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LIVER PROTECTIVE ACTIVITY OF *COCCINIA GRANDIS* FRUITS EXTRACT AGAINST ANTI-TUBERCULAR DRUGS INDUCED LIVER TOXICITY IN RATS

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Keywords:

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ABSTRACT: To investigate the hepatoprotective activity of *Coccinia grandis* fruit extract against anti-tubercular drugs induced hepatotoxicity in rats. 50% ethanolic extract of *Coccinia grandis* (CGE 200 and 400 mg/kg body weight) was administered daily for 9 days in experimental animals. To develop hepatotoxicity, animals were administered orally with Isoniazid (50 mg/kg, p.o.) and Rifampicin (100 mg/kg, p.o.) at 2 h after the doses of CGE every day for nine consecutive days except for rats in the normal group. The hepatoprotective activity was determined using different biochemical parameters such asalanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (ALB), Bilirubin (BIL), Cholesterol (CHL) and lactate dehydrogenase (LDH). Histopathological examinations further accomplished the hepatoprotective effect of the CDE. The results obtained demonstrated that the treatment with *Coccinia grandis* significantly ($P<0.05$-$P<0.001$) and dose-dependently prevented the drug-induced increase in serum levels of hepatic enzymes. Histopathology of liver tissue showed that *Coccinia grandis* attenuated the hepatocellular necrosis, regeneration, and repair of cells toward normal. The results of this study strongly indicate the protective effect of *Coccinia grandis* against liver injury, which may be attributed to its hepatoprotective activity, and thereby scientifically support its traditional use.

INTRODUCTION: The development of drug-induced hepatotoxicity (DIH) during chemotherapy for TB is the most common reason leading to interruption of therapy. Wide variations have been found in the incidence of hepatotoxic reactions during short-course chemotherapy from different countries with the reported incidence being 3% in the USA, 4% in UK, 11 % in Germany, 9.9% in Argentina, 13% in Hong Kong, 36% in Japan, 26% in Taiwan and 8–36% in India [1].

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It was globally estimated by WHO that about 10.4 million cases of TB were there in 2017 out of which two-thirds were in eight countries, including India (27%), Indonesia (8%), China (9%), Nigeria (4%), Pakistan (5%), Philippines (6%), South Africa (3%) and Bangladesh (4%). However, about 15-20% of all TB cases are of EPTB. The EPTB scenario with HIV pandemic constitutes more than 50% of all cases of TB in HIV-positive patients.

However, TB mortality rate between 2000–2017 reduced up to 42%. TB incidence has decreased by an average of 2% per year and in 2017case fatality rate down by 16% from 23% in 2000 [6]. In about thirty high-burden countries, India has reduced the prevalence rate by 50% as set by Stop Partnership Programme for TB [1, 2]. Hepatotoxicity refers to liver dysfunction or liver damage that is associated

with an overload of drugs or xenobiotics. The chemicals that cause liver injury are called hepatotoxins or hepatotoxicants. Hepatotoxicants are exogenous agents of clinical importance that might include an overdose of some specific medicinal compounds such as nimesulide, acetaminophen, antitubercular drugs such asrifampicin, isoniazid, ethambutol, *etc.*), industrial chemicals such as beta galactosamine, CCl_4, alcohol, thioacetamide, *etc.*, that can result in liver injury. These may include overdoses of certain medicinal drugs, industrial chemicals, and natural chemicals like microcystins, herbal remedies, and dietary supplements. Hepatotoxicity may result not only from direct toxicity of the primary compound but also from a reactive metabolite or an immunologically-mediated response affecting hepatocytes, biliary epithelial cells and/or liver vasculature. The hepatotoxic response elicited by a chemical agent depends on the concentration of the toxicant, which may be either a parent compound or toxic metabolite, differential expression of enzymes, and concentration gradient of cofactors in blood across the acinus [1, 4].

Hepatotoxic agents include not only some chemicals but also some drugs that are used in clinical practice. A routinely used analgesic, paracetamol, primary anti-tubercular agents, and commonly abused alcoholic beverages are implicated with hepatic injury. Such drug-induced hepatotoxicity not only limits their further use but might interfere with essential metabolic functions leading to consequences of altered carbohydrate, protein, and fat metabolism. Hepatotoxicity can be related to inhibition of cellular respiration, mitochondrial dysfunction, or changes in β oxidation of fatty acids. These, however, can cause necrosis, apoptosis, autophagy, and cell death [1, 3]. The available therapeutic interventions for liver diseases include drugs like steroids, anti-cytokines, colchicine or supplementation with a calorie-rich diet or a glutathione precursor; s-adenosyl L-methionine (SAMe) has not been able to show convincing benefit in humans and also suffer from several side effects. Thus herbal medicines have an important role in treating liver disorders considering their efficacy, safety, and lesser side effects. Several medicinal plants and their herbal formulations are used in treating liver disorders in the traditional system of medicine and ethnomedicine practice in India. There are around more than 600 commercially used herbal formulations available in the market globally, which claim to possess hepatoprotective activity [5] *Coccinia grandis* (L.) voigt (Ivy gourd), a member of Cucurbitaceae, is a dioecious, perennial and herbaceous climber *Coccinia grandis* (L.) voigt (Ivy gourd), member of Cucurbitaceae, is a dioecious, perennial and herbaceous climber *Coccinia grandis* (L.) voigt (Ivy gourd), member of Cucurbitaceae is a dioecious, perennial and herbaceous climber *Coccinia grandis* (L.) voigt (Ivy gourd), belonging to family Cucurbitaceae, is a dioecious, perennial and herbaceous climber plant [6]. The fruit, when ripped, becomes red, ovoid to elliptical, having a length 25–60 mm long, 15–35 mm in diameter, and hairless on stalks 10–40 mm long [7].

MATERIALS AND METHODS:

Chemicals and Drugs: All the chemicals which were used are of analytical grade and procured from Sigma Chemical Co., USA, and Qualigens fine chemicals, Mumbai, India.

Plant Collection and Authentication: The ripped fruits of *Coccinia grandis* were collected from the local market of Ghaziabad in the month of April and May. The plant material was authenticated by Prof. (Dr.) Vijai Malik (Department of Botany) from CCS University of Meerut. India. A voucher specimen of *Coccinia grandis* (CCSU/BOT/HRB/ 14/05) was deposited in the institute for further reference.

Extract Preparation for Animal Study: The freshly collected fruits of *Coccinia grandis* were washed with distilled water to remove dirt and soil and shade dried in a ventilated place at room temperature. Dried fruits were cut into small pieces and reduced to a coarse powder by the mechanical grinder, and further extraction was carried out with the maceration method to avoid damage due to heat. However, at room temperature, 150 grams powdered drug was suspended in 200 ml of ethanol for 72 hours. After 72 hrs, the extract was filtered and concentrated under reduced pressure below 40±1°C using a rota vaccum rotary evaporator (Model no- UDOIAB-2391 Medica instrument) dryness to get a constant weight. The % yield was found to be 19.21 % w/w.

The extract was stored in −20 °C freezer and used for Pharmacological investigation.

Animal Experiments: For the study, adult Wistar rats weighing 160 ± 20 g were procured from National Institute of Biologicals, Noida, Uttar Pradesh-201309. They were kept in the Animal House of Sunder Deep Pharmacy College, Ghaziabad. The animals were housed separately in polypropylene cages for acclimatization at a temperature of (23 ± 2 ºC) and 50–60% relative humidity, with a 12 hr light/dark cycle one week before and during the commencement of the experiment. Animals were kept on a standard pellet diet (Dayal animal feed, Unnao, India) and drinking water *ad libitum* throughout the housing period. All experimental procedures involving animals were conducted by the guidelines of the Committee for Control and Supervision on Experiments on Animals (CPCSEA). The study protocols were approved by the Institutional Animal Ethics Committee (IAEC) of Sunder Deep Pharmacy College, Ghaziabad, India (Reg. no. 1673/PO/Re/S/12 /CPCSEA).

Experimental Protocol: 25 experimental animals (Wistar rats) randomly divided into five groups consisting of five rats (n=5) per group were used in this study as detailed in following **Table 1:**

TABLE 1: ANIMALS AND DOSAGE OF DRUG IN EACH GROUP

S. no.	Group No.	Treatments	Dose
1.	Group-A	Normal control (saline solution)	1 ml (p.o)
2.	Group-B	Toxicant (Isoniazid + Rifampicin)	50 mg/kg +100mg/kg (p.o)
3.	Group-C	Toxicant + Silymarin	50 mg/kg +100mg/kg (p.o)+100 mg/kg (p.o)
4.	Group-D	Toxicant + Ethanol extract of *Coccinia grandis*	50 mg/kg +100mg/kg (p.o)+ 200 mg/kg (p.o)
5.	Group-E	Toxicant + Ethanol extract of *Coccinia grandis*	50 mg/kg +100mg/kg (p.o)+ 400 mg/kg (p.o)

Serum Collection and Organ Isolation: The vehicle or drug treatment was carried out orally from day 1 to 9 with concurrent administration of isoniazid and rifampicin. During the drug treatment period, the rats were maintained on a normal diet, and water was supplied *ad libitum*.

On day 10, blood was collected by retro-orbital plexus under mild ketamine anesthesia. The serum was separated by centrifugation at 3000rpm for 15 min and subjected to estimation of various biochemical parameters.

The isolated liver tissue was washed twice with ice-cold saline, blotted, dried and then weighed. The relative liver weight was calculated as the percentage ratio of liver weight to the body weight. A small portion of the tissue was fixed in 10% formalin solution for histopathalogical studies.

Assessments of Liver Function Test (L.F.T): Serum enzymes like, Serum alanine transaminase (ALT), Alkaline Phosphate (ALP), Aspartate Transaminase (AST), Bilurubin, Total Cholesterol and Albumin (ALB) were determined by using standard kits from Span diagnostic ltd, Surat, India. Serum lactate dehydrogenase (LDH) was estimated by using standard kits from Accurex biomedical Pvt., Ltd., Mumbai India. All estimations were carried out using UV spectro-photometer (Shimadzu, India) as per standard kit methods.

Histopathological Assessment: For histologic studies, the liver tissues were fixed with 10% phosphate-buffered neutral formalin, dehydrated in graded (50-100%) alcohol and embedded in paraffin. Thin sections (5 M) were cut and stained with routine hematoxylin and eosin stain for photo microscopic assessment. The examination was qualitative, to determine histopathological lesions in liver tissue.

Statistical Analyses: The data were represented as mean ± standard error of the mean (S.E.M.) for five rats. Student t-test was followed by individual comparison by Newman- Keuls test using GraphPrism Pad software (Version 6.05, GraphPad Software, Inc. USA) for the determination of level of significance. The probability value less than 5% ($P<0.05$) was considered statistically significant.

RESULTS:

Animal Experiment: Administration of ethanolic CGE extract in rats without introducing anti-tubercular drugs was performed to determine the CGE effect alone if it can cause hepatic damage.

The effect of *Coccinia grandis*e ethanolic extract on liver weight, body weight and serum marker enzymes was found to attenuate the toxic effect of anti-tubercular drugs on rats, thereby contributing to its antihepatotoxic potential. **Table 2** represents the impact of *Coccinia grandis* on the extent of the liver enzymes *viz.*, AST, ALT ALP, and LDH and all experimental rats. Very excessive tiers of those enzymes were proven in the toxicant handled on animal businesses. Oral management of *C. grandis* each a hundred and two hundred mg/kg bw brought an enormous discount in all of the enzymes analyzed (p<zero.05), similar to our general drug silymarin. **Table 3** illustrates the impact of *Coccinia grandis* on the extent of lipid peroxide and non-enzymatic antioxidant inside the rat hepatic tissues of manipulated and experimental business of rats. The tiers of malondialdehydenearly tripled inside the toxicant handled the organization of experimental rats whilst as in comparison with controls.

When the toxicant brought on businesses has been handled with a hundred and two hundred mg/kg bw *C. grandis* fruits extract, the malondialdehyde tiers have been decreased significantly (p<0.05). The tiers of Vitamin C and decreased glutathione additionally confirmed enormous lower in tiers inside the toxicant handled businesses and on next remedy with the fruits extract advanced dramatically. **Table 4** represents the impact *C. grandis* fruits extract on the sports of enzymatic antioxidants such as SOD, catalase and GPx, in hepatic tissues of manipulating and experimental businesses of rats. The sports have been significantly (p <0.05) dwindled with inside the hepatic tissues of toxicant brought on organization of rats. Oral remedy of *Coccinia grandis,* just like that of silymarin, significantly (p <0.05) attenuated the altered sports of those enzymatic antioxidants to close to normalcy in hepatic tissues of toxicant brought on experimental

TABLE 2: EFFECT OF ETHANOLIC EXTRACT OF *COCCINIA GRANDIS* ON PATHOPHYSIOLOGICAL MARKER ENZYMES

Groups	AST (U/L)	ALT (U/L)	ALP	LDH
Normal control (saline solution)1 ml (p.o)	91.90 ± 4.9	58.00 ± 2.5	27.33 ± 1.9	168.16 ± 6.4
Toxicant (Isoniazid + Rifampicin) 50 mg/kg + 100 mg/kg (p.o)	254.66 ± 14.5	234.50 ± 1.9	95.33 ± 1.0	230.16 ± 10
Toxicant + Ethanol extract of *Coccinia grandis (200mg/kg)(p.o)*	143.00 ± 3.8a	97.00 ± 4.2a	45.66 ± 1.9a	164.25 ± 5.4a
Toxicant + Ethanol extract of *Coccinia grandis 400 mg/kg (p.o)*	101.00 ± 3.5b	74.12 ± 2.1b	33.2 ± 1.7b	159.50 ± 10b
Toxicant + Silymarin 50 mg/kg (p.o)	118.00 ± 3.1	93.66 ± 10	39.00 ± 1.25	142.50 ± 8.5

Values are expressed as mean ± S.D (n=6). a P<0.05 DEN treated with *C. grandis* (100 mg/bw) compared with DEN induced b P<0.05 DEN treated with *C. grandis* (200 mg/bw) compared with DEN induced.

TABLE 3: EFFECT OF ETHANOLIC EXTRACT OF *COCCINIA GRANDIS* ON LIPID PEROXIDATION AND NON ENZYMIC ANTIOXIDANT ACTIVITIES

Groups	MDA	Vit C	GSH
Control	91.90 ± 4.9	58.00 ± 2.5	27.33 ± 1.9
Toxicant (Isoniazid + Rifampicin) 50 mg/kg + 100 mg/kg (p.o)	254.66 ± 14.5	234.50 ± 1.9	95.33 ± 1.0
Toxicant + *Coccinia grandis* (*200mg/kg*)	143.00 ± 3.8a	97.00 ± 4.2a	45.66 ± 1.9a
Toxicant + *Coccinia grandis* (400 mg/bw)	101.00 ± 3.5b	74.12 ± 2.1b	33.2 ± 1.7b
Toxicant + Silymarin (100mg/kg bw)	118.00 ± 3.1	93.66 ± 10	40.00 ± 1.25

Values of results are expressed as mean ±.SD for six rats. Malanodialdehyde (nm/mg of protein), Vitamin C (mg/dl) and reduced glutathione (µg /mg of protein). Values are expressed as mean ± S.D (n=6). a P<0.05 DEN treated with *C. grandis* (100 mg/bw) compared with DEN induced, b P<0.05 DEN treated with *C. grandis* (200 mg/bw) compared with DEN induced

TABLE 4: EFFECT OF ETHANOLIC EXTRACT OF *COCCINIA GRANDIS* ON ENZYMIC ANTIOXIDANT

Groups	Catalase	SOD	GPx
Control	91.90 ± 4.9	58.00 ± 2.	27.33 ± 1.9
Toxicant (Isoniazid + Rifampicin) 50 mg/kg + 100 mg/kg (p.o)	254.66 ± 14.6	234.50 ± 1.9	95.33 ± 1.0
Toxicant + *Coccinia grandis* (200 mg/bw)	143.00 ± 3.8a	97.00 ± 4.2a	45.66 ± 1.9a
Toxicant + *Coccinia grandis* (400 mg/bw)	101.00 ± 3.5b	74.12 ± 2.1b	33.2 ± 1.7b
Toxicant + Silymarin (100mg/kg bw)	118.00 ± 3.1	93.66 ± 10	40.00 ± 1.25

Catalase (U/mg of protein), Superoxide dismutase (U/mg of protein), Glutathione peroxidase (U/mg of protein). Values of results are expressed as mean ±.SD for six rats. Values are expressed as mean ± S.D (n=6). a P<0.05 DEN treated with *C. grandis* (100 mg/bw) compared with DEN induced, b P<0.05 DEN treated with *C. grandis* (200 mg/bw) compared with DEN induced.

Histopathological Studies: The histopathological evaluation of liver tissues of experimental groups (I-V) of rats (hematoxylin and eosin) was observed as described. A. indicates the phase of hepatic tissue of manipulated rat. B. Hepatic tissues of toxicant brought on the organization. C. Hepatic tissues of rats handled with *C. grandis*. D. Hepatic tissues of toxicant brought on the organization of rats handled with silymarin.

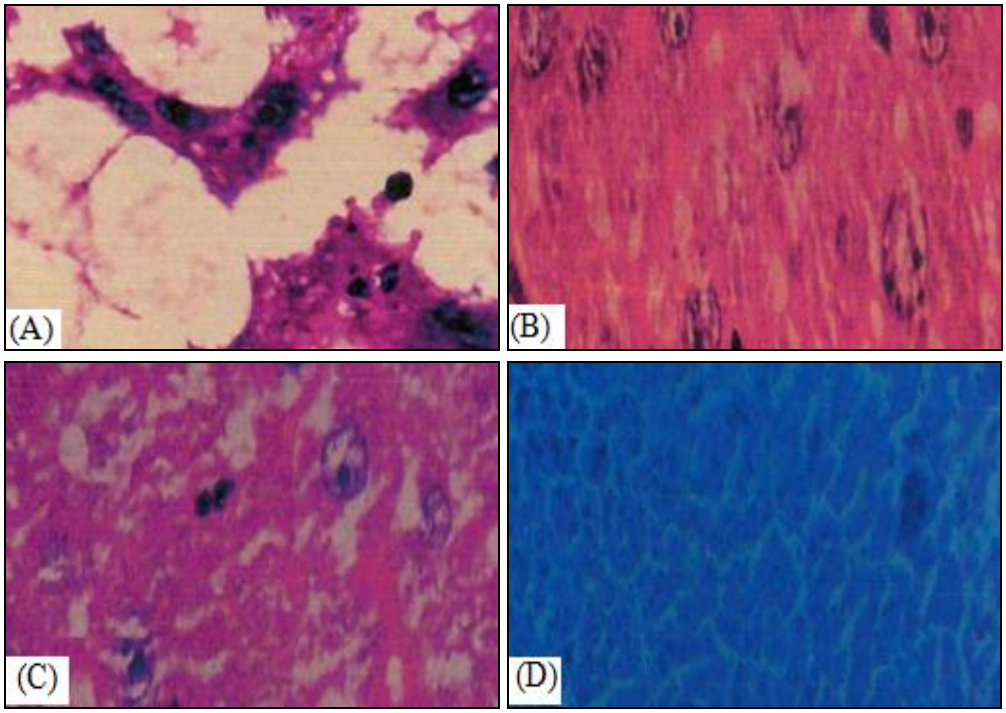

FIG. 1: HISTOPATHOLOGY OF LIVER TISSUES (HEMATOXYLIN AND EOSIN). A. INDICATES THE PHASE OF HEPATIC TISSUE OF MANIPULATED RAT. B. HEPATIC TISSUES OF TOXICANT BROUGHT ON ORGANIZATION. C. HEPATIC TISSUES OF BROUGHT ON ORGANIZATION OF RATS HANDLED WITH *C. GRANDIS*. D. HEPATIC TISSUES OF TOXICANT BROUGHT ON ORGANIZATION OF RATS HANDLED WITH SILYMARIN

DISCUSSION: The management of toxicants has proven to boom the tiers of animal's liver tissue LPO in the course of hepatotoxicity. This energetic motion can be lead via way of uncompromised manufacturing of frame unfastened radicals [8].

The boom within the side the tiers of the liver enzymes ALT, AST, ALP and LDH are indicative of hepatic damage [9].

Toxicant hepatic damage is related to the disturbance in hepatocytes membrane instability and metabolism resulting in alterations of the serum tiers of those hepatic enzymes. The boom of ALT and AST serum tiers are particular to hepatocelluar disturbance [10].

A boom in the ALP denotes disturbances in biliary frame flow. Treatment with *C. grandis* to the toxicant brought on organization brings approximately enormous lower in those enzyme tiers.

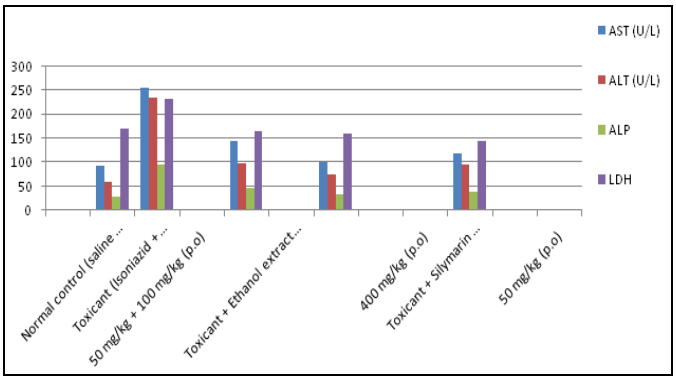

FIG. 2: EFFECT OF ETHANOLIC EXTRACT OF *COCCINIA GRANDIS* ON PATHOPHYSIOLOGICAL MARKER ENZYMES

It is documented in **Fig. 2**, **Fig. 3** and **Fig. 4** that toxicant induces a massive hepatic harm through the technology of reactive oxygen species (ROS) and a concomitant lower within the enzymatic and non-enzymatic antioxidants. In the prevailing take a look at a 3-fold boom within side the level of LPO and highest pronounced reduced parameters

levels of SOD, CAT and GPx were observed during Toxicant management. Further, the observed lower levels of non-enzymatic antioxidant (vitamin C and GSH) shows the entire disruption of the antioxidant protection mechanism of the animal liver. The management of the fruit extract of *C. grandis* at 200 mg/ kg body weight showed a massively improved level of antioxidants in toxicants brought on hepatotoxicity.

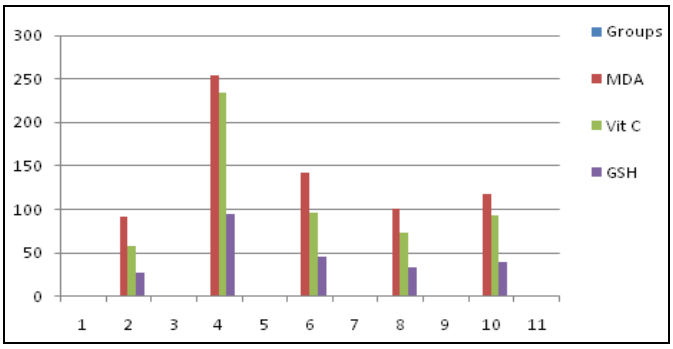

FIG. 3: EFFECT OF ETHANOLIC EXTRACT OF *COCCINIA GRANDIS* ON ENZYMIC ANTIOXIDANT

The biochemical findings are supported by histopathological observations of the animal liver in **Fig. 1**. The histopathologic styles of liver damage determined in rats with toxicants became more pronounced. Centrilobular necrosis, ballooning of hepatocytes, infiltration of lymphocytes, and steatosis of animal liver cells have been characteristic changes because of the toxicant. Moreover, animal remedies with *C. grandis* reduced the hepatocytes degeneration, decreased the lymphocytic infiltration in animal liver, and confirmed regenerative effects.

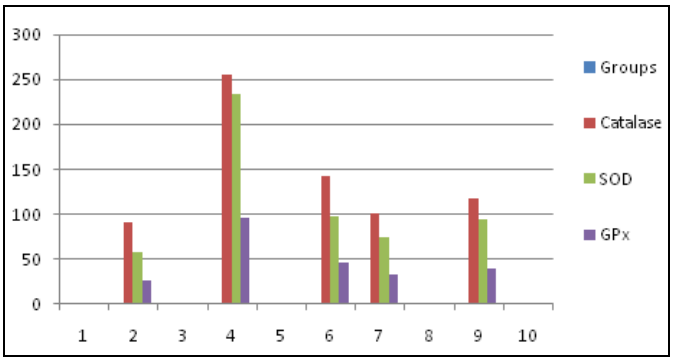

FIG. 4: EFFECT OF ETHANOLIC EXTRACT OF *COCCINIA GRANDIS* ON ENZYMIC ANTIOXIDANT

This may be used as a functional improvement of animal hepatocytes, possibly due to stimulating the regeneration of Parenchymal cells or less mobileular damage in the presence of *C. grandis*. Therefore, the prevailing research throws mild at the hepatocytes shielding nature of *C. grandis* ethanolic plant fruits extract in toxicant precipitated oxidative strain. The oral management of *C. grandis* to toxicant precipitated rats exhibited large ameliorative capability, likely through attenuating the toxicant-mediated oxidative strain and preserving the structural and functional integrity of hepatocytes. Further special experimental investigations are developing to explain how *C. grandis* ethanolic extract elicits its diverse effects.

CONCLUSION: The above results indicate that the plant *Coccinia grandis* (L.) per carp showed an antioxidant interest, especially ethanol extracts. The extracts have been studied for acute toxicity studies. Therefore, the fruit extracts were subjected to in vivo hepatoprotective investigations. In the acute liver toxicity studies, groups receiving (isoniazid + rifampicin) and plant extract showed good enough liver protection compared to the toxic group. However, *Coccinia grandis* (L.) ethanol extract extracts proved to be advanced, even supposing the petroleum ether extract showed an excellent result in each group compared to different extracts. This is due to numerous antioxidants and cytoprotective/hepatoprotective constituents. Therefore, the extracts can be beneficial in treating liver damage, resulting in better effects when administered by any chemical or xenobiotic materials. However, comparable studies were performed to determine the precise treatment mechanism. At the same time, this extract can be formulated in an appropriate dosage shape or as a polyherbal formulation. Its pharmacological assessment can be performed using suitable animal models discovered via clinical experiments on human volunteers.

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

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