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PROTECTIVE EFFECT OF *CINNAMOMUM ZEYLANICUM* BARK AGAINST ACETAMINOPHEN INDUCED HEPATOTOXICITY IN ALBINO RATS

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Keywords:

Cinnamomum zeylanicum, Acetaminophen, Hepatoprotective, Silymarin

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ABSTRACT: The objective of the current study is to investigate the hepatoprotective activity of *Cinnamomum zeylanicum* bark (CZB) extract on acetaminophen-induced hepatotoxicity in albino rats. Wistar albino rats (150-200 g) of either sex were divided into six groups, and toxicity was induced by acetaminophen (APAP) at a dose of 750 mg/kg, bw, p.o, every 72 h, for two weeks. Silymarin (100 mg/kg, p.o) was given as reference standard. CZB (100 mg/kg and 200 mg/kg, p.o) was tested for hepatoprotective activity. Various serum parameters like alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatise (ALP), total Bilirubin (TB), total protein (TP), albumin (ALB), and total cholesterol (TC) in different groups were measured. Further, the effect of the extract on super oxide dismutase, catalase, reduced glutathione, and lipid peroxidation were also estimated. The treatment with ethanolic extract of CZB reduced the elevated levels of AST, ALT, ALP, TB, and TC and also reversed the hepatic damage as compared with toxic control rats. A decreased level of ALB and TP was also significantly restored by CZB pre-treatment. It is also significantly restored the antioxidant level in hepatic tissue. Further CZB treatment also reduced histological alteration induced in the liver. The result suggests that the ethanolic extract of CZB has strong hepatoprotective agents on acetaminophen-induced toxicity in albino rats.

INTRODUCTION: The liver is a vital organ that is responsible for the metabolism of endogenous and exogenous agents [1]. It is also called hepatic and made up of hepatocytes, which carried out multiple processes essential for life. It plays an important role in drug elimination and detoxification.

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Any injury to the liver can result in many disorders ranging from transient elevation in liver enzymes to life-threatening liver cirrhosis and hepatic failure. The liver injury may be chemical toxic, therapeutic drug, alcohol, and microbial agents [2].

Hepatotoxic agents like acetaminophen, carbon tetrachloride, and thioacetamide are used as a model substance causing experimental hepatocyte and can react with the basic cellular components and consequently induce almost all types of liver lesions [3]. Liver disease has become one of the major causes of morbidity and mortality all over the world [4]. About more than two million people in

the world die annually from liver related disorder [5], much higher in developing countries like India (3% to 30%) compared to that in the advanced country (2% to 3%) with a similar dose schedule [6]. According to the united states acute liver failure study group drug-induced liver disease account for more than 50% of acute liver failure in which 39 % are caused by an overdose of acetaminophen and 13% are caused by other drugs [7]. Most of the hepatotoxic chemicals injury liver cell by inducing lipid peroxidation which alters the structure and function of cellular membrane [8]. This oxidative damage causes change in the structure fluidity and permeability of the membrane and also inactivate a few number of membrane-bounded enzyme [9]. Acetaminophen is an antipyretic or analgesic drug developed in the last century, which causes serious liver necrosis in humans and in experimental animals if taken in large doses [10]. Acetaminophen at therapeutic doses is rapidly metabolized in the liver through glucuronidation and sulfation, and an only a small portion is oxidized by cytochrome P-450 to generate a highly reactive and toxic metabolite N-acetyl-P- benzoquinoeimine (NAPQI), which is quickly conjugated by hepatic glutathione to yield a harmless water-soluble product, mercapturic acid [11]. When acetaminophen is administered at a higher dose, it metabolism through glucuronidation and sulfation is saturated, and NAPQI is synthesized in enough amounts to cause hepatotoxicity in **Fig. 1**.

In recent years the use of herbal drugs for the treatment of liver disease has increased all over the world. The herbal drugs are believed to be harmless and free from serious side effects, efficacy, and effectiveness, as they are obtained from nature and easily available [12]. Herbal-based therapeutics for liver disease have been used in India for a long time and have been popularized the world over by leading pharmaceuticals.

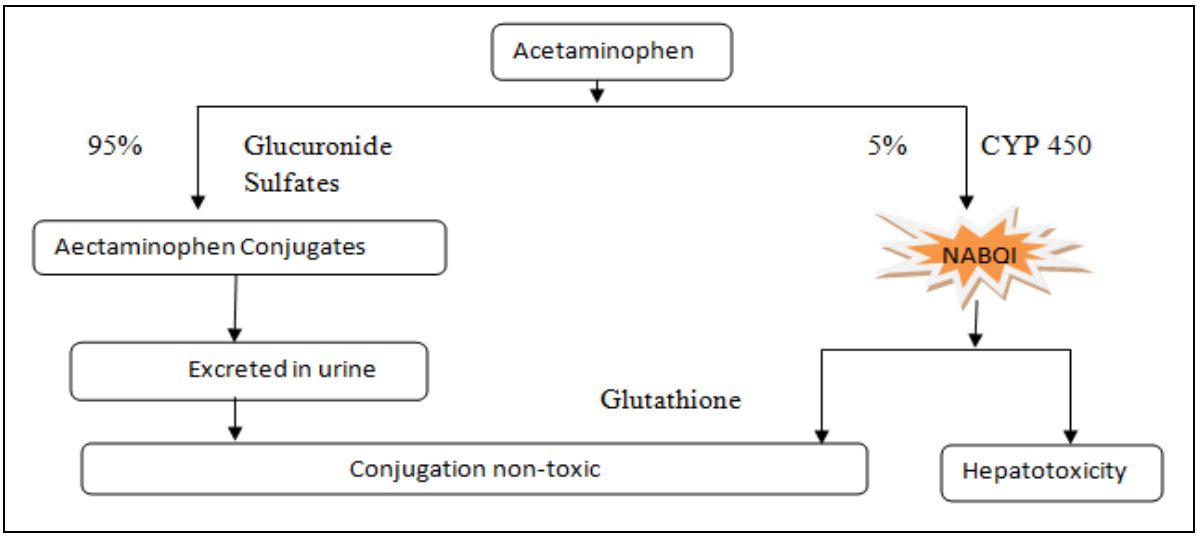

FIG. 1: ACETAMINOPHEN METABOLISM

CZB, a member of the family Lauraceae, is a tropical evergreen tree native to Srilanka and the Malabar Coast of India, also found in Jamaica, Brazil, and China. Sri Lanka is the prime supplier, and most of the world's requirements are met by it as true cinnamon [13]. The dried inner bark of the tree is used in medicine, cosmetics, and food [14], in addition to it has been employed as traditional herbal medicine to treat a variety of health conditions [15]. CZB contain major constituent like cinnamaldehyde, benzaldehyde and euginol, among these cinnamaldehyde and euginol show anti-spasmodic and muscle relaxant action mainly intestinal transit and gastric emptying [16]. It has been uses as antitussive, antiarthritis, antimicrobial [17, 18], antifungal [19], antiviral [20] antioxidant [21, 22], antiinflammatory [14], antidiabetic [23-25] anti-arrhythmic [15], anti-atherosclerotic [26] and anticancer [27, 28]. There is a worldwide trend to go back to herbal medicine in the treatment of liver disease as a synthetic drug used in the treatment of liver disease have serious adverse effect [29]. Hence, the present study is to aimed to investigate the hepatoprotective activity of ethanolic extract of CZB on acetaminophen-induced toxicity in rats.

MATERIALS AND METHODS:

Chemicals: Acetaminophen was obtained from gift sample from Arbro pharmaceutical company. Assay for hepatic marker enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatise (ALP), total Bilirubin (TB), total protein (TP), albumin and total cholesterol (TC) were purchase from Erba diagnostic Mannhein, Germany. All other reagents used in the experiment were of analytical grade.

Plant Material: The CZBs were obtained from the local market in old Delhi, authenticated and identified by Dr. Sunita Garg, CSIR-NISCAIR New Delhi. A voucher specimen (Reference No. NISCAIR/RHMD/CONSULT/2018/3261-62) has been deposited in the herbarium of CSIR-NISCAIR. New Delhi.

Preparation of Extract: The shade dried CZB was milled and extracted using ethanol in Soxhlet apparatus for 8 h. Then the extract was evaporated to dryness at 50 °C in a water bath, and the final dry extract was stored in dark at -20 °C until used for the experiments. The percentage yield of extract was 43% w/w.

Preliminary Phytochemical Study: Ethanolic extract of Cinnamomum bark were analyzed for their chemical constituents. A preliminary phytochemical analysis was carried out to determine the phytochemical constituents which were responsible for the hepatoprotective activity. Some of these methods are as follows [30, 31].

Animals: Adult albino wistar weighing 150-200 gram of either sex was obtained from All India Institute of Medical Science (AIIMS), New Delhi. The animals were housed in polypropylene cages and maintained at 24 ± 2 °C relative humidity of 57 ± 2 °C and photocycle of 12:12 h light and dark. The animals were provided with standard pellet feed with drinking water *ad libitum*. All the experimental procedure was carried out in accordance with the guideline of the institutional animal ethical committee. They were initially acclimatized for the study, and the study protocol was approved by Institutional Ethical Committee as per the requirement for a committee for the purpose of control and supervision of animals (CPCSEA), New Delhi. Before conducting the experiment, ethical clearance was obtained from the institutional animal ethical committee HIMT College of Pharmacy (1377/PO/Re/S/10/CPCSEA), GB Nagar, Uttar Pradesh.

Acute Oral Toxicity: An acute oral toxicity was performed as per OECD guidelines for the testing of chemicals Test No 423 [32]. Albino Wistar rats (n=6) were used for the acute toxicity study. The animals were kept overnight with access to water but not food, after which the ethanolic extract of CZB was administered orally at a dose of 500, 1000, and 2000 mg/kg body weight, and the animal were observed for 24 h. Further, they were observed continuously for the first 2 h for morbidity and up to 24 h for mortality. If mortality was observed in one animal, then the same dose was repeated again to confirm the toxic dose. If mortality was observed again, the procedure was repeated for lower doses.

Experimental Grouping: The selection of the dose of acetaminophen (750 mg/kg) was based on studies carried out by the previous [33, 34]. After acclimatization a period of one week, the animals were randomly divided into six groups of six animals in each group. Group, I served as untreated control and fed with normal saline (5 ml/kg b.w) daily for 10 days. Group II served as toxic and treated with acetaminophen at 750 mg/g, p.o suspended in 1% CMC three alternative days for 10 days. Group III served as per se and was given an only ethanolic extract of CZB (100 mg/kg b.w) daily for 10 days. Group IV and Group V served as the treatment group and were treated with ethanolic extract of CZB (100, 200 mg/kg, b.w) daily for 10 days. Group VI served as a standard group and was treated as silymarin (100 mg/kg, b.w) [35] orally for two weeks. Group II, IV, V, and VI were administered with acetaminophen suspension (750 mg/kg, b.w) orally for three alternative days for 10 days.

At the end of treatment, all animal was fasted for 12 h then, a blood sample was collected from all animals by puncturing retro-orbital plexus under ether anesthesia, later animals were sacrificed, and liver tissue was collected. The blood sample was analysed for biochemical markers of hepatic injury, and the tissue sample was subjected to estimate liver antioxidants and histopathological studies.

Biochemical Evaluation: Blood was drawn by puncturing the retro-orbital plexus under diethyl ether anesthesia. Whole blood for hematogram was collected in bottles containing the anticoagulant, ethyl diamine tetra-acetic acid (EDTA) while the samples for biochemical analysis were collected in plain sample bottles. Serum was separated by centrifugation at 3000 rpm for 15 min and analyzed for various biochemical parameters. Sera were stored at -20 °C before they were analyzed. After collection of blood, the animals were sacrificed by cervical dislocation, and the liver was removed. The liver of each animal was dissected and homogenized for the determination of SOD and CAT activities. Liver damage was assessed by the estimation of serum activities of ALT, AST, ALP, Bilirubin, Albumin, and triglyceride using commercially available assay kits (Erba diagnostic Mannheim, Germany).

Preparation of Liver Homogenate: Liver tissues were homogenized in 10% w/v 0.1 M phosphate buffer or 0.1 M tris buffer (pH 7) and centrifuged at 3000 rpm for 15 min. The supernatant was used for the measurement of liver enzymatic and non-enzymatic antioxidants.

Determination of *in-vivo* Antioxidant: The enzymatic antioxidant was determined by estimating superoxide dismutase [36], Catalase [37] and non-enzymatic antioxidant by reduced glutathione [38] and lipid peroxidation [39].

Histopathological Studies: After experimental period, animals were sacrificed, liver removed immediately, sliced and washed in saline and transfer into 10% formalin solution, after one-week liver tissue was dehydrated with a sequence of ethanol solutions, embedded in paraffin, cut into 5 µm section, stained with haematoxylin-eosin dye and then observed under a microscope.

Statistical Analysis: Statistical analysis was carried out using Graphpad Prism 3.0 (Graphpad Software, San Diego, California, USA). All data were expressed as mean ± SEM. Groups of data was compared with the analysis of variance (ANOVA) followed by Dennett's t-test to identify significance among groups. The value was considered statistically significant when $p < 0.05$ and highly significant when $p < 0.001$.

RESULTS:

Preliminary Phytochemical Analysis: Preliminary phytochemical studies revealed the presence of alkaloid, saponin, tannin, terpenoids, flavonoids, and phenol

Acute Oral Toxicity: The ethanolic extract of CZB was subjected to acute toxicity testing in albino rats and was monitored for 24 h. The ethanolic extract of CZB did not cause any mortality up to 2000 mg/kg, and hence 1/10thof the maximum dose administered (100 and 200 mg/kg, p.o) were selected for the present study.

Effect of Ethanolic Extract of CZB on Biochemical Parameters: In acetaminophen (APAP) treated rats, the levels of serum marker enzymes (ALT, AST, ALP, and TB) increased significantly when compared to the control of rats. Due to hepatic damage, there was decreased albumin (ALB), and total protein (TP) levels of the group was less than the control group. These increased and decreased levels of various serum marker enzymes were shown in **Table 1**.

TABLE 1: EFFECT OF ETHANOLIC EXTRACT OF CZB ON VARIOUS BIOCHEMICAL PARAMETERS IN ACETAMINOPHEN (APAP) INDUCED HEPATOTOXICITY IN RATS

Parameter	Control (1% CMC, 1ml/kg)	APAP (750 mg/kg)	EECZB (100 mg/kg) per se	EECZB(100mg/kg, bw) + APAP	EECZB(20 mg/kg, bw) + APAP	Silymarin (100mg/kg) + APAP
AST(IU/L)	145±1.75	299±3.57$^{\$\$}$	152±0.48	290±1.44*	169±1.77***	161±0.94***
ALT(IU/L)	39.6±2.02	178±1.86$^{\$\$}$	44.2±3.62	162±1.59*	78±1.21***	57.6±0.44***
ALP (IU/L)	228±1.11	502±1.97$^{\$\$}$	230±1.11	475±1.06**	297±1.36***	254±0.88***
TB (mg/dl)	0.28±0.02	0.61±0.01$^{\$\$}$	0.28±0.01	0.51±0.01*	0.45±0.01***	0.27±0.01***
ALB(mg/dl)	3.89±0.01	1.7±0.01$^{\$\$}$	3.91±0.01	1.78±0.01	3.06±0.01***	3.37±0.01***
TP(mg/dl)	7.79±0.01	5.87±0.02$^{\$\$}$	7.74±0.01	5.75±0.02	6.31±0.02*	6.65±0.03***
TC (mg/dl)	85±1.71	263±2.68$^{\$\$}$	91.5±1.35	252±1.97*	132±2.37**	104±1.97***

All values were expressed as mean ± SEM for six rats in each group. $\$\$ p < 0.001$ as compared to control groups, $***p < 0.001$, $*p < 0.05$, $**p < 0.01$ as compared to APAP groups

Antioxidant: In the rats treated with acetaminophen, a significant decreased in anti-oxidant enzymes such as superoxide dismutase, catalase, glutathione, and an increased in lipid

peroxidation was observed **Table 2**, However treatment of ethanolic extract of CZB significantly increased the antioxidant status as compared with the control group.

TABLE 2: EFFECT OF ETHANOLIC EXTRACT OF CZB ON VARIOUS BIOCHEMICAL PARAMETERS IN ACETAMINOPHEN INDUCED HEPATOTOXICITY IN RATS

Parameter	Control (1% CMC, 1ml/kg)	APAP(750 mg/kg)	EECZB (100mg/kg)	EECZB (100 mg/kg)+APAP	EECZB (200 mg/kg)+APAP	Silymarin (100mg/kg)+APAP
SOD (IU/L)	5.82±0.03	2.37±0.15$^{\$\$}$	5.95±0.04	2.93±0.02*	5.79±0.02***	6.96±0.04***
CAT (IU/L)	18.4±0.21	9.05 ±0.01$^{\$\$}$	19.1±0.01	10±0.01*	15.1±0.01***	16.1±0.01***
GSH	6.61±0.03	2.18±0.15$^{\$\$}$	6.83±0.02	2.62±0.02*	5.16±0.01***	5.78±0.02***
LPO	3.31±0.02	9.18±0.15$^{\$\$}$	3.39±0.02	8.95±0.01*	7.84±0.02***	5.06±0.01***

All values were expressed as mean ± SEM for six rats in each group. $\$\$ p < 0.001$ as compared to control groups, $***p < 0.001$, $*p < 0.05$, $**p < 0.01$ as compared to APAP groups

Histopathological Studies: Histopathological studies of control group **Fig. 2A** showed central vein no damage in liver. Liver section of APAP-treated rats showed intense neutrofil infiltrations, less sinusoid widening, hyperplasia of Kupffer cells **Fig. 2B**.

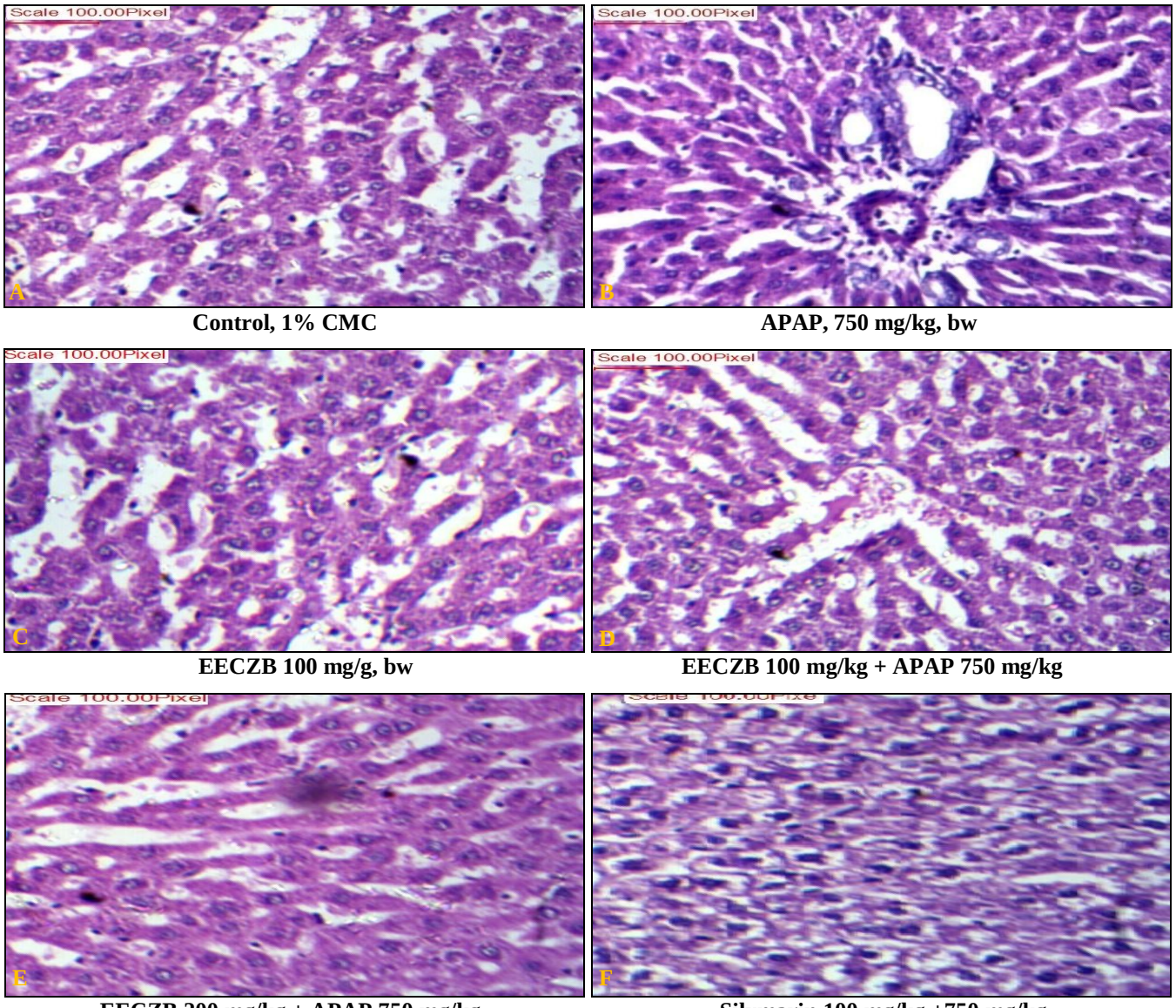

FIG. 2: HISTOPATHOLOGY OF LIVER SHOWING NORMAL HEPATOCYTE (2A), ACETAMINOPHEN INDUCED INTENSE NEUTRIFIL INFILTRATION AND HYPERPLASIA OF KUPFFER CELL (2B), NORMAL LIVER ARCHITECTURE, NO CHANGE IN HEPATOCYTE (2C), LESS SINUSOID WIDENING (2D), NO DAMAGE IN PORTAL VEIN, BILE DUCT, HEPATIC ARTERY (2E), NORMAL PORTAL TRIAD, NO DAMAGE IN LIVER TISSUE (2F)

Liver section of rats treated with 100 mg/kg, b.w of EECZB showed normal liver architecture that is no change in hepatocyte **Fig. 2C**. Liver section of rats treated with APAP and 100 mg/kg, b.w. of EECZB showed there is less acidophilic bodies, no damage in a central vein, less sinusoidal widening **Fig. 2D**. Liver section of rats treated with APAP and 200 mg/kg, b.w of EECZB showed no damage in the portal vein, bile duct, and hepatic artery, less sinusoidal widening **Fig. 2E**. Liver section of rats treated with APAP and 100 mg/kg of silymarin showed almost normal liver tissue that is no damage in portal triad, hepatocytes, and sinusoids **Fig. 2F**, indicating the hepatoprotective activity of ethanolic extract of CZB.

DISCUSSION: The present study demonstrates the hepatoprotective effect of ethanolic extract CZB on acetaminophen-induced toxicity in albino rats. The liver is one of the vital organs of the body responsible for the detoxification of toxins and drugs. Acetaminophen (APAP) is a common antipyretic agent, which is safe in therapeutic doses but can produce fatal hepatic necrosis in men, rat, and mice with toxic dose [40]. N-acetyl-p-benzoquinone imine is the toxic metabolite of APAP, which induces lipid peroxidation and cell necrosis by covalently binding to the sulfhydryl groups of protein[11]. The damaging membrane effect of N-acetyl-p-benzoquinone imine result in the leakage of the hepatocyte contents in the liver injury caused by APAP overdose [41,] and hence there is an increase in serum enzyme levels.

In this studies administration of APAP leads to increased serum levels of enzymes like AST, ALT, ALP, TB, and Cholesterol while decreased ALB and TP levels. This is indicative of cellular damage and loss of functional integrity of cell membrane in liver [42]. Due to damage of hepatocytes that is intense neutrophil infiltration and hyperplasia of Kupffer cell as shown in **Fig. 2B**, there was a decreased in production of protein, and so the total protein (TP) levels were decreased from (7.79±0.01) IU/L to (5.87±0.02) IU/L. The increased production of serum enzyme in blood was associated with intense neutrophil infiltration and hyperplasia of the liver, which causes severe hepatic injury. Moreover, the increased levels of these serum enzymes were significantly decreased by treatment with EECZB 100 and 200 mg/kg bw, implying that the extract prevented the liver. The CZB extract treatment showed dose-dependent activity, CZB extract at 200 mg/g bw showed a good result than 100 mg/kg, bw, which is given in **Table 1** for measured levels of different serum enzymes. This is also confirmed by a reduced amount of histopathological injuries in **Fig. 2D** and **2E**.

Production of ROS and glutathione depletion are an important role in acetaminophen-induced toxicity [43]. This is evident from the reduction of antioxidant status SOD, CAT, GSH) and production of LPO of acetaminophen-induced toxicity in rats. CZB extract was able to restore the levels of antioxidant suggesting its protective role in acetaminophen mediated liver injury. This was confirmed by the histopathological observation **Fig. 2**. The phytochemical constituent of CZB extracts such as alkaloid, saponin, terpenoid, tannin, flavonoid, and phenol might be contributing to its hepatoprotective activity.

CONCLUSION: To the best of our knowledge, our study is the first to report on the hepatoprotective effect of the CZB on acetaminophen-induced toxicity in albino rats. The protective effect was confirmed at two different doses. Treatment with 200 mg/kg EECZB was the most effective based on the biochemical and histopathological findings.

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CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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