



**BIOCHEMICAL, HEMATOLOGICAL, HISTOPATHOLOGICAL, AND  
MICROBIOLOGICAL EVALUATION OF EXTEMPORANEOUSLY COMPOUNDED  
CAPTOPRIL SYRUP IN LABORATORY RATS**

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**Abstract**

*Extemporaneously compounded captopril syrups are commonly used for patients unable to swallow tablets, yet data on their systemic safety and microbiological quality remain limited. To evaluate the biochemical, hematological, histopathological, and microbiological safety of extemporaneously compounded captopril syrup following oral administration in laboratory rats. Albino rats were assigned to receive compounded captopril syrup, captopril in deionized water, or deionized water (control) at 6 mg/kg for 28 days. Serum biochemical and hematological parameters were measured, and liver and kidney tissues were examined histologically. Microbiological quality of the syrup was assessed at 20–41 °C for up to 42 days. Serum biochemical and hematological parameters remained within normal physiological ranges in all groups, with no clinically significant differences. Histopathology revealed preserved hepatic and renal architecture, with no evidence of inflammation, degeneration, or necrosis. Microbiological testing showed no bacterial, yeast, or mold growth at any time point or storage temperature. Extemporaneously compounded captopril syrup demonstrates favorable short-term systemic safety and satisfactory microbiological quality. These findings support its suitability for oral administration when solid dosage forms are inappropriate. Future studies should investigate long-term safety and preservative efficacy.*

**Keywords:** Biochemical, Hematological, Histopathological, Microbiological evaluation, Compounded Captopril

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## Introduction

Captopril is an angiotensin-converting enzyme (ACE) inhibitor widely used in the management of hypertension, heart failure, and diabetic nephropathy (Katzung *et al.*, 2021). Although captopril is commercially available primarily as tablets, pediatric and geriatric patients often require liquid dosage forms due to swallowing difficulties and the need for flexible dosing (Nahata and Pai, 2017).

Extemporaneous compounding of oral liquid formulations is therefore common practice in hospital and community pharmacies. However, compounded formulations may exhibit variability in preparation, stability, and microbiological quality, raising concerns about safety and therapeutic reliability (Allen, 2016; United States Pharmacopeia, 2020). Beyond pharmaceutical quality control, toxicological evaluation is essential to ensure that compounded products do not produce adverse systemic effects.

Biochemical markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are well-established indicators of hepatic function and drug-induced liver injury (Ozer *et al.*, 2008). Hematological parameters similarly provide valuable information regarding bone marrow function, immune response, and overall physiological status (Jain, 1993).

Histopathological evaluation is a critical component of toxicological and safety studies, as it provides direct evidence of tissue- and organ-level effects of drug exposure. By examining microscopic structural changes in organs such as the liver, kidney, and spleen, histopathology enables

the detection of cellular injury, inflammation, necrosis, or degenerative alterations that may not be apparent through biochemical or hematological assessments alone (Greaves, 2012). In preclinical studies, histopathological analysis is considered a gold standard for confirming target organ toxicity and for correlating functional changes with underlying morphological lesions (Haschek *et al.*, 2013). The absence of histopathological abnormalities is therefore a strong indicator of good tissue compatibility and systemic safety of pharmaceutical formulations.

Microbiological evaluation is essential in the assessment of extemporaneously compounded pharmaceutical preparations, particularly oral liquid formulations, due to their increased susceptibility to microbial contamination. Inadequate microbial quality can compromise product safety, leading to infections or degradation of the active pharmaceutical ingredient (Allen, 2016). Regulatory guidelines emphasize the need for microbiological testing of nonsterile compounded products to ensure acceptable limits of microbial load and the absence of specified pathogenic organisms (United States Pharmacopeia, 2020). Incorporating microbiological analysis into safety assessments helps to confirm that compounded formulations meet quality standards and are safe for patient use, especially in vulnerable populations such as pediatric and geriatric patients.

While the pharmacological safety of captopril has been extensively documented, there is limited *in vivo* evidence addressing the systemic safety and microbiological

quality of extemporaneously compounded captopril syrup formulations. Most available studies focus primarily on physicochemical stability or in vitro microbiological assessment. The present study uniquely integrates biochemical, hematological, histopathological, and microbiological evaluations to comprehensively assess the short-term systemic safety and microbiological robustness of an extemporaneously compounded captopril syrup following repeated oral administration in laboratory rats.

## **Materials and Methods**

### **Experimental Animals**

Healthy laboratory rats (300–350 g) were obtained from the Department of Pharmacology, University of Jos. Animals were housed under standard laboratory conditions with free access to food and water. All experimental procedures were conducted in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals (NIH, 2011) and were approved by the institutional ethics committee.

### **Preparation of Compounded Captopril Syrup**

Captopril syrup was extemporaneously compounded using Syrup BP according to standard pharmaceutical procedures (Allen, 2016). The final concentration of the formulation was 1 mg/mL.

### **Experimental Design and Sample Collection**

Albino rats were randomly assigned into three groups (n = 6 per group):

- Group 1: Compounded captopril syrup
- Group 2: Captopril in deionized water
- Group 3: Deionized water only (control)

Treatments were administered orally at a dose of 6 mg/kg body weight once daily for 28 consecutive days. At the end of the treatment period, animals were anesthetized, and blood samples were collected via cardiac puncture into plain and EDTA tubes for biochemical and hematological analyses, respectively. Animals were subsequently sacrificed for histopathological examination.

### **Hematological Analysis**

Blood collected in EDTA tubes was analyzed for hemoglobin concentration, packed cell volume (PCV), red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), and differential leukocyte counts using standard hematological methods (Jain, 1993).

### **Biochemical and Histopathological Studies**

Serum samples were analyzed for albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and other biochemical markers using commercially available diagnostic kits, following the manufacturer's instructions. These parameters serve as established biomarkers for assessing hepatic and biliary function (Ozer et al., 2008).

After blood collection, the liver and kidneys were excised, rinsed in normal saline, and fixed in 10% neutral buffered formalin for histopathological examination (Osuntokun et al., 2021).

### Microbiological Quality Assessment

Microbiological quality of the compounded captopril syrup was assessed on days 1, 7, 14, 28, and 42. Physical appearance, including color and clarity, was visually inspected prior to testing. The formulation contained antimicrobial preservatives (sodium benzoate and sodium metabisulphite) to enhance microbiological stability.

Testing followed standard pharmacopeial procedures for nonsterile products. Although preservatives were present, no specific neutralization step was performed; serial dilutions were applied to minimize carryover effects. Absence of microbial growth was interpreted as evidence of effective preservative activity rather than intrinsic sterility.

### Total Aerobic Microbial Count

One milliliter of syrup was aseptically transferred into 9 mL sterile normal saline and serially diluted up to  $10^{-5}$ . Aliquots (0.1 mL) from  $10^{-2}$  and  $10^{-4}$  dilutions were inoculated onto Nutrient agar plates using the spread plate technique. MacConkey agar plates were also inoculated to detect *Escherichia coli* and other Gram-negative bacteria. Plates were incubated at 37 °C for 24 hours, and colony-forming units per

milliliter (CFU/mL) were determined (Gurung and Rai, 2021).

### Total Yeast and Mold Count (TYMC):

Diluted samples (0.1 mL) were inoculated onto Sabouraud dextrose agar and incubated at 25 °C for 7 days. Yeast and mold colonies were counted to calculate CFU/mL (Gurung and Rai, 2021).

### Identification of *Escherichia coli*:

Lactose-fermenting colonies on MacConkey agar were isolated, subcultured for purity, and identified based on colony morphology, Gram staining, and standard biochemical tests (Gurung and Rai, 2021).

### Statistical Analysis

Data were expressed as mean  $\pm$  standard deviation (n = 6 per group) and analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test where appropriate. Statistical significance was set at  $p < 0.05$ . Prior to analysis, data were assessed for approximate normal distribution and homogeneity of variance. Given the exploratory nature of the study and the small sample size, emphasis was placed on biological relevance as well as statistical significance.

## Results

**Table 1: Serum Hematology of Rats after Oral Dose Captopril in Different Formulations**

Parameter	Group 1 (Compounded Captopril Syrup) Mean $\pm$ SD	Group 2 (Captopril in Deionized Water)	Group 3 (Deionized Water Only) Mean $\pm$ SD	Reference Range (Rats)	p-value
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		Mean ± SD			
PCV (%)	44.0 ± 4.0	45.0 ± 6.0	45.0 ± 1.0	40–50	0.880
WBC (×10 <sup>3</sup> /μL)	10.1 ± 2.2	6.5 ± 2.1	5.7 ± 2.6	4–12	0.038
MCV	53.0 ± 1.2	54.0 ± 1.0	55.0 ± 1.0	48–70	0.120
MCH (pg/cell)	12.0 ± 1.0	12.5 ± 1.4	12.0 ± 1.9	6–22	0.450
PLT (×10 <sup>3</sup> /μL)	187.0 ± 1.0	207.0 ± 1.4	273.0 ± 1.9	150–500	0.460
Neutrophils (%)	24.7 ± 8.1	60.0 ± 2.0	50.0 ± 1.2	10–50	0.012
Eosinophils (%)	2.0 ± 0.0	1.0 ± 1.0	2.3 ± 1.5	0–5	0.340
Monocytes (%)	3.0 ± 5.0	2.3 ± 1.5	3.3 ± 2.0	0–5	0.048
Lymphocytes (%)	65.7 ± 2.5	36.7 ± 2.1	39.0 ± 4.6	40–70	0.021

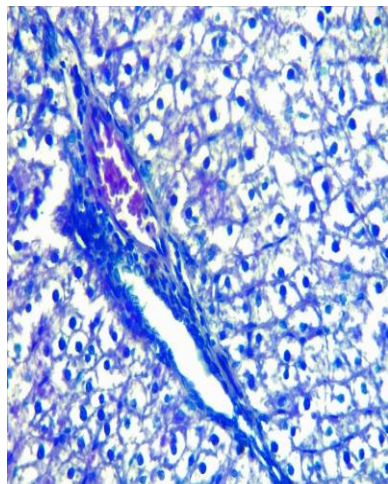
Keys: G1 = Group 1, G2 = Group 2, G3 = Group 3, > = Greater than, PCV = Packed Cell Volume, WBC = White Blood Cell, PLT = Platelet, MCV = Mean Corpuscular Volume, MCH = Mean Corpuscular Hemoglobin, SD = Standard Deviation, statistically significant differences (p < 0.05) are indicated in the text; all values remained within established physiological reference ranges.

**Table 2: Serum Biochemistry of Rats after Oral Dose of Captopril in Different Formulations**

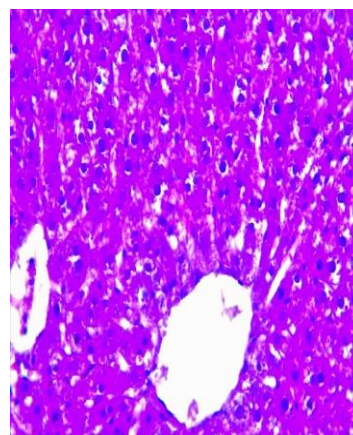
Parameter	Group 1 (Compound ded Captopril Syrup) Mean ± SD	Group 2 (Captopril in Deionized Water) Mean ± SD	Group 3 (Deionized Water Only) Mean ± SD	Reference Range	p-value
Sodium (mmol/L)	137.7 ± 1.5	136.7 ± 0.6	139.3 ± 1.2	135–145	0.12
Potassium (mmol/L)	3.9 ± 0.4	4.8 ± 0.4	4.2 ± 0.2	3.5–5.0	0.04
Chloride (mmol/L)	105.0 ± 1.5	102.3 ± 1.5	106.0 ± 0.0	95–110	0.07
Bicarbonate (mmol/L)	21.3 ± 0.6	22.3 ± 2.1	21.3 ± 0.6	20–30	0.45
Urea (mmol/L)	5.1 ± 1.0	3.9 ± 0.2	4.9 ± 1.2	2.5–5.8	0.06
Creatinine (μmol/L)	92.7 ± 1.7	84.7 ± 6.1	93.0 ± 27.2	44–132	0.39
Total protein (g/L)	62.3 ± 1.5	62.0 ± 3.6	65.0 ± 2.5	60–80	0.18
Albumin (g/L)	35.0 ± 1.0	34.7 ± 1.5	36.0 ± 0.8	35–50	0.21

AST (U/L)	8.0 ± 1.0	5.0 ± 0.0	7.3 ± 1.5	≤12	0.08
ALT (U/L)	8.7 ± 0.6	6.0 ± 0.8	9.0 ± 1.0	≤12	0.09
Albumin/Phosphate	28.3 ± 3.5	27.0 ± 1.0	34.3 ± 3.6	9–35	0.11

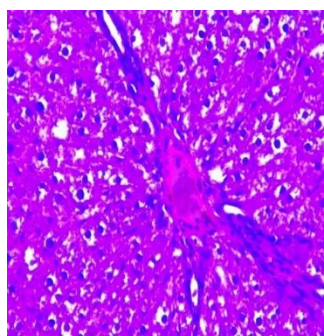
Keys: AST = Aspartate Amino Transferase, ALT = Alanine Amino Transferase, statistically significant differences ( $p < 0.05$ ) are indicated in the text; all values remained within established physiological reference ranges.



**Group 1: Captopril in Syrup**

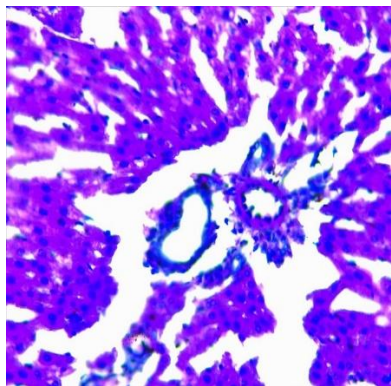


**Group 2: Captopril in Deionized Water**

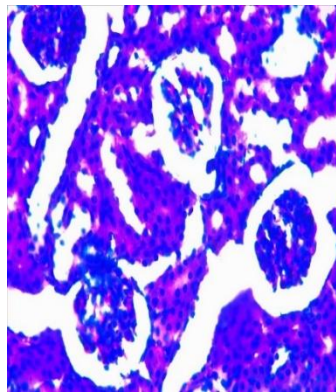


**Group 3: Control**

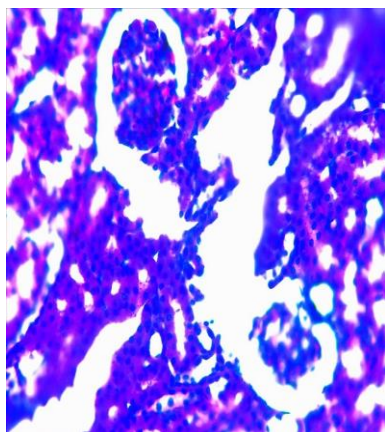
**Figure 1: Histological Section Liver Tissue of Rats (x400 Magnification)**



**Group 1: Captopril in Syrup**



**Group 2: Captopril in Deionized Water**



**Figure 2: Histological Section Kidney Tissue of Rats (x400 Magnification)**

### Scale bars

Figure 1: Representative photomicrographs of liver tissue from rats treated with captopril syrup (Group 1), captopril in deionized water (Group 2), and control (Group 3), showing preserved hepatic architecture with normal hepatocytes and sinusoids (H&E, ×400; scale bar = 50µm) while figure 2: Representative photomicrographs of kidney tissue from rats treated with captopril syrup (Group 1), captopril in deionized water (Group 2), and control (Group 3), showing preserved renal architecture with normal glomeruli and intact renal tubules, with no evidence of tubular degeneration, interstitial inflammation, or necrosis (H&E, ×400; scale bar = 50µm).

Day	Temp (°C)	Gram +ve Rods	Gram +ve Cocci	Gram –ve Rods	Gram –ve Cocci	<i>E. coli</i>	Yeast/Mold
1	20	0	0	0	0	0	0
	25	0	0	0	0	0	0
	30	0	0	0	0	0	0
	40	0	0	0	0	0	0
14	20	0	0	0	0	0	0

	25	0	0	0	0	0	0
	30	0	0	0	0	0	0
	40	0	0	0	0	0	0
28	20	0	0	0	0	0	0
	25	0	0	0	0	0	0
	30	0	0	0	0	0	0
	40	0	0	0	0	0	0
42	20	0	0	0	0	0	0
	25	0	0	0	0	0	0
	30	0	0	0	0	0	0
	40	0	0	0	0	0	0

**Table 3: Microbial Growth at Different Temperatures**

Keys: Gram +ve = Gram positive, Gram -ve = Gram negative, *E. coli* = *Escherichia coli*

### Discussion

Evaluation of serum biochemical indices in rats following oral dosing of captopril, administered either as a syrup or aqueous preparation, showed that most parameters remained within established physiological reference ranges for rodents (Feldman *et al.*, 2000; Thrall *et al.*, 2012). This indicates that neither formulation produced signs of acute biochemical toxicity. Electrolyte levels were within normal limits, and the lack of statistically significant alterations suggests that the tested dose of compounded captopril did not disrupt fluid or electrolyte homeostasis. These observations align with previous reports indicating that angiotensin-converting enzyme (ACE) inhibitors rarely induce electrolyte imbalances, except during prolonged therapy or overdose (Aronson and Ferner, 2016).

A slight increase in serum potassium was noted in the aqueous formulation group. Given that ACE inhibitors can reduce aldosterone secretion and thereby promote modest potassium retention (Yusuf *et al.*, 2000), this finding is pharmacologically expected. Nevertheless, potassium values

remained within physiological limits and were not indicative of clinically significant hyperkalemia. Indicators of renal function, including urea and creatinine, were similar across all experimental groups, with no evidence of acute renal impairment. Minor differences, such as marginally higher urea levels in the syrup-treated rats, are considered biologically insignificant and consistent with normal inter-animal variability (Thrall *et al.*, 2012). Importantly, there were no biochemical signs of nephrotoxicity. Captopril is generally regarded as renoprotective at therapeutic doses, and acute renal toxicity is uncommon (Bakris *et al.*, 2000). Comparable creatinine concentrations between treatment groups further reinforce this safety profile.

Liver enzyme activities (AST, ALT, and ALP) remained within normal reference ranges for all groups, with only slight variations that fell within expected biological limits for rats. These results suggest the absence of hepatic injury or cholestasis and are consistent with literature describing the low risk of hepatotoxicity associated with

short-term captopril exposure (Aguiar-Souto *et al.*, 2011). Total protein and albumin levels were also consistent across groups, indicating intact hepatic synthetic function and no abnormal protein loss. As ACE inhibitors are not known to significantly affect protein metabolism during short-term administration (Sharman and Low, 2008), these findings are anticipated. Overall, the serum biochemistry data demonstrate a favorable short-term safety profile for both captopril formulations, with no evidence of hepatic, renal, or electrolyte disturbances.

A statistically significant difference was observed for serum potassium levels ( $p = 0.04$ ), with Group 2 (captopril dissolved in de-ionized water) exhibiting a modest increase compared with Group 1 (captopril syrup). However, all potassium values remained within the established physiological reference range for rats (3.5–5.0 mmol/L). As such, this difference is considered statistically significant but biologically insignificant, and likely reflects normal physiological variation or formulation-related modulation rather than an adverse effect.

Hematological assessments likewise showed that values in all treated groups remained within normal physiological ranges, indicating that sub-acute oral exposure to captopril, regardless of formulation, did not result in hematological toxicity. Packed cell volume values were maintained within the normal range (40–50%) across all groups, suggesting the absence of dehydration, anemia, or hemoconcentration following treatment (Feldman *et al.*, 2000). Platelet counts were normal and showed no evidence of platelet-related abnormalities. Reported

hematologic adverse effects of captopril are typically associated with chronic use or underlying risk factors (Aronson and Ferner, 2016), supporting the absence of acute effects in this study.

Differential leukocyte counts, including neutrophils, lymphocytes, eosinophils, monocytes, and basophils, remained within established reference intervals. The aqueous formulation group exhibited a relative neutrophilia accompanied by lymphopenia, a pattern consistent with a mild stress leukogram commonly observed in rodents (Duffy *et al.*, 2018) rather than a toxic response.

Statistically significant differences were observed in total White Blood Count (WBC) count and certain leukocyte subsets. Group 1 (compounded captopril syrup) exhibited a higher WBC count compared with the control ( $p = 0.038$ ), while neutrophil percentages were elevated in Group 2 (captopril in de-ionized water) relative to Group 1 ( $p = 0.012$ ). Lymphocyte and monocyte percentages were significantly higher in Group 1 than Group 2 ( $p = 0.021$  and  $p = 0.048$ , respectively). Despite these statistical differences, all values remained within their respective reference ranges, suggesting these variations reflect physiological fluctuations rather than pathological changes. Although some hematological parameters showed statistically significant differences between groups, the small group size ( $n = 6$ ) and the absence of values outside physiological reference ranges indicate that these findings are unlikely to represent toxicologically meaningful effects.

The absence of histopathological abnormalities in the liver and kidneys across

all experimental groups indicates that compounded captopril, administered at the therapeutic dose for 28 days, did not induce structural or toxic effects in these organs. As the liver and kidneys are primary sites for drug metabolism and excretion and are highly sensitive to toxic injury in repeated-dose studies (Gad, 2016; Watkins and Klaassen, 2015), the preservation of normal tissue architecture suggests that the formulation did not exceed their detoxification or filtration capacities. No features of hepatic injury, including cellular degeneration, necrosis, inflammation, steatosis, or Kupffer cell activation, were observed, supporting a favorable hepatic safety profile (Maronpot, 2015). This is consistent with OECD guidelines, which indicate that harmful substances typically produce detectable microscopic lesions following 28 days of exposure (OECD, 2008).

Similarly, renal histology showed intact glomerular and tubular structures, with no evidence of tubular necrosis, vacuolation, interstitial inflammation, or proteinaceous casts—hallmarks of nephrotoxicity (Sasseville, 2012). These findings align with reports that compounds with low nephrotoxic potential do not elicit histological alterations under subacute dosing conditions (Tisher and Brenner, 2014). Importantly, no differences were observed between the syrup and aqueous vehicles, indicating that Syrup BP did not contribute to tissue toxicity. Given its pharmacopoeial designation as an inert excipient, this observation is consistent with established safety standards (British Pharmacopoeia Commission, 2020). Overall, the findings demonstrate that compounded

captopril, irrespective of vehicle, was well tolerated and did not cause hepatic or renal damage within the 28-day exposure period.

Microbiological evaluation of the compounded captopril syrup showed no detectable microbial growth throughout the study period, irrespective of storage temperature (20–41 °C) or sampling time (days 1–42). No bacteria, yeast, or mold were observed, indicating that the formulation maintained acceptable microbiological quality under both normal and accelerated storage conditions. This suggests effective preservative performance and formulation robustness. Syrup-based preparations are known to inhibit microbial proliferation due to their high sugar content, reduced water activity, and, where applicable, the presence of preservatives (Block, 2001; Rowe *et al.*, 2009). Importantly, exposure to elevated temperatures did not compromise microbiological stability, a finding of clinical relevance given that higher temperatures can promote microbial growth in inadequately preserved formulations (Ansel *et al.*, 2018). These results are consistent with previous reports demonstrating the microbiological stability of properly compounded captopril and other ACE inhibitor syrups over extended storage periods (Sharma and Kaur, 2013). Overall, the absence of contamination supports the microbiological safety and suitability of the compounded captopril syrup for oral administration throughout its intended shelf life.

### **Study Limitations**

This study was limited to a 28-day exposure period and a single therapeutic dose. Longer-term studies incorporating higher doses, stability-indicating chemical assays, and

formal preservative efficacy testing would further strengthen the safety profile of compounded captopril syrup. Another limitation of this study is the absence of formal method suitability testing or preservative neutralization during microbiological analysis, as recommended by pharmacopeial guidelines. Consequently, while the results demonstrate effective microbial inhibition, they should be interpreted as evidence of satisfactory microbiological quality rather than absolute sterility.

### Conclusion

Extemporaneously compounded captopril syrup was well tolerated in laboratory rats

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