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Protective effects of *Aloe vera* extract on aluminium sulphate induced alterations in serum lipid profile of male albino rats, *Rattus norvegicus*

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ABSTRACT

The present study suggests that treatment with *Aloe vera* a medicinal plant belonging to the family - *Liliaceae*, used in traditional Indian medicine system and its active constituent Aloin has a positive and therapeutic effect in lowering the lipid profile level in aluminium sulphate exposed rats for a period of 60 to 90 days. Lipid profile (total cholesterol, triglyceride, HDL and LDL) levels were found to significantly increased (P<0.05) after treatment of $Al_2(So_4)_3$ in Group II compared to normal control Group I treated with normal diet. Group III and Group IV animals treated with $Al_2(So_4)_3$ and Aloe vera extract and $Al_2(So_4)_3$ and Aloin respectively, showed significant decrease in lipid profile at (P<0.05). The present study also validates that *A.vera* extract and pure aloin was effective in reducing Al toxicity in lipid profile (Total Cholesterol, Triglyceride, HDL and LDL) of treatment in the long term 60 and 90 days of aluminium exposed rats.

KEY WORDS: *ALOE VERA*, ALUMINIUM TOXICITY, TOTAL CHOLESTEROL, TRIGLYCERIDE, HDL AND LDL

INTRODUCTION

Aluminium (Al) is the third most abundant metal present naturally in the Earth's crust. It is also present in soil, air, water, several eatables, and commercial products such as food storage material, cookware, and medicinal products including drugs. Exposure to humans occurs through different routes. The common routes of exposure include inhalation, oral, and skin. Exposure is more common among people working in Al industries. The extensive use of Al cookware leads to ingestion of small quantities of Al every day. Al is found to be a component of commonly used medications such as anti-ulcer drugs such as sucralfate, antacids containing Al, hae-

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modialysis fluid, phosphate binders and vaccines. Al is also found in anticaking agents, preservatives, fillers, coloring agents, emulsifiers and baking powders. Such extensive use of Al in consumable and non consumable products will certainly lead to Al entry and deposition in human body, (Denise *et al*., 2007; Verstraeten *et al*., 2008; Gura, 2010; Thirunavukkarasu *et al*., 2013; Kalaisevi *et al*., 2015; Sakr *et al*., 2017; Konda *et al*., 2017; Ahmed *et al*., 2018).

Al does not have any physiological role in the body but it gets stored mainly in the blood, lungs, liver, bones, brain, spleen, kidney and muscles. It may act as a competitive inhibitor for elements such as magnesium, iron and calcium because of its atomic size and electric charge and may results in anaemia and bone damage. Al-induced neurotoxicity and changes in serum lipid profile and vitamins. High level of exposure can cause toxicity such as nephrotoxicity and hepatotoxicity. It was already been reported in patients with chronic kidney disease who were on dialysis with Al-containing dialysis fluid. Al toxicity has been associated with Alzheimer's disease, dialysis, Parkinson's dementia. It is due to oxidative stress and lipid peroxidation in tissues, Protein and DNA (Tchounwou *et al*., 2012; Thomford *et al*., 2017; Azza *et al*., 2017).

Lipid is an important component of human body because it is a main constituent of cell membrane, several hormones and also performs many other cellular functions (Esther *et al*., 2013). Lipids being insoluble in the blood so it is transported from the cells by low density and high density lipoproteins (Brown *et al*., 2007; Kaji *et al*., 2013). High density lipoproteins (HDL) tend to carry cholesterol away from arteries back to the liver (Van der Veen *et al*., 2009). Therefore, high serum cholesterol level can be due to hepatic dysfunction. Although several factors, such as life style, a diet rich in cholesterol, age and hypertension, have been reported to cause heart failure (Kumar *et al*., 2011). High levels of cholesterol, particularly LDL cholesterol, are mainly responsible for hypercholesterolemia provoked cardio toxicity (Azad *et al*., 2001).

Several anti-hyperlipidemic agents are currently available; however most of them have associated with various unwanted effects. Hence, people are switching towards safer alternatives, specially derived from plants with limited side effects. The World Health Organization (WHO) has given its estimation that more than 2/3rd of the global population in recent times depends on alternative sources of treatment to fulfil the basic health care requirements and this most importantly embroils the usage of plant products. This means that nearby two-thirds of the people globally trust on plants as a reliable way of their medication. Nowadays, vigorous research is ongoing to discover nontoxic and beneficial herbs. Herbal Medicine or herbalism is the practice or art of employing herbs and herbal preparations in order to remain healthy and also for the treatment and improvement in prognosis of diseases. *A.vera* is a medicinal plant belongs to the family *Liliaceae* its active constituent aloin have antioxidant properties, protective against heavy metal toxicity. Its therapeutic applications include wound healing, diabetes, burns for easing intestinal, curing ulcers and arthritic swelling (Kumar *et al*., 2010; Sai *et al*., 2011; Jakkala *et al*., 2015; Mahor *et al*., 2016; Gupta *et al*., 2017). The aim of the present study was to investigate the protective role of *A.vera* on Al induced changes in lipid profile (cholesterol, triglyceride, HDL and LDL) of experimental rats.

MATERIALS AND METHODS

Collection and identification of plant material: The fresh leaves of *A.vera* (*Aloe barbadensis*) were collected from the Minor Forest Produce Processing and Research Centre (MFP-PARC) Van Parisar, Barkhera Pathani, Bhopal, (M.P.) India. The plant was authenticated by Dr. Zia-Ul-Hassan Head of the Department of Botany at the Saifia College of Science Peer Gate, Bhopal, (M.P.) India and the voucher specimen (403/Saifia/Bot/16) has been deposited at the Herbarium of the Saifia Science College, Peer Gate, Bhopal, (M.P.) India.

Preparation of extracts: After collection and weighing, fresh leaves of *Aloe vera* were washed with distilled water to remove dirt and dried under shade separately. The extraction of *A. vera* leaves was done according to the method (Kumar & Muthuselvam, 2009). Slight modification, Skin of the leaves were pealed and the gel inside was used for extraction. 100 gm of the gel was added to 250ml of ethanol and extracted using the Soxhlet assembly. Later on, the solvent of the extracted material was removed at low temperature in a rotary vacuum evaporator and the resulting dried extract was lyophilized in a freeze dryer.

Drugs and chemicals: In this study, Al-sulphate $(Al_2So_4)_3$ was purchased from Aldrich chemical Company (St. Lousis mo, USA) and Standard Aloin (C21H22O9) was obtained from Sigma. The diagnostic kits required for enzymatic assays were purchased from Span Diagnostics. All other chemicals used in the experiment were of analytical grade. The dose of Al-sulphate $(Al_2So_4)_3$ was 98mg $(Al_2So_4)_3$ /L (1/25 LD50). The dose of A.vera extract and Aloin were 100 mg/kg BW. These doses were selected based on basis of pilot experiments.

Maintenance of animals and approval of protocol: Healthy adult male albino rats (*Rattus norvegicus*) weighing 120-150g were used for the present investiga-

tion. They were housed in a clean polypropylene cage and maintained in an air-conditioned experimental room at 12-hour light: dark cycles. The animals were acclimatized to laboratory condition for one week prior to experiment. Standard pellets were used as a basal diet during the experimental period. The control and experimental animals were provided with purified drinking water *ad libitum*. The animals were maintained in accordance with the "CPCSEA guidelines for laboratory animal facility" (Committee for the Purpose of Control and Supervision on Experiments on Animals) and the approval number is CPCSEA Registration number SSC/06-06-22/CPCSEA, dated 26/10/2006. Before starting the experiment the animals were carefully marked on different parts of their body, which was later used as identification mark for a particular animal, so that the response of a particular mouse prior to and after the administration could be noted separately.

Acute oral toxicity studies: *A.vera* extract at the dose range of 100–2500 mg/kg body weight were administered by oral gavage method on different group of mice comprised of 6 rats in each group. Animals were kept under close observation for 4 hours after administering the fraction for behaviour, neurological, and autonomic profile and then observed for any change in the general behaviour and physical activities; mortality was recorded within 72 hours. Acute toxicity was determined according to the method (Lorke, 1983).

Induction of Toxicity/experimental design: A total of 24 male (2 months old) Albino rats (*Rattus norvegicus*) weighing 120-150g were used for the present investigation. The animals were divided into four groups (6 rats/group): Group I:-was kept as control without giving any treatment. Compared to adult controls, Group II: - animals in this group were given 17±6 ml of water supplemented with Al-sulphate to consume, corresponding to 98 mg of Al per day (Laxman *et al*., 2016) for 60 and 90 days. Group III: - This group animals were fed with normal diet and received aluminium sulphate (98 mg/kg body weight) and *Aloe vera* extract (100 mg/kg body weight) for 60 and 90 days. Group IV: - This group animals were fed with normal diet and received aluminium sulphate (98 mg/kg body weight) and Aloin (100 mg/kg body weight) for 60 and 90 days.

Animal Grouping and Treatment Schedule: Four groups of rats, six rats in each, received the following treatment schedule: Group I rats received normal diet and water *ad libitum*, as control group. Group–II rats administered twice with Aluminium sulphate (98 mg/kg/day) dissolved in (1ml/kg b.wt) water were injected dose orally for 60 and 90 days. Group III, will be administered with Aluminium sulphate (98 mg/kg/b.w.) with *Aloe vera* extract (100 mg/kg/b.w.) dose orally for 60 and 90 days and last Group-IV rats were administrated Aluminium sulphate (98 mg/kg/b.w.) with Aloin (100 mg/kg/b.w.) dose orally for 60 and 90 days.

Collection of Blood Sample and Estimation of Serum Lipid profile Investigations: Blood samples were collected by orbital sinus puncture method (Hui *et al*., 2007). Serum was separated by following procedure. Blood samples were withdrawn from orbital sinus using non heparinised capillary tubes, collected in dried centrifuge tubes and allowed to clot. Serum was separated from the clot by centrifuged at 3000 rpm for 15 min. at room temperature. Serum was collected carefully and kept at-20°C until analysis of Total cholesterol, High Density Lipoprotein (HDL) cholesterol and triglycerides by using kits supplied by Span Diagnostic Ltd. Plasma concentrations of total cholesterol, triglycerides, HDL & LDL fractions were measured by using standard methods with commercially available kits. LDL cholesterol was calculated with the Friedewald formula as follows: LDL cholesterol = total cholesterol – HDL cholesterol – (triglycerides/5) (Friedewald *et al*., 1972).

STATISTICAL ANALYSIS OF DATA: All parameters were presented as mean ± SEM. One-way analysis of variance followed by Bonferroni multiple comparisons using a computer-based fitting program (Prism, Graph Pad) were performed. Differences were considered to be statistically significant when $P < 0.05$.

RESULTS

It was obsevered that all four groups of rats received the following treatment schedule: shows the significant change in all parameters discussed here. After 60 days (Group II) showed a significant ($P<0.05$) increase in the level TC, TG, HDL and LDL due to Al toxicity compared to group I. whereas significant ($P<0.05$) decrease in TC, TG, HDL and LDL level was reported in group III and group IV (Table:1), (Fig: 1).Experimental results shows. After 60 days group III and group IV showed a significant ($P < 0.05$) decrease in the level TC, TG, HDL and LDL which is induced due to Al toxicity group II compared to group I (Table: I), (Fig: I).

After 90 day study it was observed that Al toxicity enhances compared to 60 or 90 days. It means Al on long term exposure induces toxicity in group II whereas *A.vera* extract and aloin was also effective in reducing toxicity in various parameters studied after 90 days. After 90 days group III and group IV showed a significant ($P<0.05$) decrease in the level of TC, TG, HDL and LDL which is induced due to Al toxicity group II nearest about to group I. (Table:II) and (Fig: II),

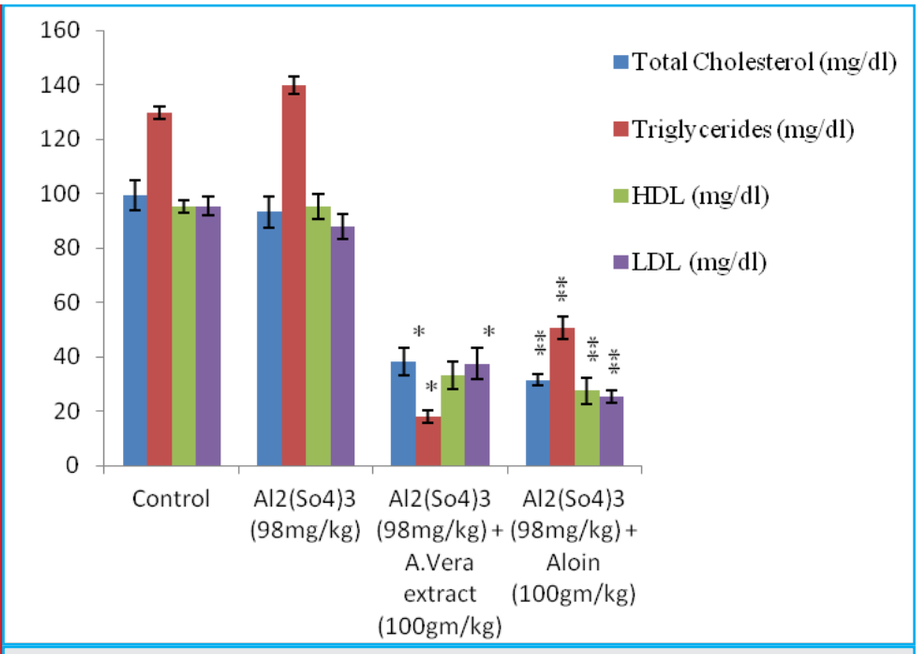

FIGURE 1. Graph showing variation in different levels of Total Cholesterol: Triglycerides, HDL and LDL against Aluminium sulphate (98mg/kg/bw) induced toxicity after 60 days.

Table 1. Effects of orally administrated A. vera extract and aloin on Total Cholesterol, Triglycerides, High density lipoproteins, Low density lipoprotein intoxicated with Aluminium sulphate after 60 days.

Group	Treatment	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
I	Normal Control	99.33±5.391	93.33±5.755	38.17±5.115	31.50±1.871
II	Al2(So4)3 (98mg/kg)	129.83±2.316	139.83±3.312	17.83±2.317	50.67±4.179
III	Al2(So4)3 (98mg/kg) + A.vera extract (100gm/kg)	95.16±2.136 *	95.17±4.446*	33.17±5.037*	27.50±4.848 *
IV	Al2(So4)3 (98mg/kg) + Aloin (100gm/kg)	95.33±3.444**	87.83±4.401**	37.33±5.715 **	25.17±2.317 **

* & **= indicates significant values, significantly different at P ≤ 0.05.

Table 2. Effects of orally administrated *A. vera* extract and aloin on Total Cholesterol, Triglycerides, High density lipoproteins, Low density lipoprotein intoxicated with Aluminium sulphate after 90 days.

Group	Treatment	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg dl)	LDL (mg/dl)
I	Normal Control	101.83±4.622	94.67±5.785	40.00±3.950	33.17±2.927
II	Al2(So4)3 (98mg/kg)	133.17±4.070	141.17±4.834	15.67±1.633	53.67±4.633
III	Al2(So4)3 (98mg/kg) + A.Vera extract (100gm/kg)	92.83±3.189*	92.50±5.925*	35.50±3.507 *	29.50±4.593 *
IV	Al2(So4)3 (98mg/kg) + Aloin (100gm/kg)	92.67±8.238 **	85.50±9.731 **	38.67±4.885 **	23.67±3.983 **

* & ** = indicates significant values, significantly different at P ≤ 0.05.

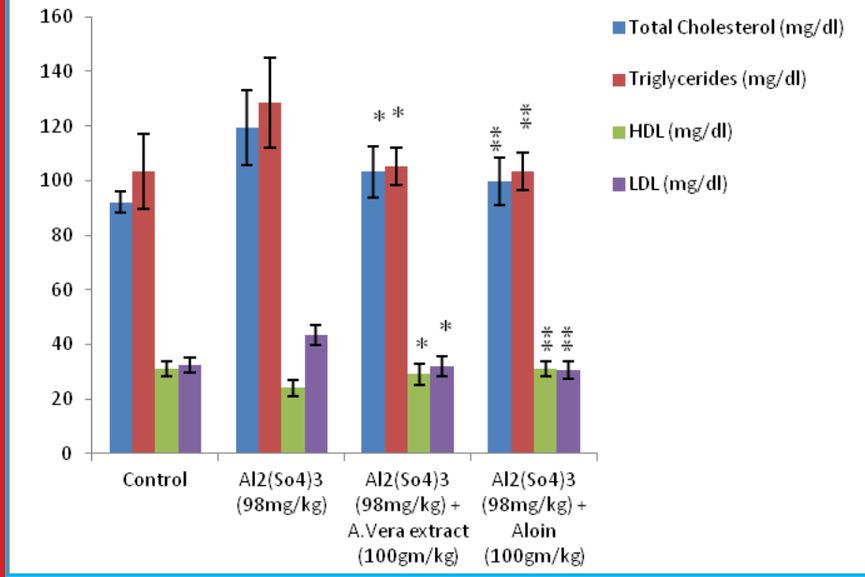

FIGURE 2. Graph showing variation in different parameter levels of Total Cholesterol: Triglycerides, HDL and LDL against Aluminium sulphate (98mg/kg/bw) induced toxicity after 90 days.

DISCUSSION

The hypertriglyceridemia and lipid oxidation were main features of this altered metabolism. Hyperlipidemia is a condition where there is an elevation of the serum levels of total cholesterol (TC) and triglycerides (TG) due to the lipid metabolism alteration, with an increase in the liver lipogenesis and lipolysis in the adipocytes. Low-density lipoprotein (LDL) is the compound containing both lipid and protein, which transport cholesterol to tissues other than the liver. High-density lipoprotein (HDL) is the compound containing both lipid and protein, which transport cholesterol to the liver for excretion in the bile. (Kalaiselvi *et al.*, 2015; Gouda *et al.*, 2018).

Aluminium (Al) is toxic to humans and animals. Its toxicity results to generation of reactive oxygen species in lipids which leads to oxidative damage of biomolecules in an organism. The present study investigated the effects of Al-sulphate in toxicity induction and beneficial effect of *A.vera*, aloin against the induced toxicity in rats. The findings of this study were that Al perturbed the metabolism of lipids (cholesterol, triglyceride, LDL and HDL) in rat. It may up-/down-regulation the levels of these lipids due to up- or down-regulated of enzyme. These perturbations were presented in the plasma as hypertriglyceridemia, hypercholesterolemia and hypophospholipidemia. the increase in plasma cholesterol as a result of ingestion of Al. Due to Al ingestion caused a preferential activation of receptor sites on the cells which favoured the synthesis of cholesterol in these organs by up-regulating hydroxymethylglutaryl coenzyme A reductase (a rate-limiting enzyme in cholesterol synthesis pathway) since virtually all cells can synthesize cholesterol or Al changes the integrity of the cell membrane thereby causing a constipation of cholesterol in the organs by modification of the composition, structure and stability of the cell membranes. The liver has been shown to be one of the target organs of Al toxicity- induced injury, liver damage is likely to cause some membrane lipids to be released into circulation; metabolism with oxidative stress and lipid peroxidation and reactive oxygen species as hydroxyl and superoxide radicals in liver alter the lipid level in serum (Kolomiytseva, 2011; Ugbaja *et al.*, 2015; Younes *et al.*, 2018).

Al causes toxic effect on biochemical parameters i.e. Cholesterol, Triglycerides It shows an increasing trend because prolonged metallic stress in the experimental animals makes adaptation difficult and creates weakness, anemia. In the field of environmental bio monitoring these parameters have been effectively used as potential biomarkers of Al toxicity in animals and human. This present study was carried out to investigate the effect of A.vera, a well-known medicinal plant with antioxidant properties, on Al-induced alterations in lipid metabolism. In comparison to controls, rats with Al toxicity displayed higher cholesterol, triglyceride, HDL and LDL concentrations in serum (Joshi *et al.*, 2013).

A.vera extract has a wide range of therapeutic applications. *A.vera* gel contains anthroquinones (aloin, aloe-emodin) which may have a variety of properties of antioxidant agent, including the protective role for heavy metal toxicity. Previous studies have also shown that as an antioxidant, plant extracts may improve the pro-oxidant effects of Al (Nada *et al.*, 2013; Jakkala *et al.*, 2016; Mahor *et al.*, 2016).

In this study, the *A.vera* extract proved to be quite effective in lowering the lipid profile (total cholesterol, triglycerides, HDL and LDL) Al toxicity. Al in the blood was significantly reduced due to administration of the *A.vera* extract since it possesses chelating properties. Administration of the *A.vera* extract for 60 and 90 days lead to decreases in cholesterol, triglycerides, HDL and LDL levels in the Al-sulphate exposed animals. This implies an exacerbating effect of *A.vera* on Al toxicity.

CONCLUSION

The present study also validates that *A.vera* extract and aloin was effective in reducing Al toxicity in lipid profile (Total Cholesterol, Triglyceride, HDL and LDL) of treatment 60 and 90 days.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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