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Protective Effect of Jamun (*Syzygium cumini*) Seed and Orange (*Citrus sinensis*) Peel Extracts Against Lead-Induced Alteration in Liver Biomarkers of Rats

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Abstract: The ameliorative effects of jamun seed extract (JSE) and orange peel extract (OPE) on lead induced alteration in liver biochemical parameters were investigated. One hundred twenty Wistar rats were divided into six groups (A-F). Group A (control): No treatment was given, Group B: lead nitrate (50 mg/kg b wt.) was given, Groups C: rats were given 50 mg/kg b wt. lead nitrate and 200 mg/kg b wt. Jamun seed extract, Group D rats were given 50 mg/kg b wt. lead nitrate and 200 mg/kg b wt. orange peel extract, Groups E: 200 mg/kg b wt. orange peel extract, and Group F rats were given a dose of 200 mg/kg b wt. jamun seed extract. The treatments were conducted for 14 days. On 7th and 14th day, blood samples were collected from each group and liver biochemical parameters were analyzed. In lead nitrate-treated rats liver biomarkers levels (serum alkaline phosphatase, serum SGOT, serum SGPT, serum bilirubin and serum lactate dehydrogenase) were increased at 7 day and 14 day whereas serum albumin levels decreased on 7 day to 14 day as compared to control. JSE and OPE exerts hepatoprotective effects against lead induced alternation in liver biomarkers as the changes in serum alkaline phosphatase, serum SGOT, serum SGPT, serum albumin, serum bilirubin and serum lactate dehydrogenase were recovered to near control values.

Keywords: Lead, Heavy metals, Liver biomarkers, Jamun seed extract, Orange peel extract, Ameliorative

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Introduction

Lead (Pb) is a highly toxic heavy metal and cause important environmental and occupational health problems in mammals (Firoozichahak *et al.,* 2022; Yadav *et al.,* 2023a). It occurs in ecosystem naturally as well as by the anthropogenic activities. The main resources of lead are lead-

based painting, leaded fuel, industrial techniques that include smelting of lead and its combustion, batteries, boat construction, lead-containing pipes, battery recycling, grids, arm industry, pigments, and the printing of books (Yadav *et al.,* 2023a). It is added to the environment through the soil, water, air and food chain (Fihria *et al.,* 2016). Pb mostly enters in animals through the alimentary and respiratory tracts and accumulated in tissues. It causes renal, neurological, embryonic, immunological, respiratory, cardiovascular, skeletal, haematological, reproductive and hepatic disorders (Melebary and Elnaggar, 2023).

Jamun (*Syzygium cumini,* family Myrtaceae) commonly known as black plum and Indian blackberry (Srivastava *et al.,* 2021a; Qamar *et al.,* 2022, Yadav *et al.,* 2023b). Jamun bark seed and fruit pulp contains – polyphenols, flavonoids, phenolic, anthocyanins, gallic acid, ellagic acid, alkaloids, ellagic acid, glycoside, isoquercetin, kaempferol, myricetin, tannins, flavonols and flavone (Rizvi *et al.,* 2022). It is used as anti-bacterial, antioxidant, anti-inflammatory, anti-microbial for the treatment of alternations such as hepatoxicity, diabetes mellitus and nephrotoxicity (Swami *et al.,* 2012; Abbas *et al.,* 2016; Kumar and Thakur, 2018, Rizvi *et al.,* 2022, Shankar *et al.,* 2023).

Orange (*Citrus sinensis*, family Rutaceae) contains various antioxidants such as hesperidin, rutin, cellulose, flavanone, glycosides, neohesperidin, naringin, hemi-cellulose, chlorophyll pigments, and other small molecules like limonene, pectin (Srivastva *et al.,* 2021b, Yadav *et al.,* 2023b). Orange peel extract restore the levels of liver parameters such as serum uric acid, serum urea, and serum creatinine (Alfarajat *et al.,* 2023). Orange peel extract contains specific antioxidant which protect against hepatotoxicity (Srivastva *et al.,* 2021b).

To the best of our knowledge there exists no study regarding the protective effect of JSE and OPE on the lead induced alteration in the liver biomarkers such as serum alkaline phosphatase, serum SGOT, serum SGPT, serum albumin, serum bilirubin and serum lactate dehydrogenase of rats. Hence, the aim of this present study was to evaluate the protective effects of Jamun (*Syzygium cumini*) seed extract and orange (*Citrus sinensis*) peel extract on lead induced changes in liver biomarkers of rats.

Materials and Methods

One hundred twenty Wistar rats (50-60 g b wt.) were procured from Asia Scientific Emporium, Varanasi, India and acclimatized for 14 days under laboratory conditions (27- 30°C with a 12 h dark/light cycle) in polypropylene cages. Standard diet and water were provided *ad libitum* to rats. The doses of lead, JSE and OPE given to the rats were based on the reports of the earlier investigators--- Lead (60 mg/kg b wt. – Offor *et al.,* 2017; 50 mg/kg b wt. – Eruotor *et al.,* 2023; 50 mg/kg b wt. – Sooud *et al.,* 2022; 50 mg/kg b wt. – Fatoki *et al.,* 2022); jamun peel extract (200 mg/kg b wt. – Srivastava *et al.,* 2021; 400 mg/kg b wt. – Kumar *et al.,* 2019; 400 mg/kg b wt. -- Sarma, 2014; 250 mg/kg wt. – Sharma *et al.,* 2013; 600 mg/kg b wt.- Sankar *et al.,* 2023); orange peel extract (200 mg/kg b wt. – Mohamed *et al.,* 2014; Srivastava *et al.,* 2021a; Yadav *et al.,* 2023b; 250 and 500 mg/kg b wt.—Ekhatar *et al.,* 2022).

Purified lead nitrate [Pb (NO_3)] was purchased from Qualigens Fine Chemicals, Mumbai, India and dissolved in distilled water to obtain the desired dose. Orange (*Citrus sinensis*) peel and jamun (*Syzygium cumini*) seed extracts were prepared according to Srivastava *et al.,* (2021a, 2021b, Yadav *et al.,* 2023b). The present study was approved by the Research Degree Committee (RC/FSc/ZOO/2019-2020/07/22), D.D.U. Gorakhpur University, Gorakhpur.

Experimental design:

The acclimatized rats were randomly divided into six numerically equal (n = 20) groups (A-F), and treated as -- Group A (control): No treatment was given, Group B: lead nitrate 50 mg/kg b wt. was given, Groups C: 50 mg/kg b wt. lead nitrate and 200 mg/kg b wt. Jamun seed extract was given, Group D rats were given 50 mg/kg b wt. lead

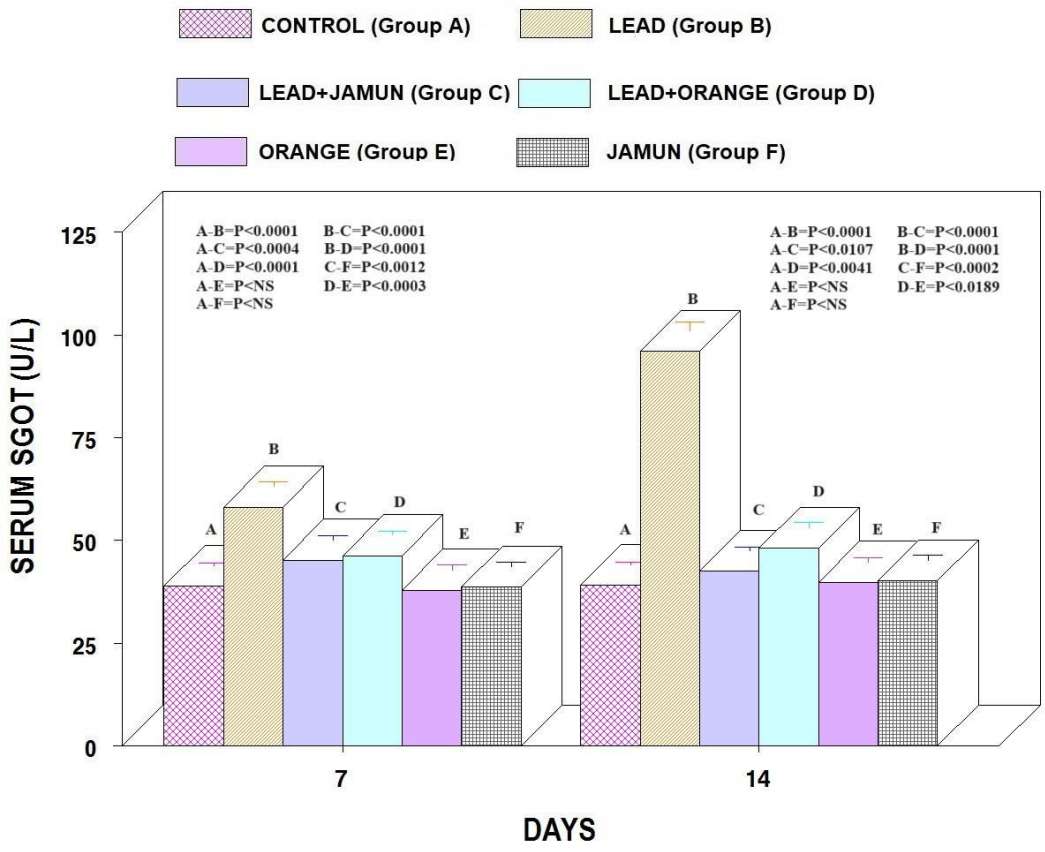

Fig. 1: Serum SGOT levels (U/L) of Wistar rat treated either with lead, lead+jamun seed extract, lead+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

nitrate and 200 mg/kg b wt. orange peel extract, Groups E: 200 mg/kg b wt. orange peel extract was given, and Group F rats were given a dose of 200 mg/kg b wt. Jamun seed extract.

10 rats from each group were fasted overnight and killed under light ether anaesthesia on 7th day and 14th day. Sera were separated after collection of blood by centrifugation at 3000 rpm for 5 min. and stored at -20°C. Analysis of serum alkaline phosphatase, serum SGOT, serum SGPT, serum albumin, serum bilirubin and serum lactate dehydrogenase were performed by using analytical kits (Beacon Diagnostics Private Ltd, India). Each sample was analyzed in duplicate.

Statistical analysis:

Values are expressed as mean ± SE. Multiple group comparisons were performed by using ANOVA (One way Analysis of Variance). Student's t test and Bonferroni post hoc test was used for group comparisons. The significant levels were set at $P < 0.05$.

Results

Serum SGOT:

Normal value of serum SGOT levels ranged between 38.86±0.76 to 39.1±0.62 (U/L). Serum SGOT levels of group B (lead treated rats) showed a progressive increase (as compared to control) from day 7($P<0.0001$) to day 14 ($P<0.0001$) (Fig. 1). Serum SGOT levels of group C rats (Pb+ JSE treated) exhibited an increase on day 7 ($P<0.0004$) and on day 14 ($P<0.0107$) as compared to group A (control) whereas there was noticed a decrease on day 7 ($P<0.0001$) and day 14 ($P<0.0001$) as compared with group B rats. The

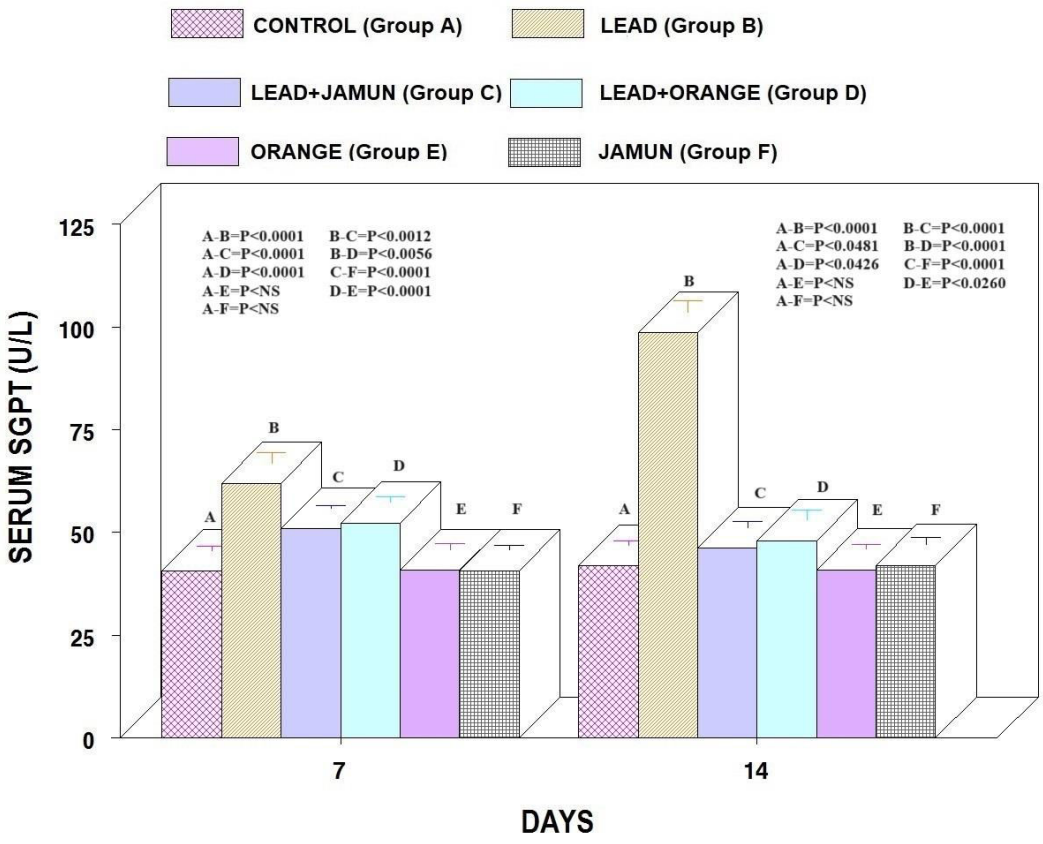

Fig. 2: Serum SGPT levels (U/L) of Wistar rat treated either with lead, lead+jamun seed extract, lead+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

SGOT levels of group D (Pb+ OPE treated) rats exhibited an increase on day 7 (P<0.0001) and on day 14 (P<0.0041) as compared to control (group A) whereas a decrease was noticed on day 7 (P<0.0001) and day 14 (P<0.0001) as compared to group B rats. Serum SGOT levels of group E (OPE) and group F (JSE) treated rats showed no change as compared to group A (control) rats (Fig. 1). Analysis of variance (ANOVA) indicated that the treatments were significant (7 day-- F=55.403, P< 0.0001; 14 days-- F=301.70, P< 0.0001).

Serum SGPT:

The SGPT value of control rats ranged between 40.66±1.05 to 41.86±1.12 (U/L). Rats treated with Pb (group B) showed a progressive increase from 7 day (P<0.0001) to 14 day (P<0.0001) as compared to control rats (Fig. 2). In group C (Pb+ JSE treated rats) the serum SGPT levels showed an increase on day 7 (P<0.0001) and day 14 (P<0.0481) as compared to control (group A). However, the values exhibited a decrease on day 7 (P<0.0012) and day 14 (P<0.0001) as compared to group B (lead treated rats). In lead and orange peel extract treated rats (group D), the SGPT levels showed an increase on day 7 and day 14 as compared to group A (control). The levels in this group depicted a decrease on day 7 and day 14 as compared to group B (lead treated rats). The value of serum SGPT of group E (OPE) and group F (JSE) rats remained unchanged as compared to the group A (control) rats (Fig. 2). Analysis of variance (ANOVA) indicated that the treatments were significant (7 day-- F=37.623, P< 0.0001; 14 days-- F=137.62, P< 0.0001).

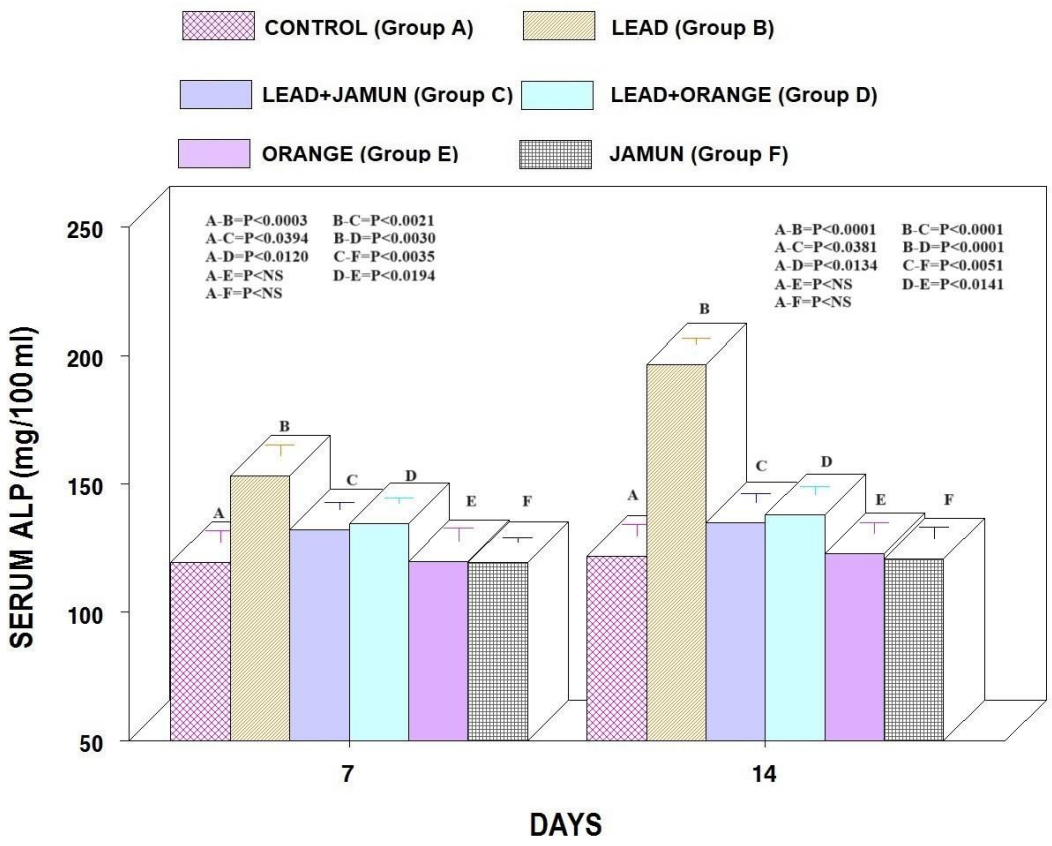

Fig. 3: Serum ALP levels (mg/100 ml) of Wistar rat treated either with lead, lead+jamun seed extract, lead+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

Serum ALP:

Serum ALP value of control rats ranged between 119.48±4.48 to 121.86±4.38 mg/100 ml. Lead treated rats (group B) showed a significant rise in ALP value on day 7 (P<0.0003) and day 14 (P<0.0001) as compared to control rats (Fig. 3). Serum ALP value of group C (Pb+JSE) rats exhibited a decline on day 7 (P<0.0021) and day 14 (P<0.0001) as compared with group B. Group D (Pb+OPE) rats exhibited a decline on day 7 (P<0.0030) and day 14 (P<0.0001) as compared with group B. There was no marked change noticed in group E (OPE) and group F (JSE) rats as compared to the value of control rats (Fig. 3). Analysis of variance (ANOVA) indicated that the treatments were significant (7 day-- F=13.656, P< 0.0001; 14 days-- F=76.483, P< 0.0001).

Serum bilirubin:

Serum bilirubin levels of control rats ranged between 0.596±0.02 to 0.609±0.09 mg/100 ml. Rats treated with lead (group B) showed significant increase in serum bilirubin levels on day 7 (P<0.0001) and day 14 (P<0.0001) as compared to group A (Fig. 4). The serum bilirubin levels of group C rats depicted an increase on day 7 (P<0.0017) and day 14 (P<0.0427) as compared to the control (group A). In group C (Pb+ JSE) rats serum bilirubin levels decreased on day 7 (P<0.0001) and 14 (P<0.0001) as compared with group B. In group D (Pb+ OPE) treated rats serum bilirubin levels decreased on day 7 (P<0.0003) and 14 (P<0.0001) as compared with group B. Bilirubin levels of group D rats exhibited an increase on day 7 and day 14 as compared to control (group A). The serum bilirubin values of

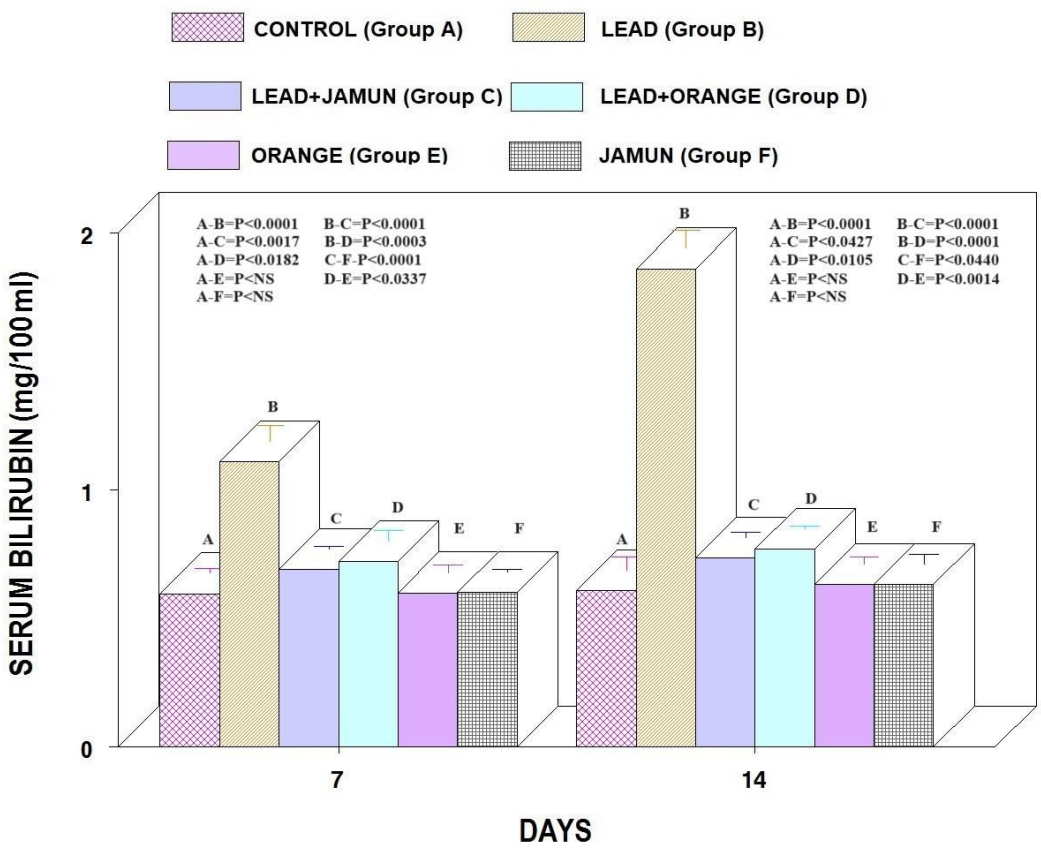

Fig. 4: Serum bilirubin levels (mg/100 ml) of Wistar rat treated either with lead, lead+jamun seed extract, lead+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

group E (OPE) and group F (JSE) rats have not shown any change with regards to values of control rats (Fig. 4). Analysis of variance (ANOVA) indicated that the treatments were significant (7 day-- F=35.445, P< 0.0001; 14 days-- F=137.67, P< 0.0001).

Serum Albumin:

Serum albumin levels of control rats ranged between 3.86±0.02 to 3.91±0.03 mg/100 ml. The serum albumin levels of group B (day 7 – P = <0.0001; day 14 – P = <0.0001), group C (day 7 – P =<0.0001; day 14 - P = <0.0001) and group D (day 7 - P = <0.0001; day 14 – P = <0.0010) rats exhibited a decline as compared to control rats (Fig. 5). In group C serum albumin levels showed an increase on day 7 (P = <0.0017) and day 14 (P = <0.0001) as compared to group B. There was no significant change in group D on day 7 as compared to group B however, the values were significant on day 14 (P<0.0001) with regards to values of group B. The serum albumin levels of group E (OPE) and group F (JSE) rats was almost same as in control rats (group A) (Fig. 5). Analysis of variance (ANOVA) indicated that the treatments were significant (7 day-- F=43.688, P< 0.0001; 14 days-- F=181.54, P< 0.0001).

Serum LDH:

Serum LDH levels of control rats (group A) ranged between 192.11±4.21 to 194.95±4.5 U/L. The serum LDH levels showed an increase in group B (7 day - P< 0.0001; 14 day - P< 0.0001), group C (7 days - P< 0.0009; 14 days - P< 0.0205) and group D (7 day - P< 0.0003; 14 day - P< 0.0022) as compared to group A (control) (Fig. 6). The values in group C exhibited a decrease on day 7 (P<0.0005) and day 14 (P<0.0001) as compared to group B (lead treated rats). There was a decrease in LDH value of group D rats (7 day - P< 0.001; 14

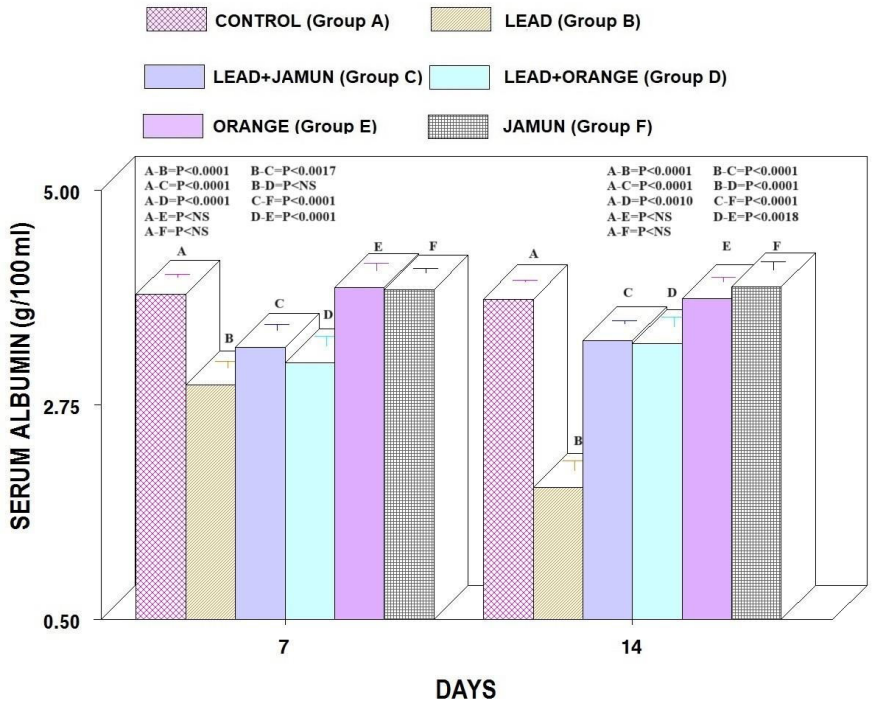

Fig. 5: Serum albumin levels (g/100 ml) of Wistar rat treated either with lead, lead+jamun seed extract, lead+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

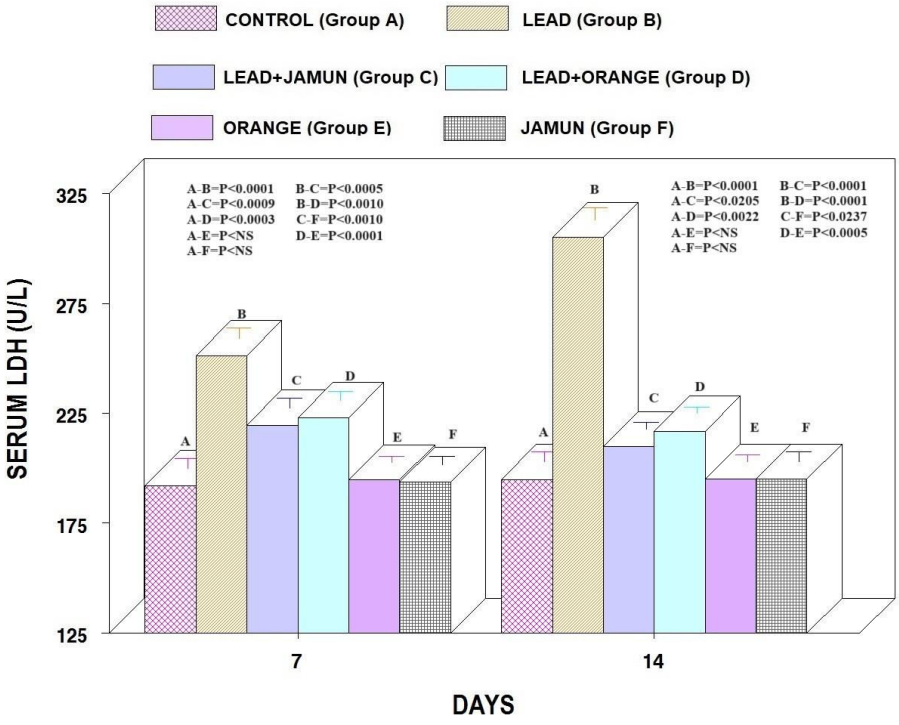

Fig.6: Serum LDH levels (U/L) of Wistar rat treated either with lead, lead+jamun seed extract, lead+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

day - P< 0.0001) as compared to group B rats. The LDH levels of group E (OPE) and group F (JSE) rats remained unaltered as compared to control rats (Fig. 6). Analysis of variance (ANOVA) indicated that the treatments were significant (7 day-- F=34.894, P< 0.0001; 14 days-- F=112.11, P< 0.0001).

Discussion

Lead is highly toxic heavy metal present in environment and accumulates in liver tissues and caused alternation in morphological, physiological and biochemical functions of rats (Asgharian *et al.,* 2022, Yadav *et al.,* 2023a). In the present study, JSE and OPE showed hepatoprotective effects against lead induced alteration in hepatic biomarkers such as serum albumin, serum SGOT, serum SGPT, serum bilirubin, serum alkaline phosphatase and serum lactate dehydrogenase levels in rat. Administration of lead (Pb) significantly increased serum alkaline phosphatase, serum SGOT, serum SGPT, serum bilirubin and serum lactate dehydrogenase levels and decreased serum albumin levels in rats.

In the present study, serum SGOT levels significantly increased in Pb treated rats. This is in conformity with reports of other investigators who have also noticed increased serum SGOT level in rats after exposure to toxicants/drugs--- Carbon tetrachloride (Bhutale and Jat., 2023); Monosodium glutamate (AlThobaiti, 2023); Arsenic (Shankar *et al.,* 2023) and Paraquat (Okolonkwo *et al.,* 2023). In the present study rat treated with lead and jamun seed extract (group C) or orange peel extract (group D) exhibited decreased serum SGOT levels at 7 day and 14 day when compared to lead exposed rats. Shankar *et al.,* (2023) have also reported similar results when the rats were treated with *Syzygium cumini* seed extract in combination with Arsenic. Abbas *et al.* (2016) have also noticed decreased SGOT levels in mice after treatment with jamun pulp extract against chromium induced hepatotoxicity. It can be inferred that both JSE and OPE possess hepatoprotective potential against lead toxicity in rat.

The serum SGPT levels increased in lead exposed rats. This derives support from the studies of other workers who have also recorded increased SGPT levels in rat after treatment with various toxicants/drugs ---- Carbon tetrachloride (Bhutale and Jat., 2023); Arsenic (Shankar *et al.,* 2023); Paraquat (Okolonkwo *et al.,* 2023); Paracetamol (Senthilkumar *et al.,* 2014) and Rifampicin (Pelapelapon *et al.,* 2023). In the present study when combined dose of lead and JSE (group C) or OPE (group D) was given to rat, serum SGPT level significantly decreased as compared to lead treated rats. Shankar *et al.,* (2023) have also reported similar results when the rats were treated with *Syzygium cumini* seed extract in combination with Arsenic. Abbas *et al.* (2016) have also noticed decreased SGPT levels in mice after treatment with jamun pulp extract against chromium induced hepatotoxicity. The foregoing study clearly indicates that JSE and OPE showed hepatoprotective activity against lead induce alteration in SGPT of rats.

In this study, increased serum bilirubin levels were recorded in Pb treated rats (group B) from day 7 to day 14. In past, few workers have also reported increased serum bilirubin levels in rats after exposure to several toxicants/drugs --- Arsenic (Shankar *et al.,* 2023); Paracetamol (Senthilkumar *et al.,* 2014); Cadmium (Noor *et al.,* 2022); Carbon tetrachloride (Bhutale and Jat, 2023) and Acetaminophen (Kadiyala *et al*., 2023). In rats treated with lead and jamun seed extract (group C) or orange peel extract (group D) there was a decrease in serum bilirubin levels from 7 day to 14 day as compared to group B. Similar findings have also been reported by Shankar *et al.,* (2023) have also reported in rats treated with *Syzygium cumini* seed extract in combination with Arsenic. The observations of Abbas *et al.* (2016) lend support to the present study as they have also noticed decreased bilirubin levels in mice after treatment with jamun pulp extract against chromium induced hepatotoxicity. In the present study the recovery of serum bilirubin levels towards control values clearly indicates that jamun seed extract and orange peel extract

possess hepatoprotective effect against lead induced hepatotoxicity in rats.

Serum albumin levels significantly decreased after treatment of lead to rats (group B) at 7 day and 14 day. The present observation derives support from the earlier studies by other investigators who have also recorded similar results after treatment with toxicants--- Cadmium (Noor *et al.,* 2022); Arsenic (Shankar *et al.,* 2023) and Acetaminophen (Kadiyala *et al.,* 2023). The combined treatment of lead and JSE (group C) or OPE (group D) to rats caused increased serum albumin levels as compared to rats treated with lead only. It indicates restoration of serum albumin level near to control levels which suggests hepatoprotective role of JSE and OPE extract. Shankar *et al.* (2023) obtained similar results when the rats were treated with *Syzygium cumini* seed extract in combination with Arsenic. Abbas *et al.* (2016) have also noticed increased albumin levels in mice after treatment with jamun pulp extract against chromium induced hepatotoxicity

In present study, serum ALP levels of rats were increased after treatment with Pb at 7 day and 14 day. Similar observations have also been noticed by other investigators after treatment with various toxicants in rats-- Cadmium (Noor *et al.,* 2022); Acetaminophen (Kadiyala *et al.,* 2023); Arsenic (Shankar *et al.,* 2023) and Paraquat (Okolonkwo *et al.,* 2023). When lead was given in combination with JSE and OPE, the serum ALP levels progressively decreased from 7 day to 14 day (as compared with group B). It revealed hepatoprotective activity of JSE and OPE. The present study is in conformity with the observations of Shankar *et al.* (2023) who have also noticed similar findings when the rats were treated with *Syzygium cumini* seed extract in combination with Arsenic. Decreased ALP levels in mice has also been recorded by Abbas *et al.* (2016) after treatment with jamun pulp extract against chromium induced hepatotoxicity.

In this study, significant increase in serum LDH levels was noticed after treatment with lead in rats (group B) at 7 day and 14 day as compared to control. In past, increase in serum LDH levels have been reported after treatment with various toxicants--- Acetaminophen (Kadiyala *et al.,* 2023) and Methyl Parathion (Dere *et al.,* 2021). Serum LDH levels were progressively decreased after treatment with combined dose of lead and JSE or OPE from day 7 to day 14 as compared to group B. It is indicative that JSE and OPE exhibited hepatoprotective action against lead induced alteration in serum LDH levels of rats.

In the present study no alternation was recorded in serum alkaline phosphatase, serum SGOT, serum SGPT, serum albumin, serum bilirubin and serum lactate dehydrogenase levels in rat after treatment with JSE and OPE alone. There exists no study regarding the preventive action of JSE and OPE on lead induced toxicity in liver biomarkers of rats.

Conclusion

Lead treatment to rats caused increased serum alkaline phosphatase, serum SGOT, serum SGPT, serum bilirubin and serum lactate dehydrogenase and decreased serum albumin. The alterations induced by lead was restored by treatment with JSE and OPE. This indicates that JSE and OPE possess some phytochemicals which act against lead induced hepatotoxicity.

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