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HEPATOPROTECTIVE POTENTIAL OF *Physalis peruviana* L. FRUIT EXTRACTS ON LEAD ACETATE INTOXICATED RATS

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ABSTRACT

Physalis peruviana has been widely used as a medicinal herb for treating various diseases since ancient times. This study aimed to examine the hepatoprotective potential of the ethanolic extract of *P. peruviana* fruit (EPPF) against lead acetate (LA) intoxicated male albino rats. The experimental rats were divided into ten groups of 4 animals. Animal of Group I served as normal, Group II animals were administered orally 15 mg/Kg body weight of LA, Group III to V animals received EPPF 150mg/kg, 300 mg/kg and 600 mg/kg respectively, Group VI animals received standard silymarin 50 mg/kg, and Group VII to X were treated with LA (15 mg/kg) with EPPF 150, 300, 600 and std 50 mg/kg, orally for 32 days respectively. The degree of protection was measured by estimating hematological parameters such as Hb, RBC, WBC, PCV, platelets, MCV, MCHC, and ESR and biochemical parameters such as urea, creatinine, Cholesterol, HDL, LDL, VLDL, bilirubin, SGOT, SGBT, ALP, GGT, protein, albumin and globulin. Lead acetate induced alterations of hematological and biochemical parameters were observed in group II animals and these levels brought back to normal in the animals treated with EPPF at the concentrations of 150, 300 and 600 mg/kg which was significantly similar to silymarin treated animals. The data of the results obtained depicted that the fruit extract of *P. peruviana* was found to have promising protective efficacy against lead acetate induced liver toxicity.

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1 Introduction

Lead is a well-known heavy metal known as an environmental pollutant and has harmful effects on human health (Gagan et al., 2012). It is transferred *via* the food chain to human and animals (Azman et al., 2015); and its toxicity depends on its chemical nature administrated to the animal, the route of administration, and the frequency and duration administered to animals (Chaurasia et al., 2016; Kumaresan et al., 2016). Further, lead provokes excess production of reactive oxygen species (ROS) and consequently improves lipid peroxidation, reduces the saturated fatty acids, and increases the unsaturated fatty acid contents of membranes. Moreover, it has been shown to elicit ROS production in a range of cells leads to oxidative stress (Gautam & Flora, 2010; Sharma et al., 2011; El-Neweshy & El-Sayed, 2011; Mobarak & Sharaf, 2011). The liver is an essential organ that can eliminate toxic substances and defend the other organs that exposure to various toxin sources. About 33% of the lead is accumulated in liver tissue after absorption and causes changes in its regular metabolic activities due to its toxicity and modification in histological structures (Vineeth Daniel et al., 2019).

Epidemiological data specify that fruit and vegetable consumption caused a reduction in morbidity and mortality from several dangerous diseases and this is due to their high content in polyphenols, vitamins, minerals, and other bioactive molecules (Wang et al., 2014; Hu et al., 2014). Reports on the rising role and values of medicinal plant products in the maintenance and optimization of health have led to research on the efficacy of these medicinal plants/nutrient products' effects on the amelioration of the metal-induced toxicity (Nwokocha et al., 2012).

Physalis peruviana (Family: Solanaceae) is an herbaceous, semi-shrub plant, annual in the temperate zones and perennial in the tropics and sub-tropics. It was first reported in the Andean region, mostly Colombia, Peru, Ecuador, and presently cultivated in several regions throughout the world (Osorio-Guarin et al., 2016; Park et al., 2016; Adebayo et al., 2019). *P. peruviana* is widely used in folk medicine for treating diseases such as malaria, asthma, hepatitis, dermatitis, cancer, diuretic, rheumatism, antispasmodic, diuretic, antiseptic, sedative, analgesic, cataract-cleaning, antidiabetic, and anti-parasitic properties (Kasali et al., 2013; Cakir et al., 2014; Joshi & Joshi, 2015; Lashin & Elhaw, 2016; Eken et al., 2016; Higaki et al., 2016; Chang et al., 2016). Various therapeutic applications have been attributed to the cape gooseberry, including anti-asthmatic, anti-septic, strengthener of the optic nerve, remedy for throat infections, anti-ulcer potential, antiparasitic, antiamoebic, as well as albumin from kidneys, controlling cholesterol level (Arun & Asha, 2007; Hassanien, 2011). The study aimed to evaluate the ability of the ethanol extract of *P. peruviana* fruit to reduce the hepatotoxic effects of lead acetate in male rats by estimating levels of important hematological parameters, liver enzymes, total serum protein, and bilirubin.

2 Materials and Methods

The fruits of *P. peruviana* were collected from 2-3 months old healthy plants growing at the Medicinal plant Garden, Sri Akilandeswari Women's College, Wandiwash, Tamil Nadu, India**.** The plant was taxonomically identified and confirmed by the authorities of Dr. P. Jayaraman, Director, Plant anatomy research center, Chennai, Tamil Nadu, India. The fruits were subjected to shade drying for 10-15 days and it was powdered mechanically and stored in an air-tight container. About 40 gm of fruit powder was extracted with 200 ml of ethanol; this extraction was carried out by hot percolation method using Soxhlet apparatus. It was concentrated to dryness under a controlled temperature of 40-50°C and preserved in the refrigerator till further use.

2.1 Experimental Design

Male albino rats (40) were obtained from the Centre for Laboratory Animal Research (CLAR). The experiments were designed and performed according to the ethical norms approved by CPCSEA, India, protocol number of approbation allocated for the Institutional Animal Ethical Committee (IAEC) of Saveetha institute medical and technical sciences, Chennai, Tamil Nadu and the approved protocol for the present study was BRULAC/SDCH/SIMATS/IAEC/3-2020/050. The animals were housed (4 rats per cage) in an environmentally controlled temperature (22 ± 2°C) with a 12:12-hr light/dark cycle and they were fed with a standard laboratory diet and had free access to water. Initial LD_{50} studies were carried out to determine the maximum dose that did not produce any death in the rats. The experimental animals were divided into 10 groups of 4 animals. Animal of Group I served as normal received distilled water, Group II animals were administered orally 15 mg/Kg body weight of lead acetate (LA), ones in a week for 32 days, Group III to V animals received EPPF 150mg/kg, 300 mg/kg and 600 mg/kg respectively, Group VI animals standard silymarin 50 mg/kg, Groups VII to X were treated with LA (15 mg/kg) with EPPF 150, 300, 600 and silymarin 50 mg/kg, orally for 32 days respectively. The rats were anesthetized using chloroform vapour before dissection at the end of the treatment period. Blood samples were collected by cardiac puncture into two different tubes, one containing anticoagulant (EDTA) and the other without anticoagulant. The EDTA was added to the blood in the tube for the determination of hematological parameters and without EDTA was used for the preparation of serum samples. For serum separation from blood, the blood was permitted to clot by keeping at room temperature for 1 hour and then refrigerated for another 1 h. The resultant fluid portion was centrifuged at 1000 rpm for 10 min, and then the clear serum (supernatant) was separated and stored at -30 ℃ until required for analysis (Tuck et al., 2009).
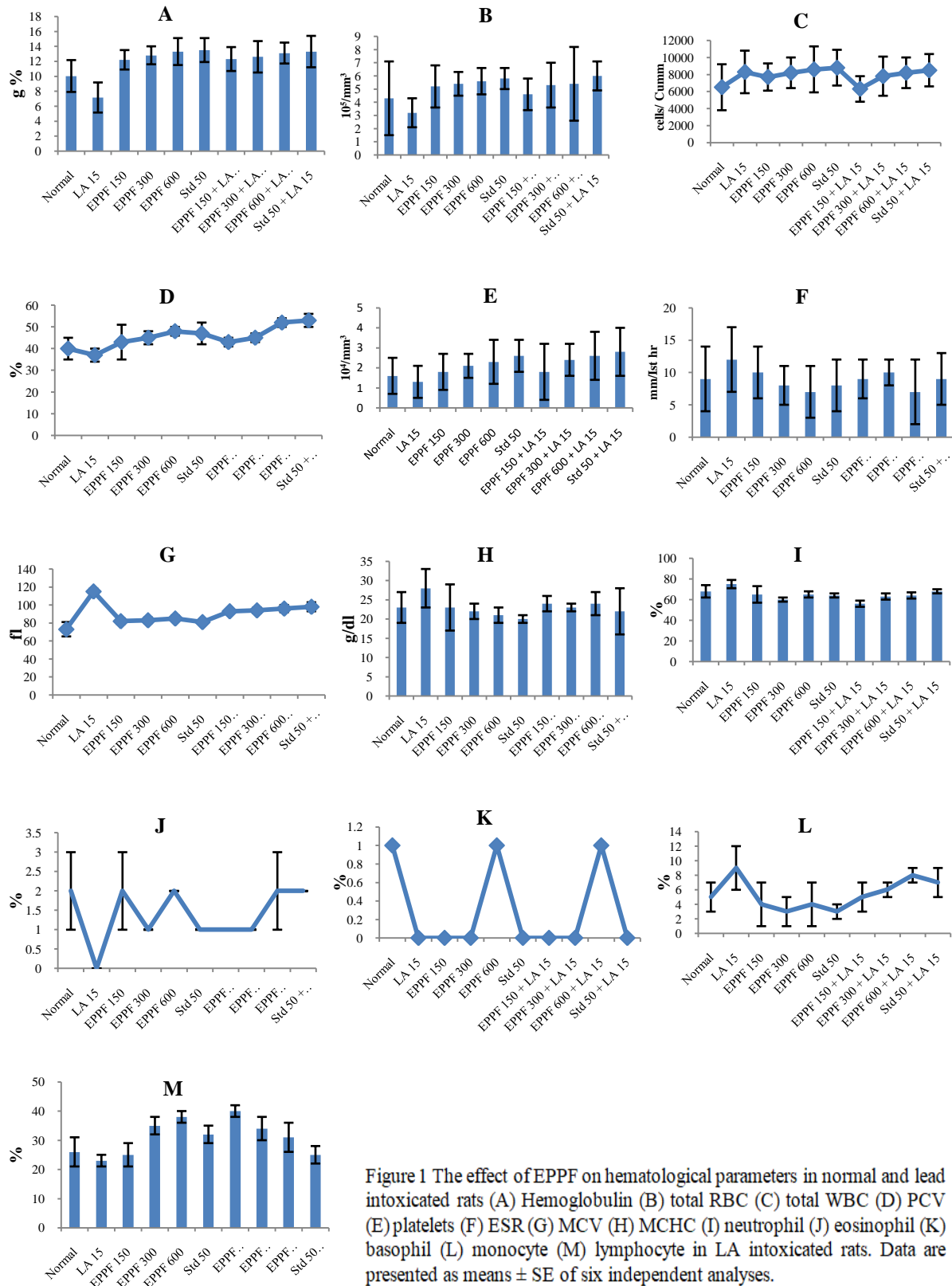
Figure 1 The effect of EPPF on hematological parameters in normal and lead intoxicated rats (A) Hemoglobulin (B) total RBC (C) total WBC (D) PCV (E) platelets (F) ESR (G) MCV (H) MCHC (I) neutrophil (J) eosinophil (K) basophil (L) monocyte (M) lymphocyte in LA intoxicated rats. Data are presented as means ± SE of six independent analyses.
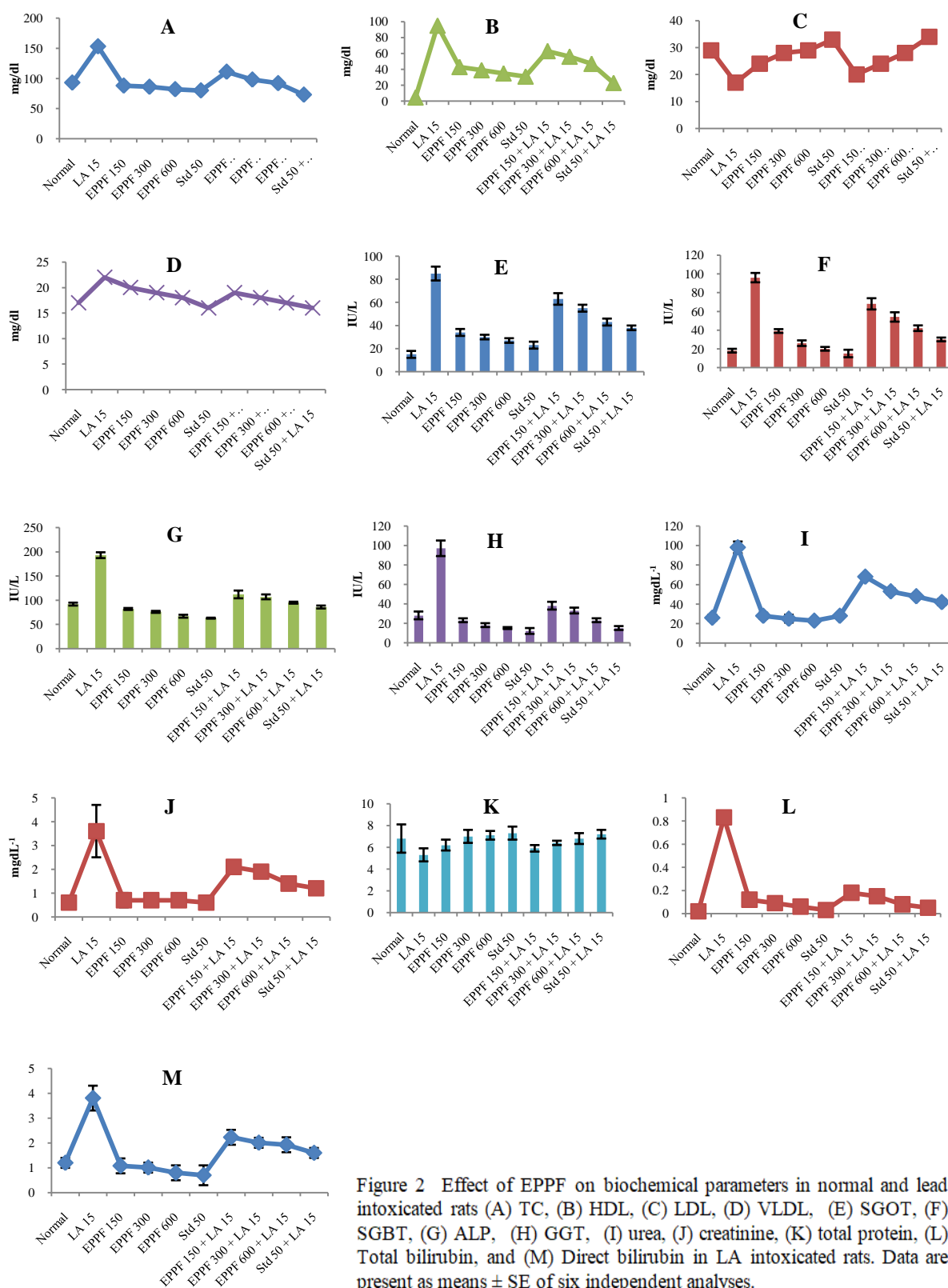
Figure 2 Effect of EPPF on biochemical parameters in normal and lead intoxicated rats (A) TC, (B) HDL, (C) LDL, (D) VLDL, (E) SGOT, (F) SGBT, (G) ALP, (H) GGT, (I) urea, (J) creatinine, (K) total protein, (L) Total bilirubin, and (M) Direct bilirubin in LA intoxicated rats. Data are present as means ± SE of six independent analyses.

2.2 Hematological parameters

The hematological parameters including hemoglobin (Hb), Total RBC, Total WBC, packed cell volume (PCV), platelets, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), neutrophil, eosinophil, basophil, monocytes, lymphocytes, and erythrocyte sedimentation rate (ESR) were analyzed by the method of Barbara & Brown (1980).

2.3 Biochemical analysis

Serum samples collected from different groups were analyzed for urea, creatinine, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoprotein (VLDL), bilirubin (Bil-total & Bil-direct), SGOT, SGBT, Alkaline phosphatase (ALP), GGT, and total protein as per the colorimetric methods (Reitman & Frankel, 1957).

2.4 Statistical analysis

In the present study, the data were expressed as the mean and standard error of the mean (SEM). Data were analyzed by one way analysis of variance (ANOVA) using the SPSS software.

3 Results

The lead acetate administered group (Group II) has exhibited a sudden reduction in the hemoglobulin, total RBC, PCV, platelets and lymphocytes levels by 7.16 ± 2.01 g %, 3.2 ± 1.1 10^5/mm^3, 37.0 ± 3.0 %, 1.3 ± 0.8 10^4/mm^3 and 23.0 ± 2.0% when compared to normal group which revealed 10.03 ± 2.13 g %, 4.3 ± 2.8 10^5/mm^3, 40.0 ± 5.0%, 1.6 ± 0.93 10^4/cu.mm and 26 ± 5%, respectively. After the treatment with EPPF along with LA, a significant increase in the total RBC, hematocrit, platelets, and lymphocytes were reported (Fig 1A, 1B, 1D 1E, 1I). The highest amount of Hb, total RBC, PCV, platelets, and lymphocytes were observed in the LA intoxicated rats treated by 600 mg/kg of EPPF while the lowest amount was observed in the lowest dose of EPPF (150 mg/kg). Whereas, the LA alone administered group has shown a elevation in the total WBC (8300 ± 2500 cells/ Cumm), ESR (12.0 ± 5.0 mm/Ist hr), MCV (115.0 ± 3.0%), MCHC (28.0 ± 5.0 g/dL), neutrophil (75.0 ± 4.0%) and monocytes (9.0 ± 3.0%) as compared to the normal group (6500 ± 2700 cells/ Cumm, 9.0 ± 5.0 mm/Ist hr, 73.0 ± 8.0%, 23.0 ± 40 g/dL, 68.0 ± 6.0% and 5.0 ± 3.0%, respectively). Further, the EPPF alone or the combination of EPPF with LA treated groups reduced the total WBC, ESR, MCV, MCHC, neutrophil, and monocytes counts as compared to LA treated rats and these values are near to control rats (Fig 1C, 1F, 1G, 1H, 1J, 1K, 1L, 1M). Among the three concentrations of EPPF against LA, the highest concentration (600 mg) has registered the very closer value of control rats than others and also almost similar to the standard drug-treated group (Figure 1).

The hepatotoxic agent, LA caused significant liver damage as indicated by an increase in the level of liver chemistry biomarkers such as; cholesterol (153 ± 5.7 mgdL^{-1}), LDL (95 ± 1.3 mgdL^{-1}), VLDL (22 ± 5 mgdL^{-1}), SGOT (85 ± 6 IU/L), SGBT (96 ± 5 IU/L), ALP (193 ± 6 IU/L), GGT (97 ± 8 IU/L), urea (98 ± 6 mgdL^{-1}), creatinine (3.6 ± 1.1 mgdL^{-1}) and bilirubin (3.8 ± 0.5 mgdL^{-1}) and a decrease in the level of HDL (17 ± 1.3 mgdL^{-1}) and total protein (5.3 ± 0.6 mgdL^{-1}) when compared to control animal group (Figure 2).

Rats pre- and post-treated with ESSF at 150 mg/kg, 300 mg/kg, and 600 mg/kg doses has significantly reduced the levels of cholesterol, LDL, VLDL, SGOT, SGBT, ALP, GGT, urea, creatinine, bilirubin, and significantly increased the levels of HDL and total protein as compared to the LA administered controls. The observations from the EPPF treatment were very closer to the normal group. The data of the results very clearly depicted that the selected fruit extract has promising protective efficacy against lead acetate-induced liver toxicity at the dose of 600 mg/kg as compared to that of the other two lower doses and the results were compared with standard drug silymarin (Figure 2).

4 Discussion

Nowadays, liver disorders are amongst the most serious health issues in the world and their management and treatment options remain limited despite remarkable signs of progress in modern medicine. Therefore, testing and the use of botanical hepatoprotective agents are substantially increasing. Lead acetate, a potent hepatotoxic agent, is the most widely used criterion for evaluating the hepatoprotective activity of plant extracts. This study evaluated the antihepatotoxic capacity of *P. peruviana* fruit against lead acetate-induced hepatotoxicity in albino rats. Results of the present study are in agreement with the findings of previous researchers who reported the hepatoprotective potential of the various fruits extracts such as fruits of *Musa paradisiaca* (Issa et al., 2018), *Passiflora edulis* (Nerdy & Ritarwan, 2019), *Cordia obliqua* (Tharun et al., 2020), *Prunus domestica* (Soni & Tanwar, 2020), *Terminalia bellirica* (Gupta et al., 2021).

The hematological parameters are important indices of the physiological and pathological status of animals and humans (Adeneye et al., 2006). It can also use to determine the extent of the deleterious effect of foreign compounds on the blood of the albino rats (Odeyemi et al., 2009). In the present study, the decreasing amount of Hb, total RBC, PCV, platelets, lymphocytes, and elevated levels of WBC, ESR, MCV, MCHC, neutrophil, eosinophil, basophil, monocytes were observed in LA treated group. The reduction in Hb, RBC, and PCV are probably due to the production of reactive oxygen species (ROS) under the influence of heavy metal which destroys the red blood cell membrane and its functions (Tariq, 2007). The elevation of WBC, MCV, and MCHC might be due to the elevated inflammatory

reaction as a result of lead toxicity. These results are in agreement with the findings of Bersenyi et al. (2003) and Simsek et al. (2009).

Whereas, pre and post-treatment with EPPF reversed the levels of blood parameters as compared with those of the control group. The higher doses (600 mg/kg) exhibited more effect compared to lower doses, these effects might be because of possessing phenolic compounds such as flavonoids and tannins which possess strong antioxidant activity and may assist to protect the cells against the oxidative damage caused by free-radicals (Sathyadevi & Subramani, 2015). Phenolic compounds have been proved as metal chelators, radical scavengers, reducing agents, singlet oxygen quenchers, and hydrogen donors (Wong & Kitts, 2006). As such, these particular secondary metabolites in the *P. peruviana* fruits might have been chelating the lead in the blood and other tissues as well as mopped-up lead-induced free radicals in the blood which will eventually free hematopoietic tissues of oxidative stress. From the present observations, it is revealed that the tested ethanolic fruit extract of *P. peruviana* was devoid of the toxic effect of lead acetate. Thus results of the present study can be concluded that the EPPF showed protective efficacy of lead acetate-induced haemotoxicity in rats.

Serum levels of liver enzymes such as cholesterol, LDL, HDL, VLDL, SGOT, SGBT, ALP, GGT, bilirubin, urea, creatinine, total protein, and globulin are important markers of liver function. In this study, elevated levels of cholesterol, LDL, and VLDL were found in the rats treated with LA which was significantly higher than that of control rats. It might be attributed that lead-induced activation of 3-hydroxy-3- methylglutaryl coenzyme A reductase and HMG CoA synthase (the two rate-limiting enzymes in cholesterol synthesis) or it may be due to feedback inhibition (Sawada et al., 2005). In contrast, marked depletion of HDL was observed in lead acetate intoxicated rats. A liver disorder resulting from exposure to lead acetate has been suggested to decrease the HDL-C content, cause dyslipidemia and disturb the biological functions of HDL-C (Samarghandian et al., 2015). Oral administration of fruit extract significantly prevented the severity of liver damage and thereby marked depletion of cholesterol, LDL, and VLDL and improvement in the level of HDL. These values were closer to the control group animal. Also, a similar result was observed in the standard drug-treated group. Similar observations were reported by previous studies (Jesuorsemwen et al., 2016; Al-Attar, 2020; Abdelhamid et al., 2020).

The present study revealed a significant increase in SGPT, SGOT, ALP, and GGT levels in serum at lead acetate treated group than control rats. Liver enzymes such as SGPT, SGOT, ALP, and GGT are marker enzymes for liver function and integrity (Adaramoye et al., 2008). Liver injury following lead exposure is well characterized by elevated levels of plasma hepatic marker enzymes which indicate cellular leakage and loss of functional integrity of hepatic membrane architecture (Al-Attar, 2011; Attia et al., 2013). Oral administration of *P. peruviana* fruit extracts against lead acetate, SGOT, SGPT, ALP, and GGT in serum were improved as compared to the lead acetate treated group. Similar results were reported by Subash et al. (2011), Adewale et al. (2015), and Yogananth et al. (2015).

The elevation in the levels of urea, creatinine, and bilirubin has been reported in LA treated animals when compared to control rats due to lead acetate toxicity caused hepatocyte degeneration and blockage of bile ducts. The treatment of fruit extract in lead acetate intoxicated rats reversed the levels of urea, creatinine, and bilirubin and these parameters were nearer to the control group. The study report was correlated with the previous other studies which have been already reported similar results (Saraswat et al., 1993; Murugavel & Pari, 2007; Manna et al., 2008).

In the current study, the rats treated with LA were shown a significant decrease in the levels of serum total proteins and albumin when compared to the control group. There was no significant difference in the level of globulins. This might be due to either poor liver function or liver damage by lead acetate, which is associated with loss of structural integrity of cells (Goswami & Bhattacharya, 2000). The significant restoration of these trace elements level was found in rats treated with EPPF, but the highest hepatoprotective activity was found in a higher dose of 600 mg/kg as compared to standard drugs. Similarly, Badr & Naeem (2019) reported that the total protein, albumin, and globulin reduction by aflatoxin have been improved by *P. peruviana* presence in diets. The study correlated the hepatoprotective activity of *P. peruviana* fruit extract has shown better hepatoprotective activity and it may be due to the presence of alkaloids, phenols, and tannins which exhibited free radical-scavenging and antioxidant activities (Chang et al., 2008; Toro et al., 2013; Hassan et al., 2017).

Conclusion

From the present studies, it can be concluded that treatment with EPPF has therapeutic value in the management of adverse effects associated with lead exposure, especially on the liver in albino rats, based on the results of this study. The efficacy of the fruit extract of *P. peruviana* would have a wide scope in the future. Hence, this will open a new model for the production of alternative therapeutic medicine for the treatment of the liver injury.

Acknowledgement

Conflict of Interests

The authors declare that they have no conflict of interest.

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