



**ASSESSMENT OF SAFETY AND MICROBIAL QUALITY OF COMPOUNDED
CARBAMAZEPINE SYRUPS**

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Abstract

Chemically, carbamazepine is 5H-dibenzo azepine-5-carboxamide. It is a highly lipophilic, neutral tricyclic molecule, crystalline powder that is practically odourless and white to off-white in colour. It is a sodium channel blocker that acts by differential binding to energy-gated sodium channels in their inactive conformation. It is recommended for the treatment of generalized tonic-clonic seizures and partial seizures with simple or complicated symptomatology, trigeminal neuralgia, and bipolar disorder. This medication is readily available in tablet dosage forms and company manufactured liquid dosage forms as well. In the absence of the liquid dosage forms, the medication is extemporaneously prepared using readily available syrups as the vehicle. The compounded carbamazepine syrups have been used in practice but there is little information about the safety and quality. The aim of the study was to assess the microbiological quality of the compounded carbamazepine syrups and also study the safety by evaluating the effect of these preparations on kidney function, liver function, haematology and histopathology of laboratory rats. Microbiological quality of the formulations was evaluated by determining the total aerobic microbial count, total mold and yeast count, and identification of E. coli. The safety study was conducted by using laboratory rats which were grouped into treatment, positive control and negative control groups, where syrup compounded carbamazepine, distilled water compounded carbamazepine and distilled water were administered respectively for 28 consecutive days. The liver function test, kidney function test, hematological tests and histological examinations were all conducted and the findings were compared to reference/normal values. All the samples passed the microbiological quality test across the test period of 42 day for all the storage conditions. The rats

had normal levels of electrolyte, urea, creatinine, liver enzymes as well as total protein and albumin. Haematological parameters were also within the normal range. Histological examination of the kidney revealed normal findings corresponding to the kidney function test results. Liver histology was also basically normal, however cytoplasmic vacuolation was observed in the treatment and positive control groups which was linked to the drug metabolic activities. The findings suggest that compounded carbamazepine syrups had very good microbial quality and were found to be safe.

Keywords: carbamazepine, *E. coli* liver function, kidney function, histopathology.

Introduction

The "Swiss Chemist Walter Schindler" made the discovery of carbamazepine in 1953 at the J.R. Geigy AGin Base in Switzerland. It was first marketed as a drug to treat trigeminal neuralgia in 1962 under the "Tegretol" brand. Later, its anti-epileptic properties were discovered (Bagal *et al.*, 2025).

Carbamazepine has a high oral bioavailability in humans (Marino *et al.*, 2012). Urine only removes a small amount of it. Carbamazepine 10,11 epoxide is an active metabolite of carbamazepine, with anticonvulsant properties similar to those of its parent medication (Chbili *et al.*, 2017).

Therapeutic concentrations of carbamazepine have been observed to range from 6 to 12 µg/mL. The main enzymes involved in the drug's metabolism, CYP3A4 and CYP2B6, are strongly induced by carbamazepine; this phenomenon is referred to as auto-induction. During the first few weeks of dosing, this feature causes the plasma drug levels to dramatically decline (Ware *et al.*, 2016).

Common etiology for carbamazepine toxicity is coadministration of other medications. Any inhibitor of cytochrome P450, such as grapefruit juice, will cause elevated levels of carbamazepine. An intentional overdose of

carbamazepine is less common and usually seen with a suicide attempt in a severely depressed patient during the initial administration of the medication. The mortality rate due to carbamazepine toxicity is around 13 % (Ware *et al.*, 2016).

A prior study found that rats given a therapeutic dose of levetiracetam or carbamazepine for 28 days had significantly higher amounts of malondialdehyde and alkaline phosphatase. Superoxide dismutase activities, on the other hand, dramatically dropped after receiving either levetiracetam or carbamazepine. When compared to the control group, the carbamazepine and carbamazepine + levetiracetam treatment groups showed a considerable increase in alanine-aminotransferase activity. The carbamazepine-treated group's liver sections displayed modest vascular congestion. (Osuntokun *et al.*, 2021).

In practice, conventional carbamazepine dosage forms include immediate release tablets, sustained release tablets and suspensions. Many a times, in absence of or lack affordability of the liquid dosage forms for paediatric use, the carbamazepine tablets are compounded extemporaneously and administered to this category of patients. The

vehicles used include, distilled water, glycerol, multivitamin or vitamin C syrups and sometimes Syr BP. The focus of this work is to study the microbial quality and safety of the compounded carbamazepine syrups using Syr BP as a vehicle. This is important as it will give an idea on the impact of the vehicle and the method of preparation on the delivery, quality and safety of the formulations.

METHOD

Microbiological Quality Assay

Carbamazepine syrups were extemporaneously prepared at the strength of 2 mg/mL and stored at four storage conditions. A refrigerator, the laboratory desk, the store, and an elevated temperature. In order to achieve an elevated temperature, a portable room heater was used. It was turned on every day between 9:00 and 9:30 am and left running until 4:30 or 5:00 pm to simulate the rise and fall in temperature that occurs in real life during the day, particularly in hot climates during the summer. In order to replicate the nature of a household's power supply, the refrigerator was also let to run for roughly 48 to 72 hours before being turned off for a further 3 to 5 hours and, on some days, for 7 to 10 hours before being turned back on. Those stored on the lab desk, however, were allowed to remain there. All of the bottles are opened and closed daily to check for any physical changes in the formulation and to replicate the conditions these preparations would encounter in real life.

Total Aerobic Microbial Count (TAMC)

Aseptically, 1 mL of each sample was taken out and put into 9 mL of regular saline for serial dilution to 10^5 . For the medication to dissolve properly, diluted samples were thoroughly combined. To isolate *Escherichia coli* and all live bacteria, 0.1 mL of each sample (from 10^{-2} and 10^{-4}) was aseptically disseminated onto nutrient agar and MacConkey agar. After that, inoculated plates were incubated at 37°C for 24 hours. For every mL of syrup sample, the average number of colony forming units (cfu) was calculated by counting the bacterial colonies using a colony counter (Gurung and Rai, 2021).

Total Mold and Yeast Count (TYMC)

To count the mold and yeast, 0.1 mL of dilution was plated on Sabouraud dextrose agar. The plates were then incubated at 25°C for five to seven days. Using a colony counter to count the fungal colonies, the average amount of CFU for each milliliter of syrup sample was determined (Gurung and Rai, 2021).

Identification of *E coli*

Separation and refinement were applied to the unique colonies grown on MacConkey agar plates. Their physical, biochemical, and cultural characteristics were then employed to describe them (Gurung and Rai, 2021).

Biological Studies

In the animal house of the Faculty of Veterinary Medicine, University of Maiduguri, Maiduguri, Nigeria, nine albino Wistar rats were obtained and kept in a 12-hour light/dark cycle, natural temperature, and humidity. Approval was given after

ethical clearance was filed for. The animals were employed for the investigation as detailed in the subsections below after being acclimated for seven days by giving them free access to water and a standard pellet diet (Osuntokun *et al.*, 2021).

Three groups were formed from the nine rats (three rats per group). Positive control, negative control, and treatment group. Syrup BP was used as the vehicle to compound carbamazepine, while distilled water was used as the vehicle in another preparation. For twenty-eight days in a row, the treatment group received a dose of 25 mg/kg/day of carbamazepine syrup, the positive control group received a dose of 25 mg/kg/day of carbamazepine formulated in distilled water, and the third group received distilled water. The animals' blood samples were taken in sample vials after the 28th day and kept in a fridge with ice packs. Afterwards the various biochemical and haematological tests were conducted. After the animals were sacrificed, their livers and kidneys were taken out and kept for later use in histological examination.

Tissue processing

The tissues were processed using Automatic Tissue Processor (Leica Type). Tissue dehydration was carried out through ascending grades of ethanol (70%, 80%, 90%, and Absolute). Clearing was performed using xylene to replace the dehydrating agent and render it translucent. Paraffin wax infiltration was carried out to impregnate the tissue to make it firm for sectioning.

Embedding

The processed tissues were embedded in paraffin wax using Leica embedding station.

The tissues were placed in a metal embedding molds containing molten paraffin wax, it was carefully oriented to ensure optimal histological presentation. Embedding cassettes were placed over the molds, molten paraffin was poured and allowed to cool and solidify to form paraffin embedded tissue blocks.

Sectioning

The Paraffin-embedded tissue blocks were trimmed using Leica rotary Microtome. The section obtained was placed onto a float plate containing 20% alcohol using forceps, floated on a warm water bath to eliminate folds and wrinkles and then mounted onto albuminized clean grease free microscope slides. Slides were dried on a hot plate to enhance tissue adhesion.

Haematoxylin and Eosin (H&E) Staining

Mounted tissue sections were deparaffinized in xylene and rehydrated through descending grades of ethanol (absolute, 90%, 80% 70%) to distilled water. Nuclear staining was performed using hematoxylin for 10 minutes, followed by differentiation in 1% acid alcohol and bluing in Scott tap water. Counterstaining was carried out with 1% eosin for 1 minute to demonstrate cytoplasmic and extracellular tissue components. The stained sections were subsequently dehydrated in ascending grades of alcohol (70%, 80%, 90%), cleared in xylene, and permanently mounted with DPX.

Histological Evaluation

Stained sections were examined using a light microscope at various magnifications. histomorphological features, including tissue

architecture, cellular integrity, and pathological alterations, were assessed and documented (Osuntokun *et al.*, 2021).

Results

4.5 Microbiological Quality Assay

The microbial quality of the compounded carbamazepine syrup preparations was evaluated. Based on the USP recommended acceptance criteria for the microbiological quality of non-sterile dosage forms which prescribes the acceptable limit for Total Aerobic Microbial Count (TAMC) as $<10^2$ cfu/mL, Total Mold and Yeast Count (TYMC) as $<10^1$ cfu/mL and absence of *E. coli* (1 g or 1mL), the preparations were scored. All the sample passed the microbiological quality test across the test period of 42 days (Table 1).

4.6.2 Electrolyte Urea Creatinine and Liver Enzyme Level of the Laboratory Animals

The blood samples from the rats of all the groups were analyzed for electrolyte, urea, creatinine levels. More so, liver enzymes as well as total protein and albumin levels were also analyzed. All the above parameters were found to be within the normal range/reference values for the treatment, positive control and negative control groups. Table 2 below shows details of the values and reference values.

4.6.3 Haematological Parameters of the Laboratory Animals

Haematological parameters of the laboratory animals were evaluated by taking blood

samples from the rats of all the groups. Full blood count and differentials were conducted. All the above parameters were found to be within the normal range/reference values for the treatment, positive control and negative control groups. Table 3 below shows details of the values and reference values.

4.6.4 Histology of the Liver and Kidney of the Rats

Histological examination of the liver sections basically showed normal pattern across all the groups. Haematoxylin and Eosin (H and E) dye was used.

1. The hepatocytes were prominent, purple-stained and organized in cords or plates across all the sub-groups. The nuclei appeared blue/purple, while the cytoplasm and interstitial material appeared pink as shown in Fig. 1 A, B and C.
2. The central vein was also observed as characterized by structures in the center of the hexagonal lobule. The lighter, less stained channels between the hepatocyte cords confirms the presence of sinusoidal vessels.

The above characteristics represents the normal histological formation.

However, in the treatment and positive control groups unlike the negative control group some peculiar features were observed. These include:

1. Clear intracellular spaces: within the hepatocytes seen, clear, unstained spaces were observed in the cytoplasm, especially around the dark purple nuclei.

2. Cell swelling: some of the hepatocytes appeared swollen, due to the presence of these vacuoles.
3. Nuclear displacement: in some of the situations, the vacuoles appeared large enough to push the nucleus towards the edge of the cell. The feature is associated with macrovascular fatty change (steatosis).
4. Irregular strands of cytoplasm: the other parts of stained (pink) cytoplasm appears condensed into irregular strands that are compressed against the cell membrane or the nucleus.

All the above observed characteristics are consistent with cytoplasmic vacuolation in the hepatocytes as shown in Fig. 1 A and B.

Histological examination of the kidney specifically the renal cortex also revealed normal histological formation across all the groups. Haematoxylin and Eosin (H and E) dye was used.

Features observed as shown in Fig. 2 A, B and C include:

1. Glomeruli: it appeared as dense spherical or oval structures (stained purple). The glomeruli are contained within a light white space known as the bowman's capsule. Their major role is the filtration of blood as they contain dense network of capillaries.
2. Renal tubules: these surrounds the glomeruli and make up the bulk of the tissue, appearing as cross and longitudinal sections of various shapes (stained pink and light purple). These tubules are lined with simple cuboidal epithelium. Some show clear brush borders (proximal convoluted tubule) while others have a clear lumen (distal convoluted tubule).

Haematoxylin stain is responsible for staining acidic components like the cell nuclei (containing DNA and RNA) a dark blue-purple colour. While Eosin stains basic components like cytoplasm and extracellular fibres (like collagen and elastic fibres) a pink or red colour.

Table 1: Microbial Quality Assessment of the Compounded Carbamazepine Preparations

Assay Day	Storage		TAMC		TYMC		<i>E. coli</i>
			TAMC value within the acceptable limit	TAMC value beyond acceptable limit	TYMC value within acceptable limit	TYMC value beyond acceptable limit	
Day 1	Refrigerator (18±2 °C)	0	0	0	0	Nil	
	Lab Desk (25±2 °C)	0	0	0	0	Nil	
	Store (29±2 °C)	0	0	0	0	Nil	
	Elevated T (41±2 °C)	0	0	0	0	Nil	
Day 14	Refrigerator (18±2 °C)	0	0	0	0	Nil	

Day 28	Lab Desk (25±2 °C)	0	0	0	0	Nil
	Store (29±2 °C)	0	0	0	0	Nil
	Elevated T (41±2 °C)	0	0	0	0	Nil
	Refrigerator (18±2 °C)	0	0	0	0	Nil
Day 42	Lab Desk (25±2 °C)	0	0	0	0	Nil
	Store (29±2 °C)	0	0	0	0	Nil
	Elevated T (41±2 °C)	0	0	0	0	Nil
	Refrigerator (18±2 °C)	0	0	0	0	Nil
	Lab Desk (25±2 °C)	0	0	0	0	Nil
	Store (29±2 °C)	2	0	0	0	Nil
	Elevated T (41±2 °C)	2	0	0	0	Nil

Table 2: Electrolyte Urea Creatinine and Liver Enzyme Level of the Laboratory Animals

Parameter	Treatment Group (N=3)	Positive Control (N=3)	Negative Control (N=3)	Reference Values ⁺	p-value
Na ⁺ mmol/L Mean ± SD	138 ± 2.5	140 ± 2	136 ± 1.5	(135-145)	0.1328
K ⁺ mmol/L Mean ± SD	3.8 ± 0.3	3.7 ± 0.2	5.0 ± 0.1	(3.5-5)	0.0005*
Cl ⁻ mmol/L Mean ± SD	103 ± 2.5	99 ± 1.7	103 ± 2.5	(95-110)	0.1179
HCO ₃ ⁻ mmol/L Mean ± SD	19 ± 0.6	22 ± 1	20 ± 1	(20-30)	0.0160*
Ur mmol/L Mean ± SD	4.8 ± 1.5	4.8 ± 1.5	3.5 ± 0.2	(2.5-5.8)	0.3870
Cr mmol/L Mean ± SD	80 ± 15.9	91 ± 9.9	72 ± 5.8	(44-132)	0.2000
TP g/L Mean ± SD	67 ± 1.2	60 ± 1.5	67 ± 3.8	(60-80)	0.0197*
ALB g/L Mean ± SD	36 ± 0.0	34 ± 3.5	34 ± 2.9	(35-50)	0.5880
ASAT IU/L Mean ± SD	7 ± 3.2	5 ± 1	6 ± 1	(≤12)	0.5181
ALAT IU/L Mean ± SD	7 ± 0.6	6.3 ± 0.6	7 ± 1.5	(≤12)	0.6325
ALP IU/L Mean ± SD	25 ± 5	25 ± 5.8	22 ± 1.5	(9-35)	0.6613

Key

Na ⁺ =	Sodium
K ⁺ =	Potassium
Cl ⁻ =	Chloride
HCO ₃ ⁻ =	Bicarbonate
Ur =	Urea
Cr =	Creatinine

TP = Total Protein
 ALB = Albumin
 ASAT = Aspartate Amino Transferase
 ALAT = Alanine Amino Transferase
 ALP = Alkaline Phosphatase

*Statistically significant (p<0.05)

†(Odiegwu *et al.*, 2021; Okpoghono *et al.*, 2023)

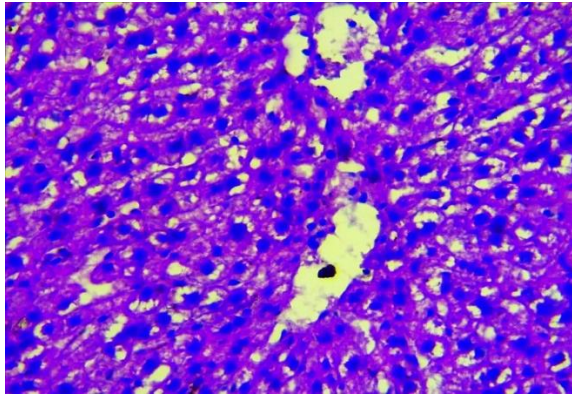
Table 3: Full Blood Count and Differentials of the Laboratory Animal

Parameter	Treatment Group (N=3)	Positive Control (N=3)	Negative Control (N=3)	Reference Values [†]	p-value
PCV % Mean ± SD	49 ± 5.1	45 ± 2.3	46 ± 2.5	(36-54) %	0.4099
WBC Mean ± SD	10 ± 2.1	7.7 ± 0.6	9.6 ± 3.4	(4.4-14.8 × 10 ⁹ /L)	0.4798
MCV Mean ± SD	53.5 ± 1.3	50.2 ± 2.1	49.0 ± 1.0	48-70 fL	0.0280*
MCH Mean ± SD	15 ± 3	12 ± 2	11 ± 0.5	6-22 pg per cell	0.1286
Platelet Mean ± SD	128 ± 52	180 ± 81	87 ± 15	(140-450 × 10 ⁹ /L)	0.2084
Neutrophil Mean ± SD	1.9 ± 0.7	2.0 ± 0.8	1.8 ± 0.6	(1.8-7.5 × 10 ⁹ /L)	0.9420
Eosinophil Mean ± SD	0.09 ± 0.05	0.10 ± 0.06	0.1 ± 0.01	(0.0-0.5 × 10 ⁹ /L)	0.9531
Monocytes Mean ± SD	0.53 ± 0.25	0.37 ± 0.15	0.09 ± 0.01	(0.2-1.0 × 10 ⁹ /L)	0.0482*
Basophil Mean ± SD	0.02 ± 0.06	0.03 ± 0.06	0.05 ± 0.07	(0.0-0.2 × 10 ⁹ /L)	0.8447
Lymphocytes Mean ± SD	3.5 ± 1.8	3.7 ± 1.1	3.8 ± 1.0	(1.0-4.0 × 10 ⁹ /L)	0.9624

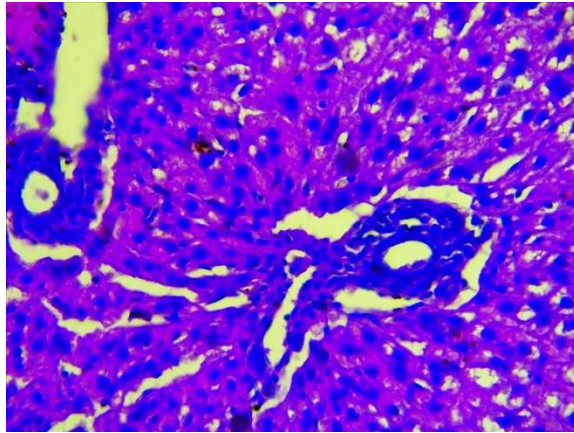
Key
 PCV = Packed Cell Volume
 WBC= White Blood Cell
 RBC= Red Blood Cell
 MCV= Mean Corpuscular Volume
 MCH= Mean Corpuscular Haemoglobin

*Statistically significant (p<0.05)

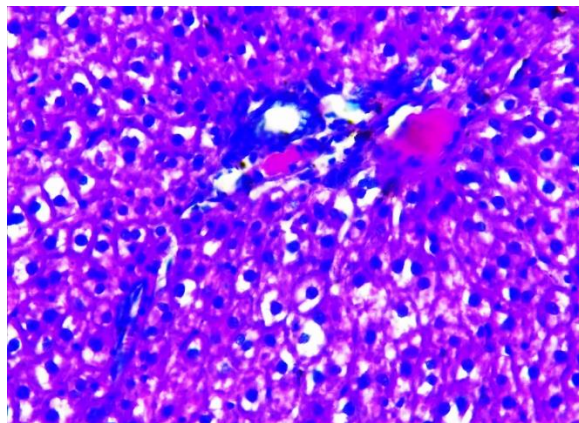
†(Abu *et al.*, 2025)



A: Treatment Group

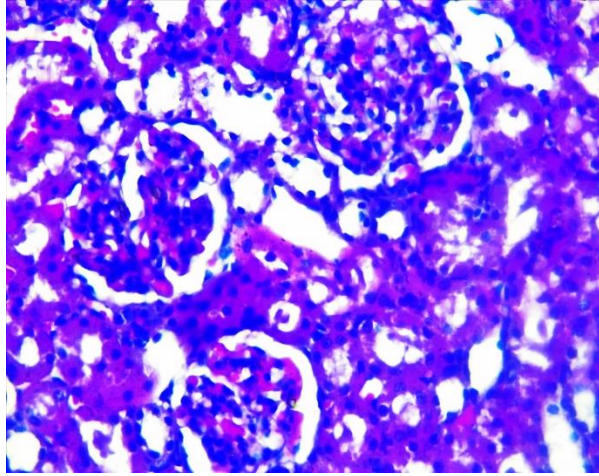


B: Positive Control

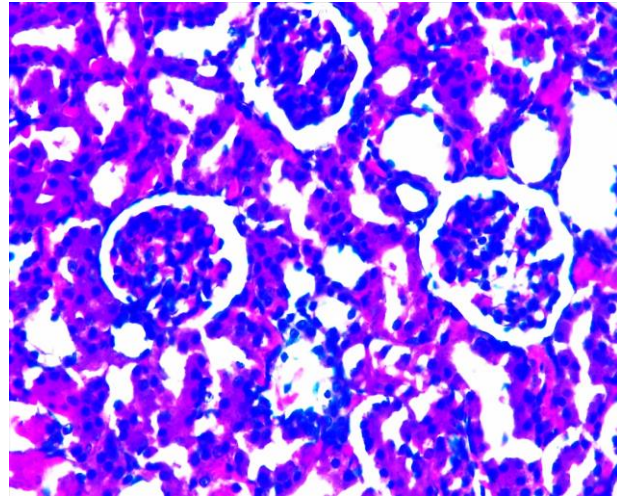


C: Negative Control

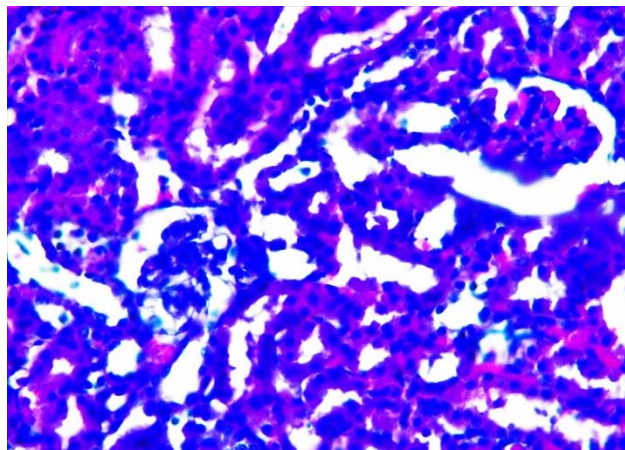
Fig. 1: Histological Section of Liver of the Rats ($\times 400$ Magnification)



A: Treatment Group



B: Positive Control



C: Negative Control

Fig. 2: Histological Section of Kidney of the Rats ($\times 400$ Magnification)

Discussion

Microbiological Quality Assay

The microbiological quality assay results are presented in Table 1. The findings showed that all the formulation samples tested had zero microbial count except two that had some level of microbial presence but it was found to be within accepted range based on the United States Pharmacopeia (2021) specification. The findings are unlike that of Gurung and Rai, (2021) where some levels of contaminations were reported that were out of the accepted range. The results are also not in agreement with Mugoyela and Mwambete (2010) who reported 100% contamination in some selected cough syrup samples, as well as Kabir and Hossain (2013) and Jameel (2017) who also reported significant level of contaminations. Some of the reasons that explain the absence of contamination in the samples from the current study include, the high concentration of sugar in the syrup BP used as the vehicle for compounding (66.7 %) which is self-preserving and the presence of two additional preservatives in the syrup BP viz: sodium benzoate and sodium metabisulphite.

A higher rate of microbial contamination rate could be attributed to several reasons: defect in production, poor to non-adoption of Good Manufacturing Practice, ineffective or inadequate preservatives and poor-quality control measures (Al-Kaf *et al.*, 2015). More so, loosely cocked and not firmly closed bottle lids can also serve as a source of microbial contamination. The microbial contamination is also influenced by the storage temperature as shown by Nwachuku and Olugbose (2009) who demonstrated that

the total viable count of bacteria and fungi increases with increase in temperature.

Biochemical, Haematological and Histological Studies on Rats

The findings from the haematological, liver function and EUCr investigations all indicated that there were no observed abnormalities or deviations in these parameters. This implies that the formulation of carbamazepine in the syrup BP does not alter the safety profile of the medicine in the aspects studied. Upon conducting statistical analysis on the biochemical and haematological data, K^+ , HCO_3^- , TP, MCV and monocytes were observed to manifest statistical significance. However, this significant difference observed does not translate to clinical concern as all the values were within the normal range values. Overall, this means that the formulation is capable of delivering the medicine safely. It also indicates that there was no observed interaction between the syrup components and the carbamazepine that could amount to toxicity or unwanted effects not peculiar to the primary drug.

The histological findings as shown also indicates the syrup BP use in compounding does not have impact on the liver and kidney histology. It further confirms and re-affirms the results obtained from the liver and kidney function tests. However, cytoplasmic vacuolation of hepatocytes were observed in the treatment and positive control groups. Some of the reasons for such scenario include exposure to harmful substances, accumulation of intracellular substances like

glycogen, fat and water, cellular stress, potential dysfunction, or sometimes drug metabolism activities (Shubin *et al.*, 2016). Drug metabolism activities is the most likely reason for the observed cytoplasmic vacuolation in this study.

Overall, the results from the biological studies were in agreement with the findings reported by Osuntokun *et al.* (2021), except for few aspects where it was demonstrated that certain liver enzymes were elevated. The difference observed could be due to physiological state of the animals used and vehicles used to administer the medications. However, it is worthy to mention that a major limitation for this study is the sample size used (3 rats per group). Despite the findings and deductions derived thereof, a larger sample size is recommended to subsequent

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researchers to have results that can be suitably generalized with good statistical power thereby giving a stronger data on the safety of these formulations.

Conclusion

All the formulations passed the microbiological quality assay with reference to USP as microbial growth was not detected across all the samples except two, however, they were below the minimum allowable limit for liquid oral preparations. The compounded carbamazepine syrups were shown to be safe as revealed by the results of kidney function test, liver function test, haematology and histological examinations. All the findings were within normal values and the histology generally displayed normal cytomorphology.

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