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Ameliorating Effect of Ginger Extract (*Zingiber officinale* Roscoe) on Liver Marker Enzymes, Lipid Profile in Aluminium chloride Induced Male Rats

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ABSTRACT

Nowadays, aluminium (Al) exposure has been increasing and it has the potential to be toxic in animal and humans. In recent years, ginger has become a subject of interest because of its beneficial effects on human health. The purpose of the present study to investigate the effect of ginger extract on serum biochemical parameters of aluminium chloride ($AlCl_3$) induced male rats. 24 Wistar rats (6 in each group) distributed into 4 groups. Control group received distilled water as vehicle; In E1 group, animal received $AlCl_3$ orally (100 mg/kg bw), E2 group received $AlCl_3$ (100 mg/kg bw) and simultaneously with ginger extract (50 mg/kg bw) and E3 group received ginger extract alone (50 mg/kg bw) for 60 days. At the end of the experimental period, blood samples were collected for separating the serum for biochemical analyses. The results showed that oral administration of aluminium revealed a significant increase in the levels of serum glucose, total protein, globulin, albumin, urea, uric acid, creatinine, lipid profile and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) and no change was noted in bilirubin. The extract of ginger decreased the activities serum levels of AST, ALT, ALP, lipid profile and all the parameter studied. It was concluded that the consumption of ginger protects the liver and kidney against the Aluminium toxicity. In addition, ginger is capable of improving hyperlipidemia and the impaired kidney functions.

Keywords: AST, ALT, ALP, ginger, lipid profiles.

INTRODUCTION

Metallic compounds on land and water pose potential health hazards to living things. Aluminum is the third most prevalent and the most abundant metal in the earth's crust, representing approximately 8% of total mineral components. [1] It is found in our food product, medicines and also added to drinking water for purification purposes. [2] It is widely used in cosmetics, cookware utensils and containers, food additives, structural material in the construction, automotive, aircraft industries, in the production of metal alloys, in the electric industry and in medicine as antacids, antiperspirants. The other uses of aluminium include decorations, fencing, highway signs, cans, dental crowns and dentures. [3] Human exposure to large quantity of aluminium in nature and its many uses is made through intake of major sources i.e. drinking water, food residues, cooking utensils of packaging, food and beverage and aluminum-containing medications. [4]

It is well established that aluminium as neurotoxicant and the different forms of Al have been shown to be systemic toxicants [5]; nowadays, increased attention is

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being paid to aluminum on various organ systems. Salts of aluminium may bind to DNA, RNA which inhibits enzyme such as hexokinase, acid and alkaline phosphatases, phosphodiesterase and phosphooxydase. [2] Chronic exposition to this element can cause alterations in skeletal, nervous, hematopoietic and respiratory systems. [6-7] Aluminium exposure caused impairments in glucose utilisation, agonist-stimulated inositol phosphate accumulation, free radical-mediated cytotoxicity, lipid peroxidation, reduced cholinergic function, impact on gene expression and altered protein phosphorylation. [8]

The chronic consumption of aluminium produces neuro-toxic effect on humans and animals [9] and has been implicated in several chronic disorders. Liver is considered as the major site for detoxification of toxic metabolites and functions as metabolic centre for various nutrients such as carbohydrates, proteins and lipids [10]; kidney is involved in the elimination of toxic substances. [11] Due to their ability to reabsorb and accumulate metals, kidneys are one of the first target organs of metal toxicity. [12]

Medicinal plants play a key role in human health care. About 80% of the world population relies on the use of traditional medicine, which is predominantly based on plant material. [13] Ginger (*Zingiber officinale* Roscoe) is one of the most commonly used herbal supplements and its substantial use for different medical condition remedies has been documented. Phytochemical studies showed that ginger is rich in a large number of bioactive substances, including gingerols and shogaols [14] and some related phenolic ketone derivatives. Ginger is used medicinally for its hepatoprotective and antioxidant [15], antidiabetic and hypolipidemic [16-17] and anti-obesity [18] effects. The study by Ajith *et al.*, [19] was carried out to evaluate the protective effect of ginger against cisplatin-induced oxidative stress and acute renal failure in kidneys of mice.

Therefore, our purpose for carrying out this study was to investigate on the effects of ginger on Aluminium toxicity of liver marker enzymes, lipid profile and kidney biomarker.

MATERIALS AND METHODS

Chemicals

Aluminium chloride ($AlCl_3$) was obtained from Sigma Chemical Co. (St Louis, Mo, USA). The dose of $AlCl_3$ (100 mg/kg body weight) was selected based on the study by Priya Anand and Bimla Nehru. [20]

Ginger extracts preparation

The ginger rhizomes were thoroughly washed, peeled, pulverized, and completely dried, coarsely, minced and made into fine powder. The ginger powder was suspended in distilled water and each animal received 0.5 ml of ginger suspension at a dose of 50 mg/kg body weight every day. The low dose of ginger used here is with reference to the average daily intake by human beings, learnt from a survey conducted in India. [21]

Animals

Adult albino rats (Wistar strain) weighing 250-260 g were used in this study. Animals were maintained as per the guidelines of the Institute Animal Ethical Committee. All the animals were housed in polypropylene cages at standard husbandry conditions (Temperature: 23 ± 2°C, Relative humidity: 60-70%, 12h: 12h light /dark cycle) and were provided with standard pellets and water *ad libitum*. They were initially acclimatized for the study. The experimental protocols were approved by the Institutional Animal Ethical Committee (IAEC Approval No 140/PHARMA/SCRI, 2013). After 15 days adaptation period the rats were divided into four groups of 6 animals each.

Experimental groups

Group I – Control group: Rats given water orally, daily for 60 days.

Group II – Experimental group I (E1): Rats given $AlCl_3$ (100 mg/kg body weight) orally, daily for 60 days.

Group III – Experimental group II (E2): Rats given $AlCl_3$ 100 mg/kg body weight simultaneously with ginger extract (50 mg/kg body weight) orally, daily for 60 days.

Group IV – Experimental group III (E3): Rats given ginger extract (50 mg/kg body weight) orally, daily for 60 days.

During the treatment period, the feed consumed every day was recorded and the body weight was taken on every day and the percent changes were calculated. 24 hours after the last treatment, blood samples were collected from the retro-orbital sinus of all animals at the end of the experimental period. The collected blood sample was allowed to clot at room temperature for 20 minutes and centrifuged at 3000rpm for 15 minutes to separate the serum. Serum was used to estimate the biochemical parameters; Glucose, total protein, albumin, bilirubin, ALT, AST, ALP, urea, uric acid, creatinine, cholesterol, triglycerides and high density lipoprotein (HDL) were measured by a RA- 50 Semi Auto analyzer (Bayer) using Siemens Diagnostic kits.

Statistical Analysis

All the data were analyzed using *student t' test* and the data were expressed as mean± SEM. The *P* value of <0.05 was considered to be statistically significant against control.

RESULTS

Effects of oral administration of Aluminium chloride and supplementation of ginger extract on rats serum biochemical parameter is illustrated in Table 1, 2, 3 and 4. Administration of aluminium (E1 group) showed significant increase in glucose ($P<0.05$), total protein ($P<0.001$), albumin ($P<0.001$), globulin ($P<0.01$) and no change was observed in bilirubin when compared to control animals. While, the administration of ginger extract with aluminium (E2) and Ginger alone (E3) groups maintained the normal levels of value similar to control in above said parameters except protein and

albumin. Ginger administration significantly decreased the protein (P<0.05) and albumin (P<0.001) level when compared to control (Table 1).

Table 2 represents the activities of serum AST, ALT and ALP in $AlCl_3$ and ginger treated animals. Aluminium administration significantly increased the activities of ALT (P<0.05), AST (P<0.05) and ALP (P<0.05) when compared to control. There was a normal activity of all enzymes were observed in E2 and E3 groups.

Table 3 illustrates the administration of aluminium significantly increased the level of urea (P<0.01), uric acid (P<0.001), creatinine (P<0.05) and the normal level was observed in ginger administered groups. Further, Table 4 shows the levels of cholesterol, triglycerides and HDL in aluminium chloride and ginger treated animals. As results indicates that aluminium administration showed the significant increase in cholesterol, triglycerides and HDL (P<0.05) when compared to control. But the animals treated with ginger with aluminium chloride and ginger alone groups showed normal levels of lipid profile when compared to control.

Table 1: Protective effect of ginger extract on Al induced liver biomarker

Parameter	Control	$AlCl_3$	$AlCl_3$ + Ginger	Ginger alone
Sugar (mg/dl)	86.6 ± 6.397	108.8 ± 6.795*	97.3 ± 9.048	115.5 ± 8.754
T.Protein(g/dl)	6.0 ± 0.167	8.2 ± 0.438***	6.0 ± 0.423	5.5 ± 0.092*
Albumin(g/dl)	2.8 ± 0.054	3.2 ± 0.062***	2.6 ± 0.163	2.4 ± 0.090**
Globulin(g/dl)	3.2 ± 0.188	5.0 ± 0.418**	3.4 ± 0.188	3.1 ± 0.111
Bilirubin (mg/dl)	0.5 ± 0.021	0.5 ± 0.022	0.58 ± 0.047	0.58 ± 0.030

The results are expressed as Mean ± SEM (n = 6) per treatment and respective control groups. Levels of significance values are *p<0.05, **p<0.01, ***p<0.001 compared with control group. P <0.05 considered to be statistically significant.

Table 2: Ameliorative effect of ginger extract on $AlCl_3$ induced liver marker enzymes

Parameter	Control	$AlCl_3$	$AlCl_3$ + Ginger	Ginger alone
Serum ALP U/L	254.3 ± 11.51	306.3 ± 14.95*	263.0 ± 14.05	260.0 ± 19.13
SGOT (AST) U/L	130.6± 2.367	146.1 ± 5.677*	145.1 ± 8.162	136.6 ± 6.067
SGPT (ALT) U/L	50.0 ± 2.007	60.3 ± 3.223*	57.8 ± 3.309	51.6 ± 3.824

The results are expressed as Mean ± SEM (n = 6) per treatment and respective control groups. Levels of significance values are *p<0.05, **p<0.01, ***p<0.001 compared with control group. P <0.05 considered to be statistically significant.

Table 3: Effect of ginger extract on kidney biomarker of $AlCl_3$ induced rats

Parameter	Control	$AlCl_3$	$AlCl_3$ + Ginger	Ginger alone
Urea (mg/dl)	36.0 ± 1.826	49.1 ± 3.313**	42.6 ± 2.163*	39.3 ± 2.274
Uric acid (mg/dl)	1.03± 0.117	1.91 ± 0.111***	1.45 ± 0.364	1.36 ± 0.123
Creatinine(mg/dl)	0.8 ± 0.030	0.7 ± 0.025*	0.68 ± 0.047	0.76 ± 0.049

The results are expressed as Mean ± SEM (n = 6) per treatment and respective control groups. Levels of significance values are *p<0.05, **p<0.01, ***p<0.001 compared with control group. P <0.05 considered to be statistically significant.

Table 4: Protective effect of ginger extract on lipid profiles of $AlCl_3$ induced rats

Parameter	Control	$AlCl_3$	$AlCl_3$ + Ginger	Ginger alone
Cholesterol(mg/dl)	46.0 ± 4.195	62.8 ± 5.062*	51.6 ± 4.487	49.0 ± 4.159
Triglycerides(mg/dl)	102.6 ± 7.577	129.3 ± 8.268*	117.6 ± 11.44	106. 3 ± 8.289
HDL(mg/dl)	43.3 ± 3.254	53.6 ± 2.905*	49.6 ± 4.943	45.8 ± 3.323

The results are expressed as Mean ± SEM (n = 6) per treatment and respective control groups. Levels of significance values are *p<0.05, **p<0.01, ***p<0.001 compared with control group. P <0.05 considered to be statistically significant.

DISCUSSION

Aluminium is one of the trace elements with toxic effect on living organism. However, in recent years, increased attention is being focused on possible adverse effects of aluminium on human health. The primary effects of aluminium on the liver and kidney function are thought to be mediated via damage to cell membranes.

Glucose, protein, globulin, albumin, Bilirubin

The present study reveals that the administration of aluminium chloride significantly enhanced the levels of serum glucose, total protein, albumin, globulin and no change was observed in bilirubin. Significantly elevated plasma glucose levels were observed in alloxan-diabetic rats fed on aluminium chloride when compared with normoglycemic group. [22-23] The rise in blood glucose may indicate, Aluminium toxicity caused a disruption in carbohydrate metabolism, through enhancement of the breakdown of liver glycogen, possibly mediated by an increase in adrenocorticotrophic and glucagon hormones and/or reduced insulin activity. [24] Significantly enhanced level of glycogen in liver was observed in aluminium chloride treated animals. [25]

In this study, administration of ginger extract significantly reduced serum glucose level when compared with aluminium treated group and the reduction was reached to control animals. Pretreatment with ginger inhibited the induced hyperglycemia and hypoinsulinaemia was reported. [26] Ginger juice significantly lowered the blood glucose in diabetic and non-diabetic animals. [27] Furthermore, the blood glucose was lowered after administration of ethanolic extract of ginger in diabetic rats. [28]

However, the increased level of protein was observed in aluminium treated rats of our findings. It might be due to alterations in protein synthesis or metabolism in

the liver. [25] In contrast, aluminium may cause loss of protein in urine due to nephritic syndrome. The decrease in the levels of protein in aluminium treated rats might be due to changes in protein synthesis and / or metabolism. [25]

Total protein levels are rough measures of protein status but reflect major functional changes in liver functions. [29] Phytochemical products including plant herbs and extracts have been used for centuries to promote liver health.

Albumin is the most abundant protein in human plasma, representing 55-65% of total protein. It synthesized in the liver that is dependent on protein intake subject to feedback regulation by the plasma albumin level. Little albumin is filtered through the kidney glomeruli and most of that is reabsorbed by proximal tubule cells and degraded by their lysosomal enzymes into fragment that are returned to the circulation. [30] In our study, there was a significant increase in serum albumin and globulin of rats treated with aluminium when compared to control, indicating poor liver function or impaired synthesis and it may be either in liver cells damage or diminished protein intake. In controversial, aluminium administration significantly decreased the albumin level [30-31] and globulin did not show any change. [31]

In this study, Aluminium administration does not produce any change in bilirubin content. In some other study, increased bilirubin in aluminium administered group was observed and it may be due to the fact that Al exposure can result in its accumulation in the liver which can be toxic to the hepatic tissue at high concentrations and may lead to the increase in bilirubin level. [32] The elevation of the serum levels of the hepatic enzymes and bilirubin are the indicators for impaired liver functions. [33]

AST, ALT, ALP

Transaminases are intracellular enzymes and the most sensitive biomarkers, released into the circulation after damage and necrosis of hepatocytes. [34] Measurement of the activities of marker enzymes, like AST and ALT can be used in the assessment of liver function. [35-36] The current study revealed a significant increase in the activity of ALT and AST in the serum of aluminium treated rats which may be a sign of impaired liver function. The hepatotoxicity was clearly observed through a significant elevation of serum AST, ALT in Al treated rats when compared with the control. It increases in serum when cellular degeneration or destruction occurs in the liver. [37] Exposure to high concentrations of aluminium can result in its accumulation in the liver and in turn to alterations in the liver function. [38]

Exposure of aluminium can result in accumulation in the liver and this metal can be toxic to the hepatic tissue at high concentrations. [39] Exposure to aluminium chloride caused necrosis to the liver with the subsequent release of ALT and AST from the injured hepatic cells to the plasma was reported. [22-25] Aluminium administration causes deteriorations of liver function which reveals increased activity of serum ALT, AST interfered in hepatic dysfunction.

ALP is a membrane bound enzyme related to the transport of various metabolites and it is a sensitive biomarker for liver disease. [40] In our study, aluminium caused a significant elevation in the activity of ALP. Furthermore, [41] reported increase in the activity of ALP can attributed to severe damage to cell membranes or increased permeability of plasma membrane. However, they reported that the increase in the activity of ALP in blood might be due to the necrosis of liver, kidney and lung. [42] In addition, exposure to aluminium increased the level of ALP which is due to increased osteoblastic activity, provoked by the disturbance of bone formation. [43] This suggests that chronic aluminium exposure induce hapatotoxicity manifested by elevation of liver function enzymes.

Several reports which showed the protective effects of ginger extract or its constituents, through their antioxidant properties and improve the hepatic dysfunctions and hepatic damage that induced by hepatotoxicants, CCl_4 and acetaminophen. [44, 19] Result of this study demonstrates that ginger extract lowered the elevated levels of the serum AST, ALT and ALP in ginger administered group when compared to the aluminium treated group. These may be attributed to ginger components which may stabilize hepatocytes plasma membrane and prevent delivery of AST and ALT to the extracellular fluid. [19] Ginger administration lowered the enhanced activity of AST and ALT in cisplatin treated animals [45] Reports by [46], who stated that ginger was used to lowers the serum glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) levels.

The observed elevation in the enzymes (AST, ALT and ALP) in aluminium administered group may be due to liver dysfunction and disturbance in the biosynthesis of these enzymes which all are indicative of liver damage and thus impaired liver function. Supplementation with ginger in $AlCl_3$ treated rats resulted in normalized activity in ALT, AST, ALP indicating improved liver function and protection against aluminium induced toxicity. This activity shows the hepatoprotective effect of ginger in aluminium treated rats.

Urea, Uric acid, Creatinine

In our findings, the elevation in serum urea, uric acid and creatinine levels in $AlCl_3$ exposed rats is considered as a significant indicator of renal dysfunction. The results are in accordance with other previous findings, who reported that aluminium accumulation in kidney promotes degeneration in renal tubular cells, inducing neprhrotoxity. [47-48] Further, aluminium treatment increased the concentration of urea in plasma [49]; and it may be due to its effect of aluminium on liver function, as urea is the end product of protein catabolism, and /or referred to kidney

dysfunction. Also this finding was in accordance to Szilagyi *et al.*, [43], who reported that alterations in serum of animals treated with aluminium and it was related to metabolic disturbances (e.g. renal function, cation-anion balance).

Ginger and ginger oil decreases the level of uric acid from cadmium treated rats. [50] This reduction could be attributed to the fact that ginger contains high content of antioxidants. Therefore, it was concluded that ginger may have a beneficial effect for urea removal from plasma. Thus, it may be considered as a therapeutic herb to manage renal function in patient with uremia but with a little reducing effect on creatinine levels. [51] Ethanol extract of ginger alone and in combination with vitamin E partially ameliorated cisplatin-induced nephrotoxicity and renal failure. [19] This may be due to the presence of polyphenols and flavonoids in ginger extract might be responsible for the antioxidant nephroprotective activities and the reduction of serum urea and creatinine levels. [19] Furthermore, ethanolic extract of ginger lowered the blood urea level in diabetic rats. [28] In this study, the effect of ginger was assessed by the determination of the levels of serum creatinine, urea and uric acid, and it revealed that the administration of ginger extract to the aluminium chloride treated animals by normalized the levels of serum creatinine, urea and uric acid.

Lipid profile

In present study, oral administration of $AlCl_3$ caused the increase in serum cholesterol, triglycerides and HDL which indicates a loss of membrane integrity. [52] This may attribute the damage in the liver. Aluminium exposure may lead to disturbance of lipid metabolism and an elevation of serum cholesterol. [39]

Ginger has significantly reduced the serum total cholesterol and triglycerides and increase the HDL in pathogenic diabetic rats. [53] It has been suggested that the aqueous extract of ginger might inhibit the intestinal absorption of dietary fat by inhibiting its hydrolysis. [54] Study by Sharma *et al*., [55] who reported that ginger have showed that the hypolipidemic effect. Ginger acts as a hypolipidemic agent in cholesterol-fed rabbits [56] and reported that an ethanolic extract of ginger prevent hypercholesterolemia and development of atherosclerosis in cholesterol-fed rabbits. [56] Ginger treatment significantly decreased both serum cholesterol and triglycerides reported by Akhani *et al*., [26] Ginger decreased the serum and liver cholesterol in hypercholesterolemic rats. [57]

Our study showed that the treatment of rats with ginger and aluminium and ginger alone groups normalized the levels of cholesterol, triglycerides and HDL. This may be due to ginger inhibit hepatic fatty acid synthesis by lowering key enzymes activities in supplying substrates, thus reducing cholesterol, HDL and triglyceride levels in serum. Further, it was confirmed that the hypocholesterolaemic effect of ginger could have possibly resulted from the inhibition of cellular cholesterol biosynthesis after the consumption of the ginger extract. [58] Ginger was found to have hypocholesterolemic effects and causes decrease glucose in blood, serum total cholesterol, and serum alkaline phosphatase in adult male rats. [53]

This study revealed that aluminium administration markedly enhanced the levels of serum glucose, total protein, albumin, urea, uric acid, creatinine, liver marker enzymes and maintained their levels similar to normal. This indicates improvement in the function of the liver and the kidney of the aluminium treated rats. Also the beneficial effects of ginger extract on serum lipids and reduced the levels of cholesterol, triglycerides and HDL is probably indicative of hepato-protective effect of ginger extract in $AlCl_3$ administration rats. Overall, the present study confirmed that aluminium and ginger act against each other and ginger normalize the liver and kidney functions.

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