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Original Article

Reno-hepatic protective effects of Jambul against chromium induced anomalies in mice

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Abstract
The adequate amounts of chromium (Cr) enhance the endocrine system and metabolism but its ridiculous use and bio-accumulation through food chain might be causing oxidative stress. That study was conducted to evaluate the protective effects of Jambul (*Syzygium cumini*) against Cr induced reno-hepatic anomalies. Male albino mice (*Mus musculus*) were equally divided (n=10) as C; control, Cr-treatedandCr-JgroupsreceivingCr^{+6} in the form of potassium dichromate ($K_2Cr_2O_7$) 50ppm for 10days *ad-libitum* while Cr-J group additionally given 0.25ml/12h Jambul Fruit Extract (JFE) for next 5days by oral gavage. On the 16th day blood, liver and kidney were collected for biochemical and histopathological analysis.Cr^{+6} treated group showed severe histological changes like necrosis, cirrhosis and dehydration in liver evident by significant elevation of Serum Glutamic Pyruvic Transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase (SGOT), Alkaline Phosphatase (ALP), total protein, bilirubin, globulin, creatine and uric acid along with reduction of SGOT/SGPT, Blood Urea Nitrogen (BUN), urea and albumin as compared to control. Treatments with JFE after Cr^{+6} exposures significantly improved the hepatic and renal functional profiles possibly by partial liver rehabilitation and regeneration. The JFE significantly recovered the histopathological alterations in reno-hepatic tissue by free radicals scavenging and metal chelating abilities due to presence of anthocyanin, flavonoids and β-sitosterol. The JFE'sprotective effects against heavy metals environmental toxicants especially Cr^{+6} is novel and cheapest; that should be sponsored for ethno-medicinal purpose.
Keyword: Cirrhosis, necrosis, oxidative stress, lipid peroxidation, flavonoids, anthocyanin, β-sitosterol, *Syzygium cumini*

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INTRODUCTION

Chromium (Cr) is considered an essential micronutrient to facilitate the insulin activation, stimulate muscular development and reduction of cholesterol (Chen *et al.,* 2010). Potassium dichromate ($K_2Cr_2O_7$) is also being used as colorant of traditional oriental sweets in Pakistan. Pollution is a universal problem and the common people are exposed to Cr intake, via environmental contaminants. The human activities like industrialization also contaminate the underground water which is frequently used for irrigation. It is well documented that heavy metals, pesticides and industrial effluents commonly enhance the oxidative stress (Zhou *et al.,* 2003). There are handsome indications that such types of supplements and industrial effluents are causative agents of numerous human diseases and have been proved toxic, in *vivo* studies of experimental animals (Park *et al.,* 2004).

`Heavy metals induce histological changes in liver, while the plants extracts have ameliorative ability against free radicals (Batool *et al.,* 2010). Heavy metals affect immune system and other body organs such as testes, kidneys and liver but abnormalities can be rectified by chelation of noxious agents from the body (Jayabarath *et al.,* 2009).The hexavalent chromium (Cr^{+6}) enhance the cell shrinkage; distort the cytoskeleton and causes necrosis

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(Rudolf and Cervinka, 2006) especially $K_2Cr_2O_7$which damage hepatic mitochondria and cause microsomal lipid peroxidation (Travacio *et al.,* 2000). Cr^{+6} induce tubular necrosis and renal failure by damaging brush border membrane also causes microscopic lesions in kidney glomeruli (Mendoza *et al*., 2006).

Reactive oxygen species denature the enzymes; essential for metabolism of free fatty acids, glycolipids and cholesterol to generate deformities in the mitochondrial membranes and injuries to hepatocytes (Smith *et al.,* 2000; Ercal *et al.,* 2001; Evans *et al.,* 2002). Oxidative stress of Cr is followed by a series of cellular events including increased synthesis of superoxide anion and hydroxyl radicals which may cause cardiovascular diseases and hyperglycemia (Dlaskova *et al.,* 2008). Lipid peroxidation is the indicator of free radicals formation alterations of electron transport chain in aerobic respiration and oxido-reductase enzymes (Laura *et al.,* 2012). Hepatocyte metabolizes, detoxify and inactivate the ROS, metals, drugs, insecticides and steroids with the help of antioxidant enzymes (Keren *et al.,* 2013).

Antioxidants synthesized in the body or obtained in the diet, have ability to remove noxious materials through their scavenging ability and inhibiting the oxidation of molecules to prevent body from oxidative stress before damaging and catalyzing the production of free radicals in the cell (Miller *et al.,* 2008).The β-sitosterol has reducing power, superoxide scavenging ability, nitric oxide-scavenging capacity and ferrous ion chelating potency (Rout and Banerjee, 2007) similarly the anthocyanin can combat with free radicals and prevent from lipogenesis (Ozsahin *et al.,* 2012).

Syzigium cumini belongs to family Myrtaceae and commonly known as black plum or Jamun or Jambul/Jamul. Bhatia and Bhajaj, (1975) had reported different chemical constituents in the seed and bark of *Syzigiumcumini*.Itsripen fruits are used to make different products like squashes, juices and medicines (Baliga, 2011). Their fruit extracts protect the cultured human peripheral blood lymphocytes from DNA damage (Jagetia and Baliga, 2003). They have antimicrobial activity inhibits the growth and induces apoptosis in cervical cancer cell (Goyal*et al.,* 2010). The flavonoid of *Syzygium cumini* can repair hepatocyte from iron damages hydrogen peroxide injuries and gamma-irradiations (Jagetia *et al.,* 2008). Pharmacologically *Syzygium cumini* bark and fruit pulp are rich source of antioxidant components (Ruan *et al.,* 2008); have hypoglycemic (De Bona *et al*., 2010), anti-inflammatory, anti-ulceric qualities (Chaturvedi *et al.,* 2009), anti-spasmodic, chemopreventive potential (Parmar *et al.,* 2010) and lipid profile normalizing aptitude (Hossain *et al*., 2011)**.** *Syzygium cumini* have antagonistic behavior against methylmercury induced systemic toxicity (Abdalla *et al.,* 2011) and is considered as medicinal plant against anamolies of oxidative stress in animals and human beings (Ayyanar and Subash-Babu, 2012).

The enzymatic changes and gene expression processes are almost same in humans and rodents (Zhang *et al*., 2013) so the mammalian model mice was selected in *vivo* study, to suggest the ameliorative recommendation from common local available economical fruit extract, which behave antagonistic to the injurious effects of hexavalent chromium on liver and kidney. This study gave the cheapest shielding effects of common available fruits of Pakistan against reno-hepatic anomalies.

MATERIALS AND METHODS

Thirty healthy 3-4months male mice *Mus musculus* (30±3g) obtained from University of Sargodha Animal House for this study and placed in separate cages 15″x 12″x 12″ made of steel bars covered with fine gauze provided paper cuttings for bedding. They were housed under controlled conditions with a 12 h light/dark cycle at 25 ± 5˚C with 45% humidity. They had free access to standard pellet diet and water *ad-libitum*. This study is in accordance with the Guidance of Ethical Committee for Research on Laboratory Animals of Sargodha University Sargodha, Pakistan.

***Preparation of Solution and Fruit Extracts*:**

Standard solution (1000 ppm) was prepared by dissolving 2.8g of $K_2Cr_2O_7$ in $1000cm^3$ (ml) of water and diluted to get 50 ppm. Ripe black fruit of *Syzygium cumini* were purchased from the local market and fully ripe berries were carefully selected, washed, air dried and the pulp was separated by means of vigorous shaking in a tightly closed sterilized wide mouth glass jar. 100 g of the pulp was blended in an electric juicer in 100 ml distilled water for 5 minutes and resulting juicy material was centrifuged at 500rpm for 5 minutes. The supernatant was immediately placed in sterilized

5ml capacity ice-cube dishes then placed in sterilized plastic bags at -30 ˚C following the standard protocol (Ahmad *et al.,* 2012).

Experimental Animal Grouping

Animals were randomly divided into 3 groups (n=10) as: Control group (C); provided distilled water throughout the study (15 days), Cr-group (Cr); 50 ppm Cr-solution (10 days) *ad-libitum* followed by withdrawal for next 5 days, Cr + Jambul group (Cr-J); as Cr-group but last 5days they were additionally given 0.25ml/12h Jambul Fruit Extract (JFE) regularly through oral gavage.

Organ Recoveries

The animals were euthanized by cervical dislocation and organs (liver and kidney) were recovered on the 16th day from each animal, fixed for 7 days to proceed further for HE histological preparations and ventricular blood was used for liver profile, liver enzymatic test and renal profile from standard laboratory of Sargodha University diagnostic center. Sections were carefully observed and photographed on trinocular research microscope (Labomed CXR_2) attached to a 7.2mega pixel digital camera (Sony DSC-W35). These photographs were digitally marked to highlight the histopatholgical abnormalities**.** Results were expressed as means±SEM and the differences between groups were evaluated with One-Way ANOVA and Duncan Multiple Range Test to indicate significant ($p<0.05$) difference of experimental groups.

RESULTS

All typical signs of normal liver histological sign such as centrally placed lobular vein and hepatocytes arranged in hepatic cords radiating from the central vein (Fig. 1, A-a) properly and showing hepatic sinusoids spaces (Fig. 1, A-b) in between hepatocytes were visible in the C group. In histological sections of control group bi-nucleated (Fig. 1, A-c) hepatocytes were frequently present. Similarly the sign of normal renal histology including rounded Glomeruli (Fig. 1, D-g) mostly scattered in cortical region surrounded by various section of renal tubules properly lined with renal cells (Fig. 1, D-h, i) around narrow central caliber were seen in C group.

Table I: Amelioration of Jambul against Cr induced anomalies in mice liver profile.

Parameters	Groups		
	C	**Cr**	**Cr- J**
SGPT(µL /L) ***	†45.09±4.34^{c}	79.07±4.72^{a}	50.02±3.17^{b}
SGOT(µL /L)***	118.05±11.41^{c}	186.03±10.23^{a}	156.5±5.48^{b}
SGOT/ SGPT *	2.86±0.46^{b}	2.45±0.23^{c}	3.35±0.18^{a}
ALP (mg/dl) ***	240.07±7.38^{b}	306.06±3.88^{a}	240.4±12.2^{b}

C: control. **Cr:** chromium treated, **Cr-J:** chromium+JFE. Values are mean ± SEM, SGPT (ALT)- Serum Glutamic Pyruvic Transaminase, SGOT (AST) - Serum Glutamic Oxaloacetic Transaminase, ALP - Alkaline Phosphatase,Statistical analysis (ANOVA: two factors without replication).* : p ≤ 0.05-0.01, * * * : p ≤ .0001, n=10,† group means ±SEM, $^{a\ b\ c}$: Anyone two groups not sharing a lower case letters differ significantly from each other(Duncan's Multiple Range comparison-post hoc analysis).

Histological slides of liver in Cr^{+6} exposures group indicate cells shrinkage, poor blood supply and loss of endocrine stimulations. The mark of nutritional deficiency and bile retention were obvious by the loss of normal hepatic architecture, evident by necrosis, cirrhosis and dehydration as compared to control (Fig. 1, B-d, e, f).

The fibrosis of liver probably followed hemorrhagic necrosis associated with lipogenesis. The irregular bands of fibrous tissues were formed by the obstruction of blood vessels indicating the beginning of necrosis in some animals of Cr^{+6} exposure group. The histological section in Cr^{+6} exposures group show comparatively enlarged glomeruli (Fig. 1, E-j) with globular shapes.

The renal tubular section surrounded the glomeruli show clear signs of cellular necrosis leaving empty spaces in tubular margins (Fig. 1, E-k) and somewhat expended tubular caliber. The tubular shape was also distorted from rounded to irregularly shapes in extreme cases and there were mega-karyotic

cells in the lining of renal tubules in Cr^{+6} exposures group as compared to control (Fig. 1, E-I).Recognizable signs of liver regeneration and renal tubules that include hepatoblasticmitosis and rehabilitation of hepatic cords along with regenerated cell accumulation indicated by yellow arrow were clearly visible in the JFE treated groups following Cr^{+6} exposures (Fig 1-C, F).

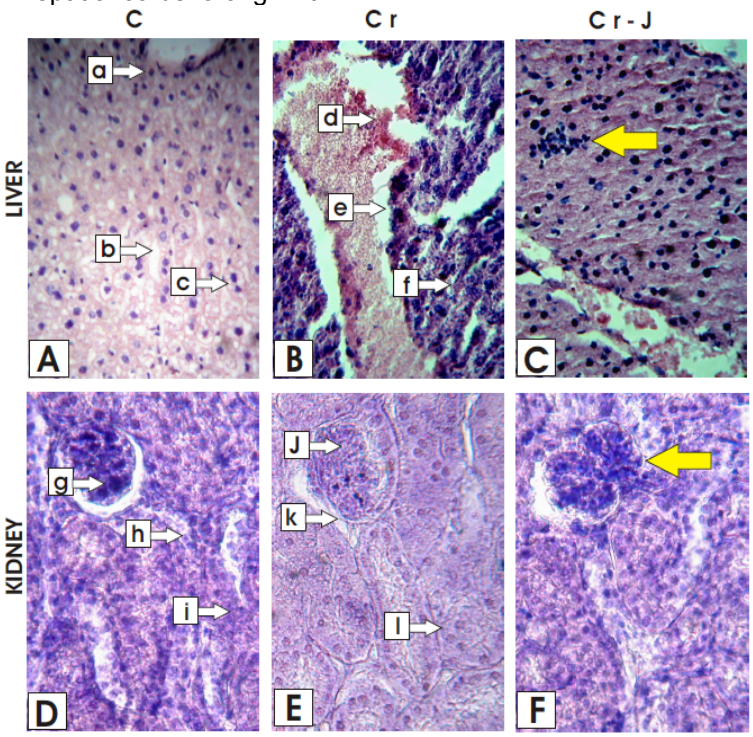

Figure 1: Histological study of Reno-hepatic Amelioration of Jambul against Cr induced Anomalies in mice at 400X.A; control liver, B; Cr treated liver, C; Jambul treated liver, D; control kidney,E; Cr treated kidney, F; Jambul treated kidney, yellow arrow indicate regeneration.a; central vein, b; sinusoids spaces, c; bi-nucleated hepatocytes, d; cirrhosis, e; necrosis, f; sign of dehydration, g; rounded Glomerulus, h; renal tubule, i; renal cells, j; enlarged Glomerulus, k; tubular necrosis, l; mega-karyotic cells

Liver Profile Variations

Highest mean SGPT levels were noted in Cr^{+6} treated (79.7 µL/L) and lowest in control group (45.9 µL/L). Although the SGPT level was higher than control however it remains lesser than the Cr^{+6}exposures group in Cr-J (50.2 µL/L). SGOT level in Cr^{+6} exposures group vs. C was noted 186.3/118.5 µL/L while the post treatment with JFE in Cr-J groups showed a normalizing effects on mean SGOT levels (156.5 µL/L). Highest mean SGOT/ SGPT ratio was recorded in Cr-J (3.35) group as compared to Cr (2.45) and control (2.86).

Highest means ALP value was noted in Cr^{+6} exposures group (306.6 mg/dl) as compared to control (240.7 mg/dl) while Cr-J have lowest value (240.4 mg/dl) summarized in Table I. Mean blood urea contents in descending order from higher to lower was Cr-J (43mg/dl) > control (31.8 mg/dl) > Cr (27.8 mg/dl) groups while mean blood urea nitrogen value was recorded in Cr-J (20.07 mg/dl) > control (14.84 mg/dl) > Cr (13.8 mg/dl) groups and mean value for creatine (0.66 mg/dl) was observed in Cr group followed by Cr-J and control groups (0.42 and 0.29 mg/dl) respectively.

Highest mean BUN/Creatine value was observed in control (56.08) group, followed by Cr-J and Cr groups (50.07 and 22.86) respectively similarly mean plasma uric acid (8mg/dl) contents in Cr group followed by control, Cr-J (5.2, 4.66 mg/dl) respectively (Table II). Highest mean plasma bilirubin level (0.84 mg/dl) was observed in Cr group followed by control, Cr-J (0.7, 0.62 mg/dl) respectively and mean plasma proteins level (6.93 g/dl) was noted in Cr group followed by Cr-J, and control groups (6.47 and 5.64 g/dl) respectively. Highest mean plasma albumin level in control (3.24 g/dl)

followed by Cr-J and Cr groups (3.12 and 3 g/dl) respectively. Highest mean plasma globulins level (2.34ng/ml) was observed in Cr-J group followed by Cr, and control groups (2.3 and 1.77 ng/ml) respectively (Table III). Statistical analysis (ANOVA) has shown highly significant variation among the groups (p≤0.001) and Duncan's multiple range test has shown significant (p≤ 0.05) difference between groups.

Table II: Protective effects of Jambul on Cr induced anomalies in renal function test.

Parameters	Groups		
	C	Cr	Cr-J
Urea (mg/dl) ***	† 31.08 ± 0.06 [b]	27.08 ± 0.66 [c]	43.00 ± 2.36 [a]
BUN (mg/dl) ***	14.84 ± 0.03 [b]	13.08 ± 0.08 [c]	20.07 ± 1.01[a]
CRT (mg/dl) ***	0.29 ± 0.03 [c]	0.66 ± 0.06 [a]	0.42±0.03 [b]
BUN/CRT ***	56.08 ± 5.09 [a]	22.86 ± 2.56 [b]	50.07 ± 4.78 [c]
UA (mg/dl) ***	5.02 ± 0.55[b]	8.00 ± 0.33 [a]	4.66 ± 0.05 [c]

C: control. **Cr:** chromium treated, **Cr-J:**Cr+JFE,n= 10, BUN; Blood Urea Nitrogen, CRT; creatine, UA; Uric Acid, Statistical analysis (ANOVA: two factors without replication), * * * : p ≤ .0001, † group means ±SEM, [a b c]: Anyone two groups not sharing a lower case letters differ significantly from each other (Duncan's Multiple Range comparison- post hoc analysis).

Table III: Ameliorative effects of Jambul extracts on Cr induced anomalies on Liver Function Test.

Parameters	Groups		
	C	Cr	Cr- J
Bilirubin (mg/dl) ***	† 0.07 ± 0.04 [c]	0.84 ± 0.02 [a]	0.62 ± 0.05 [b]
Total Protein(g/dl) *	5.64 ± 0.37 [b]	6.93 ± 0.57 [a]	6.47 ± 0.32 [a]
Albumin (g/dl) *	3.24 ± 0.01[a]	3.00 ± 0.09[c]	3.12±0.06[b]
Globulin (ng/ml) **	1.77±0.04[c]	2.3± 0.08[b]	2.34±0.13[a]

C: control. **Cr:** chromium treated, **Cr-J:**Cr+JFE,Statistical analysis (ANOVA: two factors without replication).
p ≤ 0.05-0.01, * * : p ≤ 0.001 * * * : p ≤ .0001, † group means ±SEM, [a b c] : Anyone two groups not sharing a lower case letters differ significantly from each other (Duncan's Multiple Range comparison- post hoc analysis).

DISCUSSION

Higher elevation of enzymes and cholesterol is associated with the nature of supplementation. The Cr^{+6} as food additive in dietary rice and village's sweets like Galabe of Pakistan, is highly reno-hepatic toxic. The liver plays an important role in the lipid metabolism and it is the hub of fatty acid synthesis and lipid circulation through lipoprotein synthesis. The most profound effect on the liver histology was increase in the accumulation of fat indicated by widen hepatic sinusoids spaces (Fig 1, B-E) which is the adverse effect of Cr^{+6} exposures. The elevation of SGPT, SGOT and ALP in Cr^{+6} exposures (Table I) indicate the pathophysiological changes of the liver parenchyma, hypo-functioning of the anterior pituitary, liver-biliary dysfunction, lipoprotein lipase deficiency or lipoprotein lipase cofactor deficiency corticosteroids during lipogenesis (Luís and Edmundo, 2014). The fibrosis causes distortion of the hepatic vessels and lead to an increased intra hepatic resistance. Damage hepatocytes in Cr^{+6}exposures causes impair liver function and it becomes unable to detoxify the toxicants in blood (Fig 1, B-d). The Cr^{+6} treated groups in case of liver injury; enzymes leave liver cells and mix into blood stream, to produce reno-hepatic anomalies (Fig 1-B, E). The defense against free radicals is associated with activities of SGOT and SGPT (Chaturvedi *et al.,* 2007).

The sharp increase in plasma SGPT and SGOT level, causing increase in protein catabolism in Cr^{+6}exposures groups (Table I) indicate the severe liver stress accordingly Cd

which damage the cellular junctions and disintegrate the blood barrier (Kusakabe *et al.,* 2008). In Cr^{+6} exposures groups enzymes leave the liver cells and mix up into blood stream, to produce reno-hepatic anomalies evident by elevation of SGPT, SGOT and ALP which also specify the pathophysiological changes of liver parenchyma (Table I). An increased in the circulating pool of non-esterified fatty acid causes the fatty liver diseases (Nguyen *et al.,* 2008). SGPT elevation in Cr^{+6} exposures animals indicate the hepatic-injuries like cholestasis, biliary tree obstruction, ulcerative colitis and congestive heart failure (Lieberman and Phillips, 1990). Higher creatine (CRT) after Cr^{+6} exposures (Table II) indicates dehydration similarly blood urea nitrogen (BUN) alterations are due to protein breakdown, liver failure and cirrhosis (Fig. 1-B, E).

The pancreatic insufficiency can result in lower BUN/ CRT ratios which indicate liver diseases. The Cr^{+6}may disturb the urea cycle by denaturation of urease and arginase enzymes. BUN reduction (Table II) further enhances that supposition that nitrogen decreases due to improper metabolism of protein. The low BUN value indicates central nervous system disease and posterior pituitary dysfunction, inappropriate secretion of anti-diuretic hormone (ADH) from hypothalamus. The elevation of UA (TableII) indicates increased purine catabolism, metabolic block before nitrogenous waste can be excreted, renal dysfunction, hyperparathyroidism and hypertension.

Chromium Induced Cirrhosis

TheCr^{+6}exposures animals indicate the decrease in the amount of albumin (Table III) and cause more uptake of water consumption by animals, specify the possibility of cirrhosis (Fig. 1-B, E). Severe capillaries and blood vessels damage result in loss of serum proteins; which also indicate the poor liver function (Gole and Dasgupta, 2002). The significant elevation ($p \leq 0.0001$) of protein (Table III) indicate poor protein metabolism similarly BUN alterations and BUN/CRT ratio fluctuation enhance dehydration that may cause abnormal CRT levels boost dehydration (Atef and Al-Attar, 2011).

The higher globulins and bilirubin levels (TableIII) also confirm the cirrhosis and A/G ratio specify hypothyroidism and glucocorticoid excess (Agnes *et al*., 2012) similarly the significant elevation ($p \leq .0001$) of UA (Table II) also direct improper catabolism and that metabolic block are the causative agents of hypertension (Miguel, 2010).

Amelioration of Lipid Peroxidation

Jambul considered as anti-lipid peroxidative to regulate the hepatic enzymes due to the presence of their anthocyanins, glucoside, ellagic acid, iso-quercetin, kaemferol and myrecetin constituents (Abdalla *et al.,* 2011). The JFE analogous to citrus fruits protect the membrane integrity resulting in a reduction of cells hemolysis without met-hemoglobin formation due to their flavonoids (Heroor *et al*., 2013). The JFE attenuate the hepatocellular necrosis by regulating SGOT and SGPT (Karami, *et al.,* 2013) to minimize the hepatotoxicity. The ammonia during excretion need more water so in Cr^{+6}exposures animals feel thrust, and comparatively drink more water, indicate reno-hepatic complications, which can be reversed by plant extracts (Atef and Al-Attar, 2011).

The regulation of UA by JFE accordingly *Siraitiagros venorii* (Da-Duo *et al.,* 2013) which enhance antibodies and antioxidants against ROS to reverse induce dehydration, similarly the globulin sustain chelating activities (Saeed *et al*., 2011) and total protein specify regulation of liver inflammation along with CRT (Table II), like *Allium sativum,* against $CrCl_3$ (Jamshid *et al.,* 2008). Heavy metal poisoning has already being claimed about vascular conjunction resulting into shrinkage of glomeruli in rat kidney but there is significant enlargement of glomeruli size along with necrosis in the convoluted renal tubules (Fig 1-B, E), however the JFE group indicate the highest protective effect (Abbas *et al.,* 2015). The vacuolation cause necrosis due to debris in vessels followed by large excessive lesion, also intimate alarming malfunctioning of renal tubules (Fig 1-E). The plants increased the activities of antioxidant enzymes, like catalase, superoxide dismutase, reduced glutathione and glutathione peroxidase and their regulation, indicate the sign of improvement in the physiology of liver; stabilized lipogenesis, tumbling vacuolation and maintain the enzymatic activities (Table I-II). The JFE phytochemicals are responsible to cure fibrosis by up regulating and by radical scavenging, regulating cell cycle and necrosis augmenting shielding abilities against toxicants like Olive and Morus (Alarcon *et al*., 2014).Jambul possess different medicinal properties and their ascorbic acid being important constituent in cellular metabolism; gives proper remedy against toxicant stress (Abbas *et al.,* 2015). The JFE are excellent

supplements against oxidative stress and lipid inadequate metabolism due to anthocyanins; which can ameliorate the hyperglycemia by the activation of AMP-activated protein kinase (AMPK) in controlling the lipid metabolism like L-carnitine slimming capsule which is essential for carnitinepalmitoyl transferase-1 pathway during rehabilitation (Koeth *et al.,* 2013).

CONCLUSION

The modern allopathic medicines have limited therapeutic options due to their side effects while the herbal drugs are harmless and must be used as an alternative way to cure diseases. This mammalian model conducting study is helpful in order to make recommendation of its safe and beneficial use against environmental toxicants to assess the reno-hepato toxicological implications. The outcomes of such studies may also be useful for clinical application. Further study may be needed to achieve the optimal effects of Jambul fruit extracts against insecticides and other heavy metals at molecular and genomic level.

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