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RENO-HEPATOPROTECTIVE EFFECTS OF *MURRAYA KOENIGII* LEAVES CHLOROFORM EXTRACT (MKCE) AGAINST LEAD-INDUCED OXIDATIVE STRESS IN MICE

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ABSTRACT: Lead induced oxidative stress implies morphological dysfunctions and physiological deformation in the liver. The aim of present study was to establish the protective effect of chloroform extract of *Murraya koenigii* leaves against the lethal effects of lead on the antioxidant status of mice. *Murraya koenigii* Chloroform Extract (MKCE) was prepared by maceration. Male Swiss albino mice were divided into three groups of six each. Group I (Control group) served as normal diet and water *ad libitum*, Group II (lead treated group) received an intraperitoneal injection of lead acetate (15mg/kg) daily once whereas Group III (MKCE with lead-treated group) received MKCE (50 mg/kg) orally along with a single of injection of lead acetate intraperitoneally (15mg/kg) daily once. Experimental study was continued for the consecutive seven days. On the 8th day, liver and kidneys were desiccated; homogenized in normal saline to collect supernatant into vials for estimating serum malondialdehyde, antioxidant enzymes like superoxide dismutase, catalase, reduced glutathione, glutathione peroxidase, glutathione-s-transferase and ferric reducing ability of plasma levels. It was observed that significant alteration in levels of antioxidant parameters in lead-intoxicated mice. Antioxidant parameters were significantly restored in group III. Results in the study revealed that MKCE has antioxidative effects against lead induced oxidative stress in mice.

INTRODUCTION: Exposure to heavy metals leads to a wide range of physiological, biochemical and behavioural dysfunctions in the body. Cardiovascular disease (CVD) is becoming a major world health problem although, the oxidative stress induced by chronic heavy metal exposure like arsenic, lead, cadmium, mercury have been well explained [1]. Earlier studies have been reported there is possible high risk of dyslipidemia caused by some heavy metals like lead [2], cadmium [3], nickel and chromium [4], arsenic [5], and mercury [4].

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In an observational study studied by (Kim *et al*., 2005) [7], it is stated that no significant relationship of blood lead with cholesterol level found in children. Since, the exact mechanism still remains unknown through which heavy metals may augmented cardiovascular risk factors, but there is probably postulated that impaired antioxidant status and oxidative stress may responsible for leading CVD [1].

However, the influence of heavy metals on mechanism of cardiovascular risk could be more investigated through animal experimental studies [1]. Therefore, an attempt has been taken in the study to explore the impact of lead exposure on the antioxidant status. As lipid parameters abnormalities is being major factor for oxidative stress therefore; naturally occurring chelating

agents may play an important role in sequestrating heavy metals which in turn may reduce metal induced free radicals generation.

Chelation therapy of natural products like dietary plant sterols supplementation may helpful in preventing oxidative stress, heavy metals sequestration and may act as adjuvant in cardiovascular treatment in further studies [8]. So we have chosen the chloroform extract of curry leaf as natural adjuvant for CVD in the present study. Curry leaf is a household spice and widely used as natural flavour in the food. It is rich in antioxidant and its free radical scavenging properties [9]. This plant has botanical name as *Murraya koenigii* L. Spreng belonging to family Rutaceae [9].

It contains several bioactive compounds like euchrestine B, bismurrayafoline E, mahanine, mah-animbicine, mahanimbine and essential oil which contribute antioxidant [9 - 10], anti-trichomonal [11], anti-diabetic [12], anti-noceptive [13], anti-inflammatory [14], anticancer [15] and hepatoprotective [16] and blood-pro-tective [17] effects.

On reviewing literature, there is perhaps lack of scientific evidences reported on the effects of chloroform extract of *Murraya koenigii* leaves on lead induced impaired antioxidant status.

So this study was aimed for exploring the role of *Murraya koenigii* leaves chloroform extract against the lethal effects of lead on the antioxidant status.

MATERIAL AND METHODS:

Chemicals: Lead acetate was purchased from Loba-chemie. All other chemicals were of analytical grade and obtained from Sigma-Aldrich.

Collection of *Murraya koenigii* Leaves: Fresh *Murraya koenigii* leaves were purchased from the local market in the City of Karad (Western Maharashtra) in the month of March 2015 and was validated / authenticated them from the Department of Botany, Yashwantrao Chavan College of Sciences, Karad, Maharashtra, India.

Preparation of Chloroform Extract of *Murraya koenigii* Leaves: Chloroform extract of *Murraya koenigii* leaves was macerated and obtained 6% of yield from the crude powder. Doses of lead acetate (15mg/kg i.p) and MKCE (50mg/kg p.o) were used in our previous experimental study and published reports [16-17].

Experimental Animals: Male Swiss albino mice (n = 6 in each group) weighing between 25-30g were used in the study. Animals were obtained from the Animal House, Krishna Institute of Medical Sciences, Karad, India. The animals were maintained under standard husbandry conditions at room temperature, light: dark cycle for an acclimatization period of 15 days.

Experiment was compiled with the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) for animal experimentation of laboratory and Institutional Animal Ethics Committee (Reg. No. 255/PO/2000/bc/CPCSEA) KIMS, Karad approved for the study.

Male Swiss albino mice were randomly divided into three groups with each consisting of six animals and was continued at once daily for the consecutive seven days.

Group-I (Normal): Normal diet and water only *ad libitum*

Group-II (Pb Treated): Lead acetate (15mg/kg i.p)

Group-III (Pb + MKCE Treated): MKCE (50mg/kg p. o) + lead acetate (15mg/kg i.p)

On 8th day, mice were anaesthetized under ether and sacrificed by cervical decapitation. Liver and kidney tissues were collected with vials containing saline and stored at 4 °C for further analyzing parameters.

Blood Lead Analysis: Blood lead levels in mice were analyzed by atomic absorption spectrometry in accordance to our previous studies [16-17].

Liver and Kidney Homogenates: Ten percent liver and kidney homogenates in 0.15M KCl was homogenized in glass mortar pestle and centrifuged in cold (- 4 °C) at 2000 rpm for 30 min. The obtained supernatant was added into eppendorf tubes, labelled and stored at -20 °C and assayed renal function tests in the clinical biochemistry of KIMS, Karad.

Assessment of Antioxidant Parameters:

Thiobarbituric Acid Reactive Substances (TBARS): It was determined by Okhawa *et al*., (1979) [18]. Liver and kidney homogenates were quickly placed in ice- cold Phosphate Buffer Saline (PBS). Lipid Peroxidation (LPO) was initiated by adding 100 µl of 15 mM ferrous sulfate solution to 3ml of liver homogenate. After 30 min of incubation at room temperature, 0.1ml of liver homogenate was taken in a tube containing 0.1ml sodium dodecyl sulfate (8.1% w/v), 0.75ml of 20% acetic acid and 0.75ml of 0.8% thiobarbituric acid aqueous solution and heated on water bath at 95 °C for 60 min. The volume was made up to 2.5ml, to which 2.5ml of butanol: pyridine (15:1) was added. The reaction mixture was centrifuged at 4000 rpm for 10 min. Butanol layer was read at absorbance 532nm spectrophotometrically. The activity was expressed as nmoles of MDA/mg protein.

Superoxide Dismutase (SOD): It was determined by method of Martin *et al*., (1987) [19]. Copper-zinc superoxide dismutase (Cu-Zn SOD or SOD1) activity was measured by hematoxylin auto-oxidation method. Ten percent of liver and kidney homogenates in ice-cold 50mM phosphate buffer containing 0.1mM EDTA, pH 7.4. The homogenate was centrifuged at 12,000g for 15 min and the supernatant collected.

Inhibition of haematoxylin autooxidation by the cell free supernatant was measured at 560nm. Two unit enzyme activities is 50% inhibition of the rate of autooxidation of haematoxylin in 1min/mg protein. The enzyme activity was expressed as units/min/mg of tissue protein.

Catalase (CAT): It was analyzed by method of Beers and Sizer (1952) [20]. Catalase catalyses the breakdown of H_2O_2 into H_2O and O_2 and measured the rate of decomposition of H_2O_2 spectrophotometrically at 240nm. To 1.9 ml of phosphate buffer (pH 7.0), 1.0ml of 20mM H_2O_2 was added and then the reaction was initiated by the addition of 0.1ml liver and kidney homogenates (45µg protein). Decrease in absorbance was monitored at 1 min intervals for 5 min at 240nm and activity was calculated using a molar absorbance coefficient of H_2O_2 as 43.6 M^{-1} cm^{-1}. The activity was expressed as m moles of H_2O_2 decomposed/min/mg protein.

Reduced Glutathione (GSH): Total reduced glutathione content was measured by the method of Ellman (1959) [21]. It is based on the development of a yellow colour, when 5, 5′-dithio-2-nitrobenzoic acid (DTNB) reacts with the compounds containing sulfydryl groups with a maximum absorbance at 412nm. Ten percent of liver and kidney homogenates (0.5ml) was deproteinized with 3.5ml of 5% trichloroacetic and centrifuged at 4000 rpm for 5 min. To 0.5ml of supernatant, 3.0ml 0.2 M phosphate buffer (pH 8.0) and 0.5ml of Ellman's reagent were added and the yellow color developed was measured at 412nm. A series of standards (4–20µg) were treated in a similar manner along with a blank and values were expressed as µg of GSH/mg protein.

Glutathione Peroxidase (GPx): It was assessed by method of Rostruck *et al*., (1973) [22] allowed a known amount of the enzyme preparation to react with H_2O_2 in the presence of GSH for specific time period and remaining GSH was measured by following the method of Ellman (1959) [21] as described earlier. To 0.5ml 0.4 M phosphate buffer (pH 7.0), 0.2ml of 10% liver and kidney homogenates, 0.2ml of GSH and 0.1ml of H_2O_2 were added and incubated at room temperature (25 ± 2 °C) for 10 min along with a control tube containing all reagents except enzyme source.

The reaction was arrested by adding 0.5ml of TCA, centrifuged at 4000 rpm for 5 min and GSH content in 0.5ml of supernatant was estimated. The activity was expressed as µg of GSH consumed/min/mg protein.

Glutathione-s-transferase (GST): It was measured by monitoring the increase in the absorbance at 340nm using 1-Chloro-2, 4-Dinitrobenzene (CDNB) as a substrate by the method of Habig *et al*., (1974) [23]. To 1.7ml phosphate buffer (pH 6.5), 0.2ml of GSH and 0.04 ml of liver and kidney homogenates (40µg protein) were added and the reaction was initiated by the addition of 0.06ml CDNB. The change in absorbance was recorded at 1 min intervals at 340 nm for 5 min and the activity was calculated using extinction coefficient of CDNB-GSH conjugate as 9.6$mM^{-1}cm^{-1}$ and expressed as m moles of CDNB-GSH conjugate formed/min/mg protein.

Total Antioxidant Capacity (TAC): Total antioxidant capacity was estimated in terms of Ferric Reducing Ability of Plasma (FRAP) by method of Benzie and Strain (1996) [24]. To 0.04ml of liver and kidney homogenates (40µg protein) were allowed to react with 2ml of working FRAP solution containing acetate buffer (pH 3.6), 10mM of 2, 4, 6- Tripyridyl- S- Triazine (TPTZ) in40mM HCl, and 20mM of $FeCl_3 \cdot 6H_2O$ in the ratio of 10: 1: 1 at 37 °C. Fe^{+2} - TPTZ complex was measured at 593nm and time scanning was done at 30-second intervals for 4 minutes. The activity was expressed as U/mg protein.

Statistical Analysis: Data were expressed as the mean ± S.E.M (n = 6). Statistical analysis was done using analysis of One Way Analysis of Variance (ANOVA) followed by Dunnett's test and values were considered significant at $p < 0.05$.

RESULTS: The current study estimated protection ability of MKCE either to reduce the deleterious effects of lead or to preserve the normal reno-hepatic physiologic mechanisms distorted by lead. Morphological observations showed an increased size and enlargement of the liver and kidneys in lead treated group. These changes could be reversed by MKCE supplementation.

TABLE 1: EFFECTS OF MKCE ON RENAL FUNCTION PROFILE OF RENAL TISSUE HOMOGENATES IN LEAD-INTOXICATED MICE

Groups	Creatinine (mg/dl)	Urea (mg/dl)	Total Protein (g/dl)
I	1.08 ± 0.01	40.99 ± 0.42	3.44 ± 0.19
II	1.61 ± 0.04**	73.69 ±1.08**	0.24 ±0.08***
III	1.38 ± 0.03**	59.66 ± 3.46**	1.84 ±0.10***

Data represents mean ± SEM of six mice. *P < 0.05 compared to control, **P < 0.001 compared to control

TABLE 2: EFFECTS OF MKCE ON ANTIOXIDANT PARAMETERS IN LEAD - INTOXICATED MICE

Antioxidant Parameters	Hepatic Tissue Homogenate			Renal Tissue Homogenate		
Groups	I	II	III	I	II	III
TBARS (nmol of MDA/mg protein)	0.105 ± 0.02	0.537± 0.05*	0. 268 ± 0.02**	0.12 ± 0.02	0.61 ± 0.04**	0.38 ± 0.02**
SOD (U/mg protein)	4.288 ± 0.41	0.108 ± 0.02**	0.246 ± 0.02**	2.52 ± 0.19	0.09 ± 0.006**	0.299 ± 0.07**
CAT (U/mg protein)	49.71 ± 4.45	26.99 ± 2.55***	47.11 ± 1.85**	28.47±1.47	3.07 ± 0.18**	14.30±1.54**
GSH (mg/g protein)	6.21 ± 0.31	0.309 ± 0.03**	3.24 ± 0.25**	1.62 ± 0.22	0.314 ± 0.04**	0.769 ± 0.04**
GST (mg/g protein)	0.69 ± 0.02	0.17 ± 0.015**	0.48 ± 0.02**	0.5 ± 0.02	0.05 ± 0.01**	0.2 ± 0.03**
GPx (mg/g protein)	6.06 ± 0.32	0.26 ± 0.03**	2.9 ± 0.26**	1.7 ± 0.2	0.27 ± 0.04**	0.75 ± 0.04**
TAC (U/mg protein)	0.770 ± 0.04	0.346 ± 0.09**	0.413 ± 0.11*	0.49 ± 0.03	0.08 ± 0.103*	0.166 ± 0.02**

Data represents mean ± SEM of six mice. TBARS: thiobarbituric acid reactive substances, SOD: superoxide dismutase, CAT: Catalase, GSH: reduced glutathione, GPx: glutathione peroxide, GST: Glutathione-s-transferase $^{*}P < 0.05$ compared to control, $^{**}P < 0.001$ compared to control, ^{NS}: non-significant

DISCUSSION: Our results indicate a significant alternation in the kidney biomarkers *i.e.* increased levels of creatinine and urea following by declined level of total protein (**Table 1**). The ameliorated effects of MKCE have shown remarkable variation in serum creatinine and urea in group III compared to group II. Results of our study are in conformity with Laamech *et al*., (2016) [25]. Body weight of all mice and total protein of liver tissue homogenates was estimated in the previous studies [26, 16].

Heavy metals induced toxicities have been partially protected by administration of plant extracts in the experimental animals. Some studies also have been showed the protective effects of *Allium sativum* [27], *Psidium guajava* [28], *Phyllanthus emblica* [29] and curcumin [30] against heavy metals exposure in the experimental animals. This could be associated with chelating properties and antioxidant effect of naturally occurring plants. This indicates our study is in agreement with Abdel-Moneim *et al*., (2015) [30] and Anna *et al.*, (1993) [31]. In study by Sharma *et al*., (2010), lead mediated hypercholesterolemia [27] by activating cholesterol biosynthetic enzymes *i.e.* 3-Hydroxy-3Methy Glutaryl-CoA reductase (HMG-CoA), farnesyl diphosphate synthase, and squalene synthase, CYP51 and suppression of 7a-hydroxylase, cholesterol-catabolic enzyme.

Increased MDA or LPO level in liver and kidney homogenates indicates lead-induced oxidative damage in tissue. Treatment by MKCE

significantly reverses tissue damage. MDA is the major end product of lipid peroxidation which cross-links with DNA, protein and nucleotides may lead to tumourigenesis [32]. Oxidative stress was resulted due to impaired antioxidant status; the generation of Reactive Oxygen Species (ROS) [33] and free radicals like hydroxyl ($OH^{\cdot}$).[34] Augmented LPO activity is due to ROS during metabolism and decreased LPO activity is owing to the cellular membrane stability and inhibition of cellular necrosis by *Murraya koenigii* extract [33].

SOD is a family of metallo-enzyme involves in the catalyzing dismutation of the highly reactive superoxide anion converting to O_2 and H_2O_2 [32]. Decrease in SOD activity indicates reno-hepatocellular damage in mice and thus in the supplementation of MKCE has elevated the diminished activity of SOD to significant level and also reduces the ROS induced oxidative reno-hepatic damage. CAT quenches H_2O_2 produced by SOD [32] by catalyzing in the decomposition of H_2O_2 into H_2O and O_2 [35].

Decreased level of CAT causes the elevation of LPO [35] and led to deleterious effects by accumulation of superoxide and hydrogen peroxide radicals [36]. MKCE could undo the reduced level to nearby normal level of CAT significantly ($P < 0.001$). Glutathione (GSH) is tripeptide of L-cysteine, L- glutamic acid and glycinecysteinyl moiety, non-enzymatic antioxidant and its related enzymes like Glutathione-S-Transferase (GST) and Glutathione Peroxidase (GPx) [10, 36].

It scavenges many free radical species like H_2O_2, superoxide radicals and provides the protection to protein thiols of membrane and substrate for GPx [36]. Altered level of GSH, GPx and GST are associated with an enhanced LPO. Administration of MKCE significantly ($P < 0.001$) restored the normal level of GSH, GPx and GST in a dose dependent manner. Total Antioxidant Capacity (TAC) was expressed in terms of FRAP.

Increased FRAP values after MKCE supplement in our study indicates that natural plant extracts are good source of their antioxidant and free radical scavenging properties, which is in agreement with Heidarian *et al.,* (2013) [37].

In further investigation, the pharmacological activity against lead toxicity might be use of our other studied plant extracts comparatively like *Kalanchoe pinnata* [38], *Phyllanthus acidus* [39] and *Oxalis corniculata* [40].

Ethical Approval: Institutional Animal Ethics Committee

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