

## PROTECTIVE EFFECT OF AQUEOUS EXTRACT OF LEAVES OF *MURRAYA KOENIGII*, AGAINST ALUMINUM CHLORIDE-INDUCED OXIDATIVE STRESS IN RAT LIVER AND KIDNEY

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### ABSTRACT

**Objective:** The aim of the current study was to investigate the hepatoprotective, nephroprotective, and cholesterol-lowering activity of aqueous extract of *Murraya koenigii* (MK) leaves against AlCl<sub>3</sub>-induced oxidative stress in rats.

**Methods:** Wistar albino rats were distributed into six groups (6 each). Group I (control), and Group II administered with distilled water, and aluminum chloride (AlCl<sub>3</sub>), (40 mg/kg body weight [b.w], oral), respectively. Group III rats were treated with standard Vitamin E (100 mg/kg b.w, p.o) and AlCl<sub>3</sub> (40 mg/kg b.w, oral). Group IV, V, and VI received aqueous extract of leaves of *Murraya koenigii* (AEMK) (100 mg/kg b.w, peroral [p.o], 200 mg/kg b.w, p.o, and 400 mg/kg b.w, p.o), respectively, for a period of 35 days.

**Results:** Histopathological examination was observed deformities in hepatic and renal tissues due to aluminum exposure which augment the aforementioned results. Co-administration of AEMK along with Al significantly restored the serum biomarkers to their near-normal levels and has the ability to overcome Al-induced oxidative stress, manifested by a significant reduction in hepatic and renal malondialdehyde level. It increased cellular antioxidant defense, particularly by increasing GPx, glutathione, GR, and catalase levels, preserved normal hepatic and renal histological architecture.

**Conclusion:** It could be concluded that AEMK has significant radical scavenging activity and can mop up Al-induced toxicity, suggesting hepatoprotective and nephroprotective potential.

**Keywords:** Hepatoprotective, Nephroprotective, Aluminum chloride, *Murraya koenigii*, Aqueous extract.

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### INTRODUCTION

Aluminum [1] can accumulate in many tissues, such as kidney, liver, heart, blood, bone, and brain [2]. The toxic effect of aluminum was observed to be mediated by reactive oxygen species generation resulting in the oxidative deterioration of cellular lipids, proteins, and DNA and also induces changes in the activities of tissue antioxidant enzymes [3] altered gene expression and apoptosis [4]. The induced oxidative stress by aluminum and its salts is responsible for hepatotoxicity [5], nephrotoxicity [6], cardiac toxicity, and reproductive toxicity [7] and also neurodegenerative disease and Alzheimer like neurofibrillary tangle formation [8]. Hence, the external supply of antioxidants is important to suppress caspase activation and for the defense against the deleterious effects of oxidative stress [9]. Several chelating agents and antagonists are established to reduce metal toxicity; some of them are burdened with undesirable side effects. Due to the intrinsic limitations and variability of the efficacy of heavy metal chelating agents, metal intoxication therapy is looking for the development of new therapeutic agents with different actions, especially from phytochemicals. Natural antioxidants, which alleviate the oxidative stress or induce the cellular antioxidant, can able to treat against Al poisoning. *Murraya koenigii* (MK) is known as curry leaf which is belonging to family Rutaceae. Numerous active constituents of MK are found to be potent antioxidant. It possesses numerous pharmacological effects such as anti-inflammatory, anticancer, memory improvement, and anti-obesity activities. The present research was carried out to investigate the possible nephroprotective and cholesterol-lowering activity of MK against aluminum chloride (AlCl<sub>3</sub>)-induced intoxication in terms of oxidative stress, biochemical, and histological aspects. The novelty of present research to avoid shortcomings of conventional dosage forms activity on animal study, but the present AEMK leaves are mostly effective against AlCl<sub>3</sub>-induced oxidative stress in rats.

### MATERIALS AND METHODS

#### Plant material

The fresh leaves of MK were obtained from the outskirts of Maisammaguda situated in the state of Telangana (India). The plant material was identified and authenticated by Dr. H. Ramakrishna, H.O.D, Department of Botany, Osmania University, Telangana, India.

#### Chemicals

All chemicals, used in this study, were of analytical grade. AlCl<sub>3</sub> was purchased from Sigma Chemical Company, St. Louis, Missouri, USA. Aqueous extract of MK was prepared using the maceration process.

#### Animals

Ethical approval of this experimental study was obtained from the Institutional Animal Ethical Committee of Malla Reddy College of Pharmacy, Hyderabad, with Reg. No 1217/PO/Re/S/08/CPCSEA. Thirty-six albino rats with average body weight (b.w) from 150 to 250 g were utilized in this study. They were procured from Teena labs, Plot no 41, SV cooperative industrial estates, Bachupally (V), Quthbullapur. The rats were housed in polypropylene cages and maintained under standard conditions (12 h light and dark cycles at 25 ± 3°C and 35–60% humidity).

#### Experimental design

Group I (control) and Group II administered with distilled water and AlCl<sub>3</sub> (40 mg/kg b.w, oral), respectively. Group III rats were treated with standard Vitamin E (100 mg/kg b.w, p.o) and AlCl<sub>3</sub> (40 mg/kg b.w, oral). Group IV, V, and VI received aqueous extract of leaves of *Murraya koenigii* (AEMK) (100 mg/kg b.w, p.o, 200 mg/kg b.w, p.o, 400 mg/kg b.w, p.o), respectively, for a period of 35 days.

The animals were sacrificed on the 35<sup>th</sup> day by CO<sub>2</sub> inhalation through Euthanasia Chamber and blood was immediately collected by carotid bleeding method followed by centrifugation. Livers and kidneys were dissected rapidly, a part of these tissues were minced and then homogenized with phosphate buffer using tissue homogenizer. The resultant supernatant was removed and stored at -80°C until used for antioxidant enzyme activities and lipid peroxidation (malondialdehyde [MDA]) assays.

#### Biochemical assessment

Reitman and Frankel [10] method was used to get serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Belfeld [11] method was used to get serum alkaline phosphatase (ALP). Total bilirubin was determined calorimetrically according to Schmidt and Eisenburg method. Serum urea and creatinine [12] were determined according to previous reports. Serum total cholesterol [13], triglycerides [14], high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were determined as previously described by Richmond and Fossati principle [15].

#### Biochemical estimation of markers of oxidative stress

Ellman method [16] was used to get glutathione (GSH) level, and enzymatic antioxidant catalase (CAT) activity was also assessed, according to Aebi *et al.* method [17]. Glutathione peroxidase was observed by Hafeman *et al.* method [18] with some modifications. MDA level was analyzed by estimation of the produced thiobarbituric acid

**Table 1: Effect of aqueous extract of MK leaves on body weight in AlCl<sub>3</sub>-induced oxidative stress in rats**

Groups	Initial weight (g)±SEM	Final weight after treatment (g)±SEM
Group I	197±4.47	199±1.32
Group II	226±4.41	195±4.49 <sup>^</sup>
Group III	239±3.99	228±5.89 <sup>#</sup>
Group IV	183±4.54	170±7.23 <sup>*</sup>
Group V	185±3.42	172±4.22 <sup>**</sup>
Group VI	188±6.94	175±5.91 <sup>***</sup>

NB values are expressed as mean±SEM, n=6, <sup>^</sup>p<0.01 when compared to control group, <sup>#</sup>p<0.001 when compared with AlCl<sub>3</sub>-treated group, <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with AlCl<sub>3</sub>-treated group

**Table 2: Effect of aqueous extract of MK leaves on organ weight in AlCl<sub>3</sub>-induced oxidative stress in rats**

Groups	Kidney (g)±SEM	Liver (g)±SEM
Group I	1.31±0.06	8.00±1.08
Group II	1.96±0.08 <sup>^</sup>	8.51±0.18 <sup>^</sup>
Group III	1.86±0.04 <sup>#</sup>	7.84±0.16 <sup>#</sup>
Group IV	1.89±0.05 <sup>*</sup>	8.12±1.33 <sup>*</sup>
Group V	1.64±0.07 <sup>**</sup>	7.78±1.40 <sup>**</sup>
Group VI	1.52±0.06 <sup>***</sup>	7.11±1.28 <sup>***</sup>

NB values are expressed as mean±SEM, n=6, <sup>^</sup>p<0.01 when compared to control group, <sup>#</sup>p<0.001 when compared with AlCl<sub>3</sub>-treated group, <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with AlCl<sub>3</sub>-treated group

**Table 3: Effect of aqueous extract of MK leaves in serum biochemical parameters for hepatoprotective activity in AlCl<sub>3</sub>-induced oxidative stress in rats**

Groups	SGOT (U/L)±SEM	SGPT (U/L)±SEM	ALP(U/L)±SEM	Bilirubin (mg/dl) ± SEM
Group I	8.66±0.22	10.35±0.22	110.29±0.23	0.20±0.04
Group II	19.35±0.22 <sup>^</sup>	22.35±0.22 <sup>^</sup>	274.58±0.17 <sup>^</sup>	1.62±0.17 <sup>^</sup>
Group III	7.21±0.07 <sup>#</sup>	11.98±0.12 <sup>#</sup>	120.70±0.12 <sup>#</sup>	0.80±0.04 <sup>#</sup>
Group IV	8.92±0.02 <sup>*</sup>	10.52±0.16 <sup>*</sup>	159.70±0.47 <sup>*</sup>	1.25±0.09 <sup>*</sup>
Group V	8.47±0.09 <sup>**</sup>	8.75±0.09 <sup>**</sup>	146.30±0.19 <sup>**</sup>	1.05±0.09 <sup>**</sup>
Group VI	7.52±0.09 <sup>***</sup>	5.65±0.17 <sup>***</sup>	132.60±0.21 <sup>***</sup>	0.82±0.06 <sup>***</sup>

NB values are expressed as mean±SEM, n=6, <sup>^</sup>p<0.01 when compared to control group, <sup>#</sup>p<0.001 when compared with AlCl<sub>3</sub>-treated group, <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with AlCl<sub>3</sub>-treated group

reactive substances by the method of Buege and Aust [19]. Glutathione reductase activity was measured according to previous reports [20].

#### Histopathological study

On completion of the regimen, animals [21] were sacrificed, the liver and kidney were dissected out and fixed in 10% buffered neutral formalin solution and further processed to obtain of paraffin blocks. Five-micron thick paraffin sections were prepared and routinely stained with hematoxylin and eosin and examined for the histopathological changes using the light microscope.

#### Statistical analysis

The results were analyzed [22-24] by one-way analysis of variances followed by Dunnett's test using the graph pad statistical software for comparison between different experimental groups. p<0.001 were considered statistically significant. The intergroup variation between various groups was conducted by GraphPad Prism software and t-test. Values are expressed as mean ± SEM. <sup>^</sup>p<0.01 when compared to the control group, <sup>#</sup>p<0.001 when compared with the AlCl<sub>3</sub>-treated group, and <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with the AlCl<sub>3</sub>-treated group.

#### RESULTS AND DISCUSSION

The b.w. of rats from the toxin group was significantly (p<0.0001) decreased when compared with the normal control group. Treatment with extract of aqueous extract of MK before AlCl<sub>3</sub> intoxication is reported (Table 1) dose-dependent protection.

It was observed that the weight of the kidney and liver of rats from the toxin group was significantly (p<0.0001) decreased when compared with the normal control group. Treatment with aqueous extract of MK before AlCl<sub>3</sub> intoxication has shown dose-dependent protection (Table 2).

It was reported that oral administration of AlCl<sub>3</sub> to Wistar albino rats for 35 days resulted in a significant increase (p<0.001) in serum activities of AST, ALT, ALP, and total bilirubin concentration. The levels of all these parameters showed significant improvement toward their normal levels when AEMK and Vitamin-E were concomitantly administered with AlCl<sub>3</sub> was given in Table 3.

It was observed that by oral administration of AlCl<sub>3</sub> to Wistar albino rats for 35 days resulted in a significant increase (p<0.001) in urea and creatinine level when compared with the other experimental groups. The cotreatment of rats with AlCl<sub>3</sub> and Vitamin-E, AEMK for the same period improves kidney status and retained the aforementioned parameters toward the normal level when compared with the AlCl<sub>3</sub>-treated group is shown in Table 4.

It was observed that with AlCl<sub>3</sub>-treated group serum cholesterol, triglyceride, and low-density lipoprotein-cholesterol levels were significantly higher in the groups receiving AlCl<sub>3</sub> alone compared to the standard- and extract-treated groups. There was also a significant decrease in the levels of high-density lipoprotein-cholesterol in AlCl<sub>3</sub> receiving group. The cotreatment of rats with AlCl<sub>3</sub> and Vitamin-E, AEMK for the same period, retained the aforementioned parameters toward the normal level when compared with the AlCl<sub>3</sub>-treated group was given in Table 5.

$AlCl_3$  treatment resulted in a case of oxidative stress represented by decreased level of GPx, GR, CAT, and lowered GSH contents with the elevated MDA level (an indicator of lipid peroxidation) in liver and kidney tissues homogenates. It is reported in Tables 6 and 7.

#### Histopathological results

Rats receiving  $AlCl_3$  showed distorted portal area and edema, bleeding in the portal vein, fibrosis around portal area, and vacuolar degeneration of

hepatocytes. The study of histological structures of  $AlCl_3$  +Vit-E showed normal hepatocytes lining of central vein, hepatocytes with normal nucleus and less atrophy of hepatocytes nucleus. The histomorphology of rats treated with  $AlCl_3$  then AEMK (100 mg/kg) showed bleeding in the portal vein and atrophy of some hepatocytes. The histomorphology of rats treated with  $AlCl_3$  then AEMK (200 mg/kg) showed a slight expansion of sinusoids and moderate atrophy. Rats receiving  $AlCl_3$  then AEMK (400 mg/kg) showed normal lining of the central vein and less atrophy (Fig. 1).

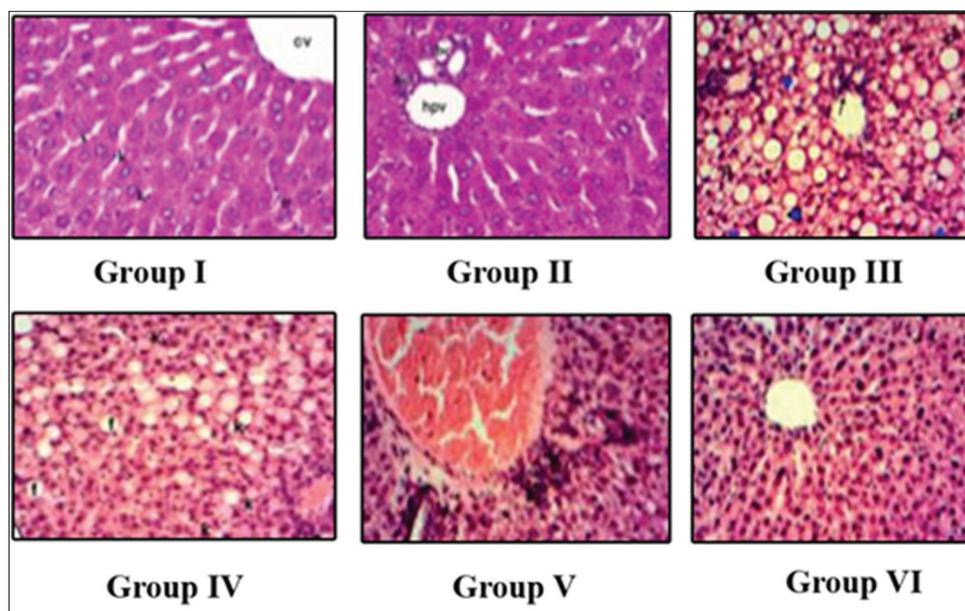
Histopathological changes in the kidney tissue were shown in Fig. 2. It was confirmed that in Group I control rats showed normal glomeruli with an intact bowman's capsule and proximal convoluted tubule, in Group II kidney sections of rats observed modest congestion of blood vessels, necrosis of the renal cells, degeneration of glomeruli, intrarenal arterial vessel showed modest thickening of the walls, and degree of tubule interstitial damage, in Group III of rats showed intact renal cortex, preserved cellularity of renal corpuscles, and intact renal tubules, in Group IV of rats showed degenerated glomeruli, and Group V rats showed moderate congestion in glomerular degeneration with tubule interstitial damage.

It was observed that aluminum can inhibit NADPH-generating enzymes such as NADP-isocitrate dehydrogenase and glucose

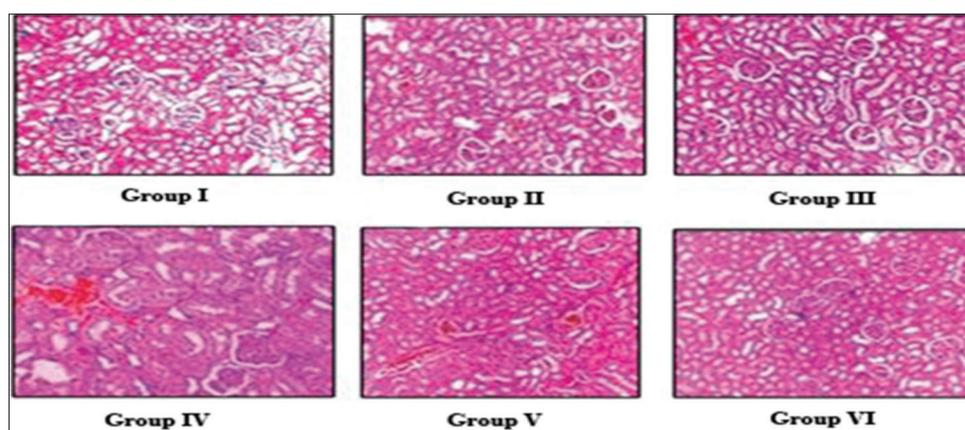
**Table 4: Effect of aqueous extract of MK leaves in serum biochemical parameters for nephroprotective activity in  $AlCl_3$ -induced oxidative stress in rats**

Groups	Urea (mg/dl)±SEM	Creatinine (mg/dl)±SEM
Group I	48.16±0.41	1.22±0.16
Group II	70.99±0.40 <sup>^</sup>	3.00±0.08 <sup>^</sup>
Group III	55.09±0.31 <sup>#</sup>	1.02±0.006 <sup>#</sup>
Group IV	61.13±0.29 <sup>*</sup>	2.175±0.11 <sup>*</sup>
Group V	56.63±0.22 <sup>**</sup>	2.104± 0.10 <sup>**</sup>
Group VI	52.33±0.45 <sup>***</sup>	1.175±0.11 <sup>***</sup>

NB values are expressed as mean±SEM, n=6, <sup>^</sup>p<0.01 when compared to control group, <sup>#</sup>p<0.001 when compared with  $AlCl_3$ -treated group, <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with  $AlCl_3$ -treated group



**Fig. 1: Histopathological changes in the liver tissue of experimental groups**



**Fig. 2: Histopathological changes in the kidney tissue of experimental groups**

**Table 5: Effect of aqueous extract of MK leaves in serum biochemical parameters for lipid-lowering activity in AlCl<sub>3</sub>-induced oxidative stress in rats**

Groups	HDL (mg/dl)±SEM	LDL (mg/dl)±SEM	Total cholesterol (mg/dl)±SEM	Triglycerides (mg/dl)±SEM
Group I	31.25±1.11	45.06±1.15	97.25±1.49	104.68±0.5
Group II	16.75±1.11 <sup>^</sup>	101.97±1.12 <sup>^</sup>	144.50±2.94 <sup>^</sup>	128.87 ±0.08 <sup>^</sup>
Group III	27.00±0.91 <sup>#</sup>	62.26±0.18 <sup>#</sup>	105±2.10 <sup>#</sup>	78.66 ±1.1 <sup>#</sup>
Group IV	14.25±0.85 <sup>*</sup>	86.85±1.05 <sup>*</sup>	117.50±0.65 <sup>*</sup>	82.83 ±1.05 <sup>*</sup>
Group V	15.50±0.65 <sup>**</sup>	81.51±1.15 <sup>**</sup>	114.25±0.48 <sup>**</sup>	86.19 ±1.1 <sup>**</sup>
Group VI	22.09±0.86 <sup>***</sup>	71.60±1.12 <sup>***</sup>	111.00±0.41 <sup>***</sup>	87.51 ±1.1 <sup>***</sup>

NB values are expressed as mean±SEM, n=6, <sup>^</sup>p<0.01 when compared to the control group, <sup>#</sup>p<0.001 when compared with AlCl<sub>3</sub>-treated group, <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with AlCl<sub>3</sub>-treated group. LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol

**Table 6: Effect of aqueous extract of MK leaves for estimation of hepatoprotective activity in AlCl<sub>3</sub>-induced oxidative stress in rat liver**

Groups	MDA (nm/g)±SEM	GSH (µg/ml)±SEM	Catalase (K/min)±SEM	GR (µ/ml)±SEM	GP <sub>x</sub> (nm/g)±SEM
Group I	155.78±0.84	27.5±0.5	21±1.0	20.83±0.60	38.33±0.5
Group II	429.12±1.4 <sup>^</sup>	13.5±0.5 <sup>^</sup>	11.5±0.5 <sup>^</sup>	11.33±0.49 <sup>^</sup>	21.16±0.47 <sup>^</sup>
Group III	155.05±1.08 <sup>#</sup>	35.7±0.5 <sup>#</sup>	18.91±0.5 <sup>#</sup>	24.66±0.92 <sup>#</sup>	34.33±0.55 <sup>#</sup>
Group IV	166.16±1.48 <sup>*</sup>	27.5 ±0.5 <sup>*</sup>	14.5±0.5 <sup>*</sup>	16.5±0.42 <sup>*</sup>	26±0.36 <sup>*</sup>
Group V	160.31±0.84 <sup>**</sup>	29.5±0.5 <sup>**</sup>	15.5±1.0 <sup>**</sup>	18±0.5 <sup>**</sup>	28.33±0.33 <sup>**</sup>
Group VI	152.46±0.93 <sup>***</sup>	32.5±0.5 <sup>***</sup>	17.5±0.5 <sup>***</sup>	21.5±0.42 <sup>***</sup>	32.33±0.5 <sup>***</sup>

NB values are expressed as mean±SEM, n=6, <sup>^</sup>p<0.01 when compared to control group, <sup>#</sup>p<0.001 when compared with AlCl<sub>3</sub>-treated group, <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with AlCl<sub>3</sub>-treated group

**Table 7: Effect of aqueous extract of MK leaves for estimation of nephroprotective activity in AlCl<sub>3</sub>-induced oxidative stress in rat kidney**

Groups	MDA (nm/g)±SEM	GSH (µg/ml)±SEM	Catalase (K/min)±SEM	GR (µ/ml)±SEM	GP <sub>x</sub> (nm/g)±SEM
Group I	152.78±0.84	24.5±0.5	21.32±1.0	20.33±0.60	36.33±0.5
Group II	422.12±1.4 <sup>^</sup>	12.5±0.5 <sup>^</sup>	10.5±0.5 <sup>^</sup>	11.83±0.49 <sup>^</sup>	22.16±0.47 <sup>^</sup>
Group III	148.05±1.08 <sup>#</sup>	36.7±0.5 <sup>#</sup>	18.71±0.5 <sup>#</sup>	22.88±0.92 <sup>#</sup>	32.33±0.55 <sup>#</sup>
Group IV	168.16±1.48 <sup>*</sup>	25.5 ±0.5 <sup>*</sup>	13.5±0.5 <sup>*</sup>	14.5±0.42 <sup>*</sup>	23±0.36 <sup>*</sup>
Group V	158.31±0.84 <sup>**</sup>	27.5±0.5 <sup>**</sup>	14.5±1.0 <sup>**</sup>	16.2±0.5 <sup>**</sup>	25.33±0.33 <sup>**</sup>
Group VI	150.46±0.93 <sup>***</sup>	30.5±0.5 <sup>***</sup>	15.5±0.5 <sup>***</sup>	19.53±0.42 <sup>***</sup>	29.33±0.5 <sup>***</sup>

NB values are expressed as mean±SEM, n=6, <sup>^</sup>p<0.01 when compared to control group, <sup>#</sup>p<0.001 when compared with AlCl<sub>3</sub>-treated group, <sup>\*</sup>p<0.005, <sup>\*\*</sup>p<0.0001 when compared with AlCl<sub>3</sub>-treated group

6-phosphate dehydrogenase. Since NADPH is shown to be a main factor for the GSH regeneration, the decreased GSH level could be also ascribed to the insufficient supply of NADPH. The higher intracellular aluminum concentration reduced protein synthesis of antioxidant enzymes and subsequently reduced their activities. Simultaneous administrations of AEMK with AlCl<sub>3</sub> replenish the antioxidant enzyme activities near to normal with an increase in GPx activities, GR, CAT, and GSH level and diminish MDA level as a marker of LPO in liver and kidney when compared with AlCl<sub>3</sub>-treated rats. This is due to the aqueous extract of MK to reduce the accumulation of free radical generation during Al-induced lipid peroxidation. AEMK is able to inhibit the free radical generation, could further reduce the oxidative threat caused by aluminum, which could mitigate the consumption of endogenous enzymatic and non-enzymatic antioxidants and increased their levels and markedly reduces the hepatic and renal LPO. In the current study, it was observed that AEMK played an important role as an antioxidant, which includes free radical scavenging and metal-chelating property and thereby improved the detrimental state of liver and kidney cells which unraveled its use as a possible attenuating agent in aluminum-induced hepatotoxicity and nephrotoxicity. Hence, overall it was observed that AEMK administration markedly reduces the hepatic and renal toxicity in rats.

## CONCLUSION

It showed that MK played an important role as an antioxidant, which includes free radical scavenging and metal-chelating property and thereby improved the detrimental state of liver and kidney cells which unraveled its use as a possible attenuating agent in aluminum-induced hepatotoxicity and nephrotoxicity.

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## AUTHORS' CONTRIBUTIONS

CK Dhanapal and BVS Lakshmi planned and designed the whole work. B. Maheswari Reddy did the whole research work. It is a part of the research work Ph.D. thesis of B.M.R.

## CONFLICTS OF INTEREST

The author declares that they have no conflicts of interest.

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