACATOM Lung and Chronic Lacasara-Tomtom lung (CHRONIC LACATOM Lung)

Effects of Lacasara-Tomtom mixture on Serum Liver Function indices in Rat

Administration of Lacasara-Tomtom mixture in *norvegicusrattus* significantly ($p<0.05$) elevated the activities of ALP, AST, ALT, levels of total bilirubin and direct bilirubin. A significantly ($p<0.05$) reduction in the levels of albumin and total protein in time dependent manner was observed.

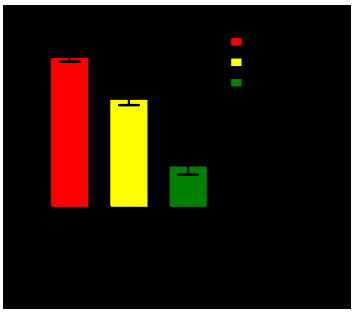

Figure 3a: Effects of Lacasara-Tomtom mixture on Albumin Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

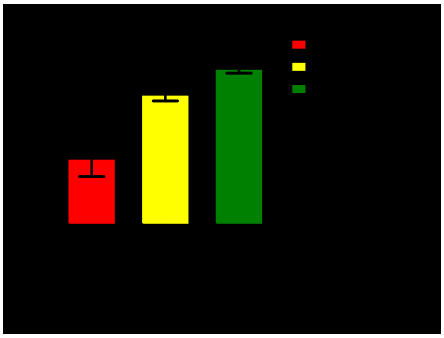

Figure 3b: Effects of Lacasara-Tomtom mixture on ALP Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

Figure 3c: Effects of Lacasara-Tomtom mixture on ALT Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

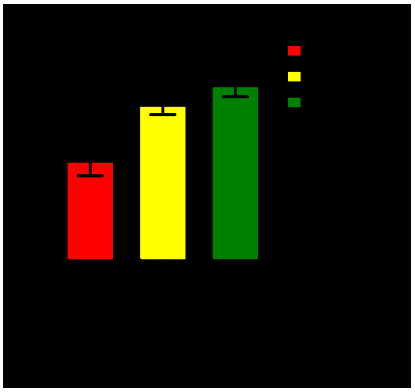

Figure 3d: Effects of Lacasara-Tomtom mixture on AST Activity in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

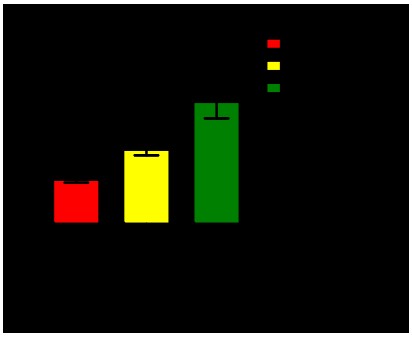

Figure 3e: Effects of Lacasara-Tomtom mixture on Total bilirubin Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

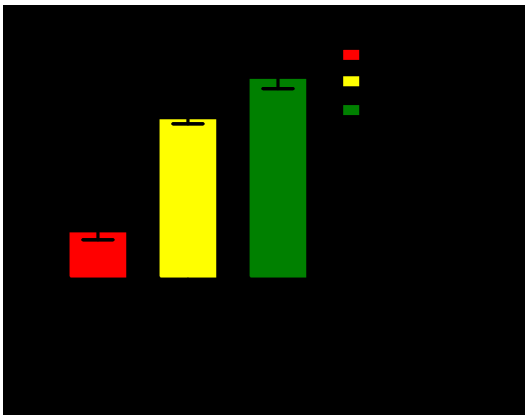

Figure 3f: Effects of Lacasara-Tomtom mixture on Direct bilirubin Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

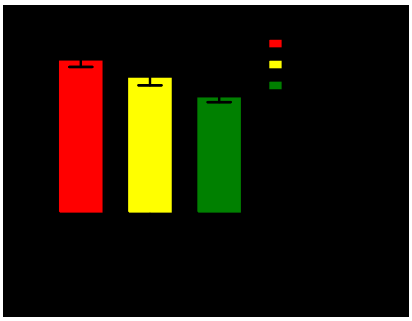

Figure 3g: Effects of Lacasara-Tomtom mixture on Total protein Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

Effects of Lacasara-Tomtom mixture on Plasma Kidney Function indices in Norvegicus Rattus

Administration of Lacasara-Tomtom mixture in rats significantly ($p<0.05$) elevated the levels of creatinine, urea, potassium, chloride and sodium levels in time dependent manner (Figures 1-5).

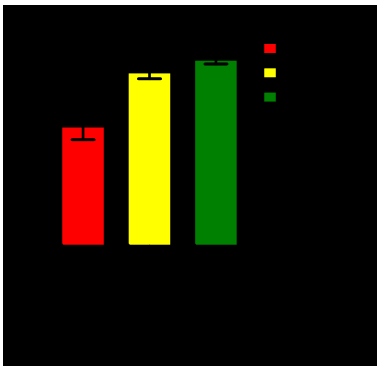

Figure 4a: Effects of Lacasara-Tomtom mixture on Creatinie Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

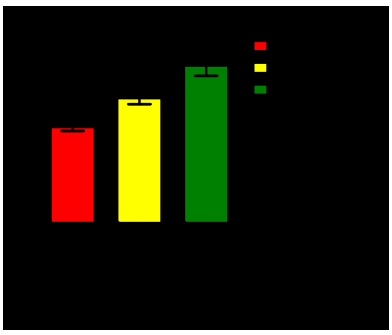

Figure 4b: Effects of Lacasara-Tomtom mixture on Urea Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

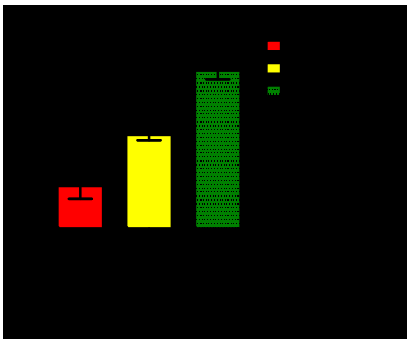

Figure 4c: Effects of Lacasara-Tomtom mixture on Potassium Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

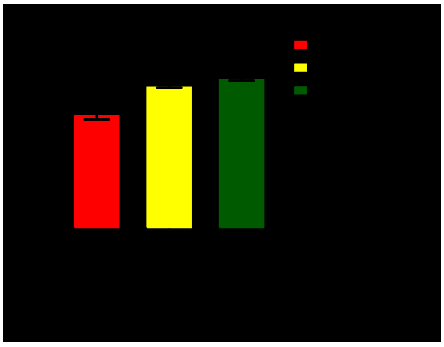

Figure 4d: Effects of Lacasara-Tomtom mixture on Chloride Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

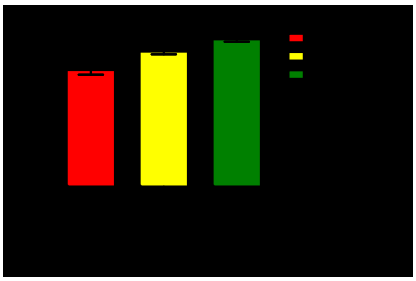

Figure 4e: Effects of Lacasara-Tomtom mixture on Sodium Level in Rats. Mean values with different sign are significantly different at P<0.05. Acute Lacasara-Tomtom (ACUTE LACATOM) and Chronic Lacasara-Tomtom (CHRONIC LACATOM)

Effects of Lacasara-Tomtom mixture on body weight of *Norvegicus Rattus*

Administration of Lacasara-Tomtom mixture in rats significantly ($p<0.05$) reduced the body weight of the experimental rats.

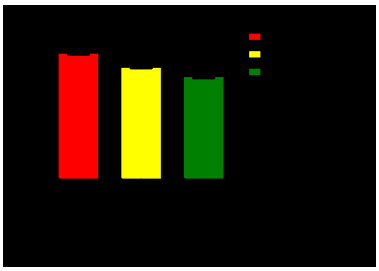

Figure 5: Effects of Lacasara-Tomtom mixture on body weight of *Norvegicus Rattus*

DISCUSSION

Plate 1 a Mag. X40 is a negative control liver section of *Norvegicusrattus* stained with H&E; The central vein **(CE).** Hepatocytes (black arrow) and the sinusoidal space **SP** (black arrow) are all well demonstrated and appeared normal. Plate 1b Mag. X40 is a liver section of same specie as in plate 1a on acute La caseratomtom mixture; section revealed ballooning **(B**) of hepatocyte as a manifestation of apoptosis (necrosis) and pink fibrin (**IN)** deposition occluding the sinusoidal space. Abusive substances and drugs are notable to cause liver diseases among which has been reported by Raj et al. (2011). The increase of serum AST and ALT observed also shown the level of hepatic necrosis seen. Plate 1c Mag. X40 is a liver section of Norvegicus Rattus on chronic oral administration of la caseratomtom mixture stained with H&E; walls of the portal triad shown hemorrhagic with dark stained deposition (A) and fibrotic tissues shown a great level of cirrhosis (F) with infiltrating polymorphs. Plate 1d Mag. X40 is a liver section of Norvegicus Rattus on chronic La caseratomtom mixture stained with periodic acid Schiff. The section shown congested with vacuolated cells (V) (necrosis) and the central vein are filled with red cells deposition and infiltrating neutrophils (N). Plate 1e Mag. X40; negative control liver section of *Norvegicus Rattus* stained with H&E, the central vein CE, sinusoidal space (Thin black arrow) and hepatocytes (Thick black arrow) are all well demonstrated and appeared normal while Plate 1f Mag. X40 is a liver section of *Norvegicus Rattus* on oral chronic administration of la caseratomtom mixture; the section shown moderately cirrhosis or fibrosis (F) of tissues and heavy infiltrating neutrophils (N). These findings agreed with the findings obtained by Shaymaa, (2019) in which there was a significant increase in AST, ALT and ALP levels in the group of rats that were induced with oxidative stress with lead acetate. The serial increase of the above liver enzymes that are known markers for hepatic damage is evidence that both acute and chronic

administration of la caseratomtom mixture is toxic to the system and capable of causing systemic organ failure as seen during the administration a situation three experimental subjects died immediately at the point of given the mixture; the autopsied samples revealed systemic organ failure; total respiratory collapse seen in the lungs, severe liver cum kidney damage observed.

Consequently, there was also an increase in bilirubin levels both direct and total in both acute and chronic groups with the chronic group having higher levels this agreed with the findings of Stocker *et al*. (1987) and Wu *et al*. (1994). This could in a bid to correct the oxidative stress imparted on the liver by the consumption of lacatomtom as Bilirubin has been recognized as a potent antioxidant. Bilirubin suppresses the oxidation of lipid in liposomes more than vitamin E, which is regarded as the best antioxidant of lipid peroxidation. Necrotic dark appearance of hemorrhagic vessels (A) and cellular vacuolations are seen and that agreed with the report of Wu et al.(1994). Plate 2b Mag. X40 is lung section of *Norvegicus Rattus* on acute administration of la caseratomtom mixture; the section shown a collapsed congested alveoli wall (C), honeycombed appearance of distorted pneumocytes with edematous background (o) unlike plate 4.2b which shown no pathological changes. Plate 2d Mag. X10 is a lung tissue section of *Norvegicus Rattus* on chronic administration of la caseratomtom mixture; the section shown a collapsed congested alveoli wall (C), honeycombed appearance of distorted pneumocytes with edematous background and fibrotic collagenous deposition **(F)** congesting the alveoli walls, seen also are inflammatory cells infiltrating the alveoli (**IN).** Plate 2e Mag. X40 is a lung section of *Norvegicus Rattus* on chronic oral administration of la caseratomtom mixture the section shown; collapse congested alveoli wall (C), honeycombed appearance of distorted pneumocytes with edematous background consistence with atypical respiratory distress. Plate 4a Mag. X40 is a negative control kidney section of a *Norvegicus Rattus* stained with H&E; section shown collecting ducts (black arrow) and podocytes and all appeared normal. Plate 4b is same specie as in plate 4.3a on acute oral administration of la caseratomtom mixture; section shown hyaline droplet in the glomerular tuft (**H**) with inflammatory cells, clear capsular spaces were seen; Plate 4d is a kidney section of *Norvegicus Rattus* on chronic La caseratomtom mixture administration stained with periodic acid Schiff, section shown extensive glomerular hyalinization with moderate renal sclerosis (**SC**), the numerous present of red blood cells (black arrow) is evidence of inflammatory lesion. The evidence of systemic damage by the lacaseratomtom mixture cannot be taking for granted. The actually revealed same histologic pattern of the most damage caused

by poisonous chemical agents and dangerous drugs; however, it should be noted that La casera is a well-known soft drink highly consumed by Nigerians though they have been a speculation and doubt concerning its safety following its ability to wash off stains better than some commercially sold detergent. No available reported evidence of lacasera allergy during this research same with tomtom candy sweet; basically, the two substance is known to be abusive when combined together, originally both substances are manufactured by different companies and were not made to be taken in combination; and this redefined abuse substance to be any two or more substances arbitrary combined and used without the permissions and safety grantee by the companies of the substances. It is worthy to note that when two or more substances produced by either same or different companies are combined a new product with entirely different biological effect will be produced.

Administration of Lacasara-Tomtom mixture in *Norvegicusrattus*significantly ($p<0.05$) elevated the level of MDA and significantly($p<0.05$) reduced the activities of catalase, SOD, GPx and level of GSH in rat lung in time dependent manner. Administration of Lacasara-Tomtom mixture in *norvegicusrattus* significantly ($p<0.05$) elevated the activities of ALP, AST, ALT, levels of total bilirubin and direct bilirubin. A significantly ($p<0.05$) reduction in the levels of albumin and total protein in time dependent manner was observed. Administration of Lacasara-Tomtom mixture in rats significantly ($p<0.05$) elevated the levels of creatinine, urea, potassium, chloride and sodium levels in time dependent manner. Administration of Lacasara-Tomtom mixture (Lacatomtom) in rats significantly ($p<0.05$) reduced the body weight of the experimental rats.Increase MDA is a strong indication of free radical synthesis as revealed in both acute and chronic administration in time dependent manner.

Conclusion

The production of codeine-like substance and the subsequent consumption of such soft drinks mixed with tomtom candy ‘Gigabyte’ for the purpose to attain a euphoric feeling commonly called highness has led most youth to the mixture of tomtom candy in soft carbonated drink called lacasera to produce lacatomtom, the consumption of this drink has deleterious effects on both the liver, kidney and lung among others. This practiced was noticed more during the covid-19 lockdown in Nigeria, where movement were highly restricted. This study revealed that

lacatomtom solution could lead to multi-systemic failure and sudden death as observed in two subjects used for this study whose autopsy examination revealed a total collapse of respiratory Centre upon initial administration of the solution. It is also worthy to note that high propensity to lacatomtom cocaine substitute is more among less engaged or unemployed youth and adults. It is a real challenge because the country has no law against anyone on excess or mixed consumption of soft drink and tomtom candy. Unfortunately, it is been observed to be consumed publicly without feeling of been prosecuted. The malnormal seen among the study subject relatively revealed the circumstances surrounding mysterious sudden death encounter by most persons already addicted to lacatomtom mixture

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