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Research Article
Antioxidant and Ameliorative Effects of Zingiber Officinale Against Aluminum Chloride Toxicity

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Abstract

Objective: The present study was performed to assess the antioxidant capacity of different doses of *Zingiber officinale* extract and its efficacy in alleviating the biochemical alterations induced by aluminum chloride in rabbits. **Material and Methods:** Twenty-eight male rabbits were allocated into four groups (7 rabbits in each); Group I: Served as normal control, Group II: Treated with aluminum chloride ($AlCl_3$) (150 mg kg^{-1} b.wt.), Group III: Treated with $AlCl_3$ and *Zingiber officinale* extract (100 mg kg^{-1} b.wt.) and Group IV: Treated with $AlCl_3$ and *Zingiber officinale* extract (200 mg kg^{-1} b.wt.). Rabbits in groups (III, IV) were orally treated daily with *Zingiber officinale* extract for 4 weeks. Data was analyzed using SPSS. **Results:** Aluminum exposure caused a significant elevation of BUN, creatinine, lipid profile, ALT, ALP, TNF-α and amylase activity. All these parameters showed the reverse trend following oral *Zingiber officinale* treatment. Aluminum exposure showed a significant decrease in hepatic GSH and catalase activity. Treatment with *Zingiber officinale* extract significantly reversed aluminum effects, in the level of GSH content and hepatic catalase activity. **Conclusion:** *Zingiber officinale* is effective in alleviating the oxidative stress and inflammation and is thus effective in improving lipid profile and hepatotoxicity and nephrotoxicity in $AlCl_3$ administration.

Key words: Aluminum chloride, zingiber officinale, GSH, antioxidant, catalase, TNF-α, ALT

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Plant derived products have been used for medicinal purposes for centuries and also being used in our daily food intake. Drugs of plant source are known to play an important role in the controlling of many diseases. Ginger is one of the world's best known spices. Ginger (*Zingiber officinale*, Family: *Zingiberaceae*), an herbal drug, produced in South-East Asia and then became prevalent in many ecological areas. Ginger (*Zingiber officinale*) is one of the most widely used spices for the seasoning of food worldwide[1]. The major chemical ingredients of the ginger rhizome are essential volatile oil and non-volatile pungent compounds, such as gingerols, shogaols, paradols and zingerone[2]. The pharmaceutical importance of ginger is due to the presence of alkaloids, glycosides, resins, volatile oils, gums and tannins etc. The active ingredients usually remain concentrated in the storage organs of the plants[3].

Aluminum is a plentiful element in the earth's layer and is widely distributed throughout the environment. Currently, aluminum salts are included in greasepaints, food handling and packing also used in various nonprescription drugs[4]. Several authors designate that an excessive and prolonged aluminum exposure directly affects hematological and biochemical parameters, interrupts lipid peroxidation and diminishes the activities of the antioxidant enzymes in plasma and tissues of animals models[5]. This impairment of the physiological pro-oxidant/antioxidant balance causes oxidative stress.

The serum biochemical profile is a key index that reveals the main organ functions. The liver and kidney are the main organs used for metabolism and excretion. Liver, the vital organ involved in numerous metabolic functions and detoxification of lethal substances, is a frequent target of a number of toxicants. The disruption in the transport function of the hepatocytes as a result of hepatic damage causes the outflow of enzymes from the liver cytosol into the blood due to altered permeability of membrane[6].

The kidney is a complex organ for its role as an organ of excretion, reabsorption and general homeostasis, has an extensive blood flow, receiving approximately 1.2 L min^{-1} and filtering on average 125 mL plasma min^{-1}. The processes of reabsorption and secretion, particularly of organic acids and bases, may, however, lead to the accumulation of toxins within the tubules, making this vital organ more susceptible to toxic insults than other organs[7].

The aim of the present study is to appraise the phytochemical characterization of the ethanol extract of ginger and evaluate the antioxidant, anti-inflammatory, hepatoprotective, hypolipidemic and nephroprotective effects against $AlCl_3$ toxicity in rabbits.

MATERIALS AND METHODS

Chemicals: Aluminium chloride anhydrous ($AlCl_3$), M.W. 133.34 was purchased from Aldrich Chemical Company (Milwaukee, WI, USA). All other chemicals and reagents used were of analytical grade.

Plant materials: Ginger (*Zingiber Officinale*) was purchased from a local market of the herbs in Hail city, KSA.

Preparation of the extract: Ten gram of ginger powder were placed in the round bottle flask; 100 mL of ethanol (70%) were added to the flask. After soaking 12 h the extract was filtered by using Whatman filter paper No. 31 the filtrate so obtained was placed in the oven to facilitate evaporation of ethanol content[8]. The crude extract was used for further investigation for antioxidant properties.

Phytochemical examination: The Phytochemical screening for the presence of alkaloids, tannins, flavonoids, phlobatannins, anthraquinone, coumarins, carbohydrates and terpenoids were carried out according to the methods of Harborne[9] and Trease and Evans[10].

Determination of antioxidant activity of ginger extract

Determination of total antioxidant capacity: Total antioxidant capacity of extract was assayed by the phosphomolybdenum method as described by Prieto *et al.*[11].

Determination of reducing power: The reducing power of extract was determined by the method of Oyaizu[12].

Experimental animals: Male white rabbits (Initial weight of 1.00±0.27 kg) were used. All animals received humane care in compliance with the guidelines of the Ethics Committee of the Experimental Animal Care Society, College of Medicine, University of Hail, Saudi Arabia. Animals were individually kept in stainless steel cages. Feed and water were provided *ad libitum*. Rabbits were fed with pellets consisted of Alfalfa pellets 35%, maize broke 15%, barley 15%, white sorghum 10%, sunflower white 5%, sunflower black 5%, wheat 10% and safflower 5%.

Design of the experiment: After one week of acclimatization period, 28 mature male rabbits were randomly divided into four equal groups of seven rabbits each. Group I: Served as normal control. Group II: Administrated with aluminum chloride ($AlCl_3$) (150 mg kg^{-1} b.wt.) were given by intraperitoneal injection[13]. Group III: administrated with $AlCl_3$ (150 mg kg^{-1} b.wt.) by intraperitoneal injection and ginger extract (100 mg kg^{-1} b.wt.) by oral gavage. Group IV: administrated with $AlCl_3$ (150 mg kg^{-1} b.wt.) by intraperitoneal injection and ginger extract (200mg kg^{-1} b.wt.) by oral gavage. Rabbits in groups (3, 4) were orally treated daily with ginger extract for 4 weeks. The doses of ginger and $AlCl_3$ were calculated according to the animal's body weight on the week before dosing.

By the end of the experimental periods (4 weeks), the rabbits were sacrificed at fasting state. The blood samples were collected and allowed to coagulate at room temperature and centrifuged at 3000 rpm for 10 min. The clear, non-haemolysed supernatant sera were quickly separated and stored at -20°C for subsequent biochemical analysis.

Liver tissues were quickly excised, weighed and homogenized in a saline solution (0.9%) and centrifuged at 3000 rpm for 15 min and the supernatant were stored at -20°C for the assay of biochemical parameters related to oxidative stress.

The determination of hepatic catalase activity was assayed as described by Cohen *et al*.[14] and hepatic content of reduced GSH was assayed by the spectrophotometric technique according to Sedlack and Lindsay^{-1} b.wt.[15].

The following biochemical tests were performed, serum ALT and ALP activities by using clinical test kits (UDI/KSA); serum BUN according to Patton and Crouch[16] and serum creatinine level as per the method of Henry[17]. Serum totalcholesterol, triglyceride and HDL-cholesterol were assayed according to Allain *et al*.[18], Jacobs and Van Denmark[19] and Gordon and Gordon[20], respectively, by using clinical test kits (UDI/KSA). Serum LDL-cholesterol and vLDL-cholesterol levels were calculated according to the following formula:

$$\text{LDL-cholesterol} = \text{TC-(TG/5)-HDL-cholesterol}^{21}$$

And:

$$\text{VLDL-C} = \text{TG/5, respectively}^{22}$$

Serum TNF-α was determined by using specific ELISA kit (R and D system) following the manufacturer's instructions.

Statistical analysis: The Statistical Package for the Social Sciences (SPSS for WINDOWS, version 18.0; SPSS Inc, Chicago) was used for the statistical analyses. Comparative analyses were conducted by using the general linear models procedure (SPSS Inc). Values of $p>0.05$ were considered statistically insignificant, while values of $p<0.05$ were considered statistically significant, values of $p<0.01$ were considered statistically highly significant and $p<0.001$ were considered statistically very highly significant.

RESULTS

Preliminary phytochemical examination: The crude extract of ginger was examined for the most common phytochemical ingredients of medicinal plants for which hepatoprotective activity of other plants has been ascribed. These included saponins, tannins, flavonols, glycosides, terpenoids, alkaloids, reducing sugars, steroids, proteins, fats and polyphenols. The results showed that the most abundant phytochemicals were tannins, alkaloids, phenols, vitamins, flavonoids and terpenoids as shown in Table 1.

Total antioxidant activity and reducing power: The total antioxidant activity is based on reduction of molybdate [VI] to molybdate [V] at acid pH and formation of a green phosphate complex, which can be quantified spectrophotometrically at 695 nm. In the current study, as shown in Fig. 1, total antioxidant capacity of ginger extracts was demonstrated. The results revealed that the antioxidant activity of the ginger extracts increased with increasing concentration of the ginger extract.

On the other hand, the reducing power assays. Increased absorbance of the reaction mixture indicates increased reducing power. Figure 2 shows the dose response for the reducing power of the extract of ginger. The reducing power values were found to be correlated with the concentration of each extract.

Biochemical analysis: As shown in Fig. 3 $AlCl_3$ -administered rabbits showed significantly ($p<0.001$) elevation in serum ALT and ALP activities as compared to normal control group.

Table 1: Phytochemical screening of ethanolic ginger extract

Chemical constituents	Ethanolic ginger extract (EGE)
Alkaloids	++
Tannins	+++
Flavonoids	+++
Phlobatannins	+
Anthraquinone	-
Coumarins	++
Carbohydrates	+
Terpenoids	++

+: Presence, +++: Presence in large quantity, –: Absence

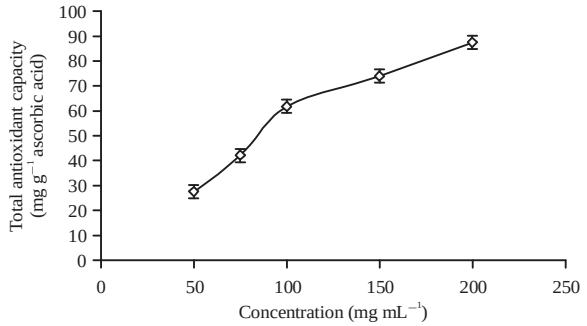

Fig. 1: Total antioxidant capacity of ginger extract
Data are expressed as (Mean±SD)

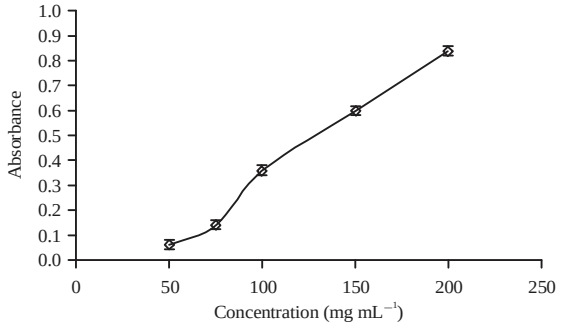

Fig. 2: Total reduction capacity of ginger extract
Data are expressed as (Mean±SD)

Whereas, a significant decrease ($p<0.001$) in the serum ALT and ALP activities after treatment by either dose of ginger extract when compared with $AlCl_3$ treated control group.

Also, as shown in Fig. 3 $AlCl_3$ administered rabbits showed markedly ($p<0.001$) increased in the level of TNF-α when compared with control group. Treatment of $AlCl_3$ intoxicated rabbits with either dose of ginger extract (100 or 200 mg mL^{-1}) markedly ($p<0.001$) decrease the level of TNF- α as compared to $AlCl_3$ control group.

On the other hand, the serum creatinine and BUN levels in the $AlCl_3$ treated control group showed a significant ($p<0.001$) increase when compared to the normal control one. The oral administration of ginger extract with either dose produced a marked ($p<0.001$) improvement in the altered serum creatinine and BUN levels of the $AlCl_3$ intoxicated group Fig. 4.

Data summarized in Table 2 show the effect of $AlCl_3$ administration and treatment with *ginger* extract on lipid profile. The administration of $AlCl_3$ produced marked elevation of lipid profile as showed by the significant ($p<0.001$) elevation in serum total cholesterol, triglycerides, vLDL- cholesterol and LDL-cholesterol levels. Concurrent oral administration of either dose of ginger extract significantly

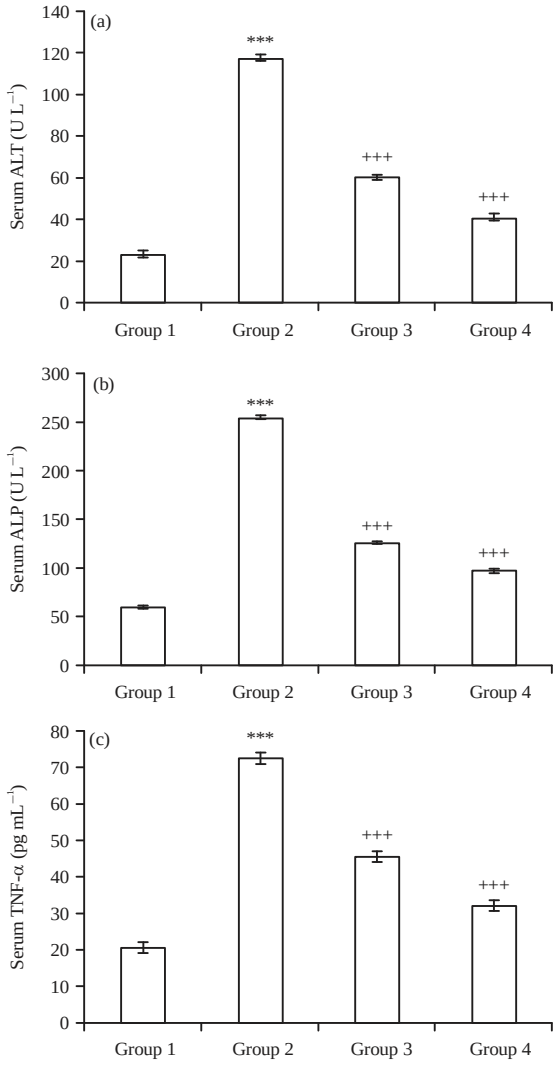

Fig. 3(a-c): Effect of ginger extract on serum ALT and ALP activities and TNF-α level
Results are expressed as Mean±SEM. ***$p<0.001$ versus normal control. $^{+++}p<0.001$ versus $AlCl_3$ control

decreased the elevated levels of serum total cholesterol, triglycerides, vLDL-cholesterol and LDL-cholesterol levels when compared with the $AlCl_3$ control group. In contrast, a significant ($p<0.001$) decline in the level of HDL- cholesterol was observed in $AlCl_3$-treated group as compared to normal control one. On the other hand, there was a significant ($p<0.001$) increase in HDL-cholesterol in ginger treated rabbits when compared to $AlCl_3$- treated group Table 2.

On the contrary, $AlCl_3$ intoxicated rabbits showed significantly ($p<0.001$) decrease in the hepatic content of GSH and catalase activity as compared to normal control group. On the other hand, ginger extract treatment with high dose (200 mg mL^{-1}) showed a significant ($p<0.01$) elevation in

Table 2: Effect of ginger extract (GE) on serum levels of lipid profile

Parameters (mg dL^{-1})	Group I	Group II	Group III	Group IV
Total cholesterol	102.00±2.95	221.14±2.55***	152.29±3.48^{+++}	103.86±3.22^{+++}
Triglycerides	145.29±3.60	246.00±2.32***	172.57±3.56^{+++}	121.57±2.32^{+++}
HDL-cholesterol	37.76±1.34	20.71±0.92***	23.57±0.78	31.00±0.93^{+++}
LDL-cholesterol	35.19±3.48	151.23±2.96***	94.20±3.43^{+++}	48.40±3.35^{+++}
v LDL-cholesterol	29.06±0.72	49.20±0.46***	34.51±0.71^{+++}	24.31±0.46^{+++}

***p<0.001 versus normal control, $^{+++}$p<0.001 versus $AlCl_3$ control, data are expressed as (Mean±SEM)

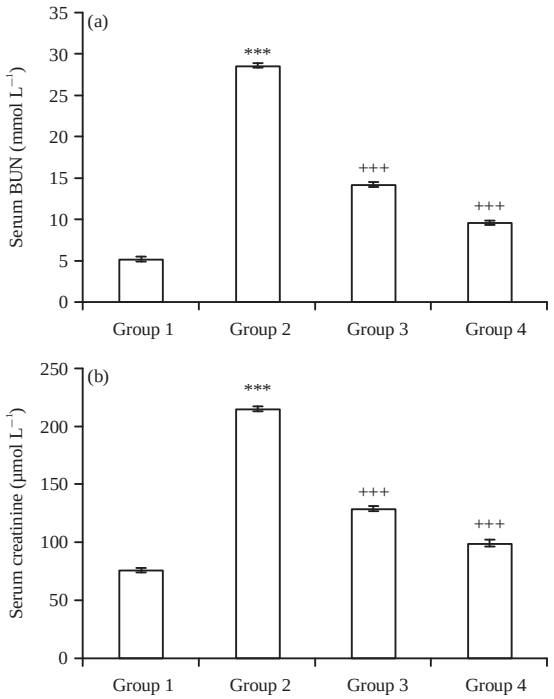

Fig. 4(a-b): Effect of ginger extract on serum BUN and creatinine levels

Results are expressed as Mean±SEM. ***p<0.001 versus normal control. $^{+++}$p <0.001 versus $AlCl_3$ control

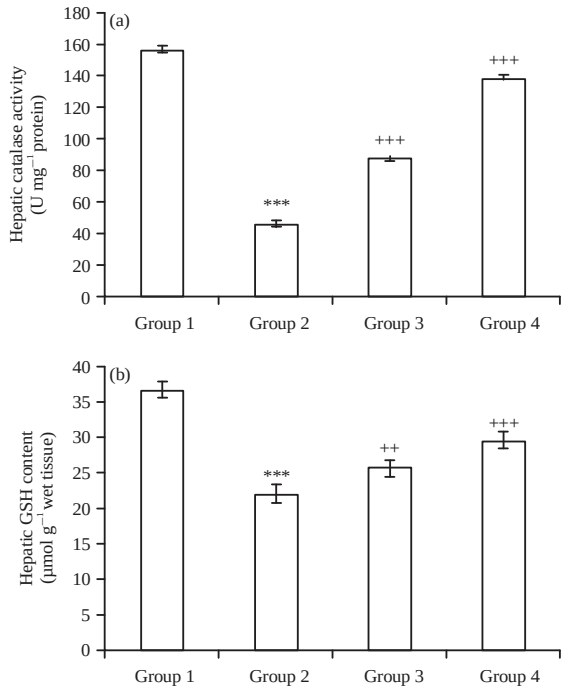

Fig. 5(a-b): Effect of ginger extract on hepatic catalase activity and hepatic reduced glutathione content in $AlCl_3$-induced toxicity

Results are Mean±SEM. ***p<0.001 versus normal control. $^{+++}$p< 0.001; $^{++}$p<0.01 versus $AlCl_3$ control

hepatic catalase activity and a significant (p<0.01) improvement in hepatic content of GSH when compared with $AlCl_3$ control one Fig. 5.

DISCUSSION

The exploration of medicinal properties of various plants is paying attention, since the last couple of decades due to their forceful pharmacological activities, appropriateness, economic feasibility and low toxicity. Recently, there has been an upgrading of finding natural antioxidants, from plant materials to replace synthetic antioxidants because the previous ones are accepted as green medicine to be safe for health controlling whereas, the latter ones are quite unsafe and their toxicity is a matter of concern[23]. Natural antioxidants belonging to the higher plants especially the typical compounds, such as vitamins, carotenoids and phenolics reveal antioxidant activity and they lessen disease-related chronic health problems. It has been denounced that there is an inverse affiliation between antioxidative status and incidence of human diseases such as malignancy, caducity, neurodegenerative disease and atherosclerosis[24].

In the current study, Phytochemical screening of ethanolic ginger extract showed the presence of alkaloids, phlobotannins, flavonoids, carbohydrates, tannins, coumarins and terpenoids and absence of anthraquinone Table 1. Similar results were obtained in the study by which showed that the phytochemical screening of ginger shows the presence of carbohydrates, alkaloids, saponins, flavonoids, polyphenols and reducing sugars in both aqueous and

petroleum ether extracts[25,26]. As a rich source, Phytochemical and mineral contents ginger can be considered a potential source of medicinal herb.

Antioxidant activity of ginger extract was assessed by determination of total antioxidant capacity and determination of reducing power. Antioxidant compounds and their activity are highly dependent on concentration of the solvent and type of the solvent[27].

Our results revealed that the antioxidant capacity of the ginger extract increased with increasing concentration of the ginger extract. Regarding, the reducing power assay, there are dose response for the reducing power of the ginger extract where increased absorbance of the reaction mixture indicates increased reducing power. Our results are in agreement with Maizura *et al.*[28] and Eleazu *et al.*[29]. Moreover, previous studies reported that the reducing power of bioactive compounds is associated with antioxidant activity[30].

Transaminases are intracellular enzymes, released into the circulation after injury of hepatocytes[31]. ALT is the most specific indicator of hepatic injury and hepatocellular necrosis. This liver enzyme catalyzes the transfer of α-amino group alanine to the alpha-ketoglutaric acid[32].

Exposure to high concentrations of Al can result in its accumulation in the liver and in turn to alterations in the liver function. The current study provoked significant alterations in the activity of ALT in the blood of $AlCl_3$-treated rabbits which may be a sign of impaired liver function and disorder in the biosynthesis of these enzymes with modulation in the permeability of the liver membrane. These results are in concordance with findings of Geyikoglu *et al.*[33], Ighodaro *et al.*[34] and Attyah and Ismail[35].

ALP is a membrane-bound enzyme related to the transport of several metabolites so it is a profound biomarker for liver disease. In the present study, $AlCl_3$ caused a significant elevation in the activity of ALP. This observation is in concordance with the earlier findings of Geyikoglu *et al.*[33] and Ighodaro *et al.*[34]. On the other hand, oral administration of $AlCl_3$ treated rabbits by ginger extract causes a reduction in the serum ALT and ALP activity. These may be attributed to ginger components which may stabilize hepatocytes plasma membrane and prevent transmission of ALT to the extracellular fluid. This finding is in agreement with results of Thomson *et al.*[36].

The current findings showed that administration of $AlCl_3$ has induced kidney injury and glomerular dysfunction evidenced by the elevated circulating creatinine and blood urea nitrogen levels. These measurements are often regarded as reliable markers of kidney damage[37] and indicate the loss of a majority of kidney function[38]. These elevated assessments are in agreement with the studies of Ahmed *et al.*[32] and Geyikoglu *et al.*[33]. Concomitant administration of either dose of *ginger* extract significantly decreased circulating creatinine and blood urea nitrogen levels. These results are in agreement with the previous studies of Gehan and Amin[39] and Abdalla *et al.*[40], who states that presence of polyphenols and flavonoids in the ginger extract might be responsible for the antioxidant nephroprotective activities and the reduction of serum urea and creatinine levels.

$AlCl_3$ administration induced a significant increase in serum level of TNF-α which represents an important mediator of inflammatory tissue damage. Studies presented evidence that nephrotoxicants could provoke an inflammatory response leading to organ injury[41]. The significantly elevated TNF-α reflects the degree of inflammation. In a dose-dependent manner, concurrent administration of *ginger* extract produced pronounced decline in serum TNF-α, indicating its anti-inflammatory efficacy. This finding is consistent with that of recent studies on ginger supplementation on anti-inflammatory mediators. Naderi *et al.*[42] found that ginger extract had an anti-inflammatory effect on elderly knee osteoarthritis patients. Active ingredients of ginger extract decreased TNF-α expression by inhibiting I-kappa B alpha phosphorylation, nuclear factor-kappa B (NF-k B) nuclear activation and protein kinase C-alpha translocation.

$AlCl_3$ administration resulted in dyslipidaemic changes, as illustrated by increasing total cholesterol, triglycerides, vLDL-cholesterol and LDL-cholesterol and a decrease in serum level of HDL-cholesterol. Concurrent oral supplementation of either doses of ginger extract significantly decreased serum levels of total cholesterol, triglycerides, vLDL-cholesterol and LDL-cholesterol and increased serum HDL-cholesterol levels. The lipid lowering effect of ginger may come from inhibition of hepatic fatty acid synthesis by lowering key enzymes activities in supplying substrates, thus reducing serum levels of cholesterol and triglyceride. Our finding is in line with a previous report[43,44]. It was recommended by Hasona *et al.*[45] that presence of phytoconstituents like flavonoid inhibits fat accumulation and ameliorates dyslipidemia and increased antioxidant defense.

Oxidative stress plays a key contributory role in many diseases including liver damage[46]. The body has anti-oxidative mechanisms to alleviate oxidative molecules, control lipid oxidation and preserve these radicals in balance. When free radicals are produced, the body preserves itself from these radicals by endogenous antioxidants[47]. Catalase enzyme is known to play an important role in scavenging reactive oxygen species. CAT decreases the H_2O_2 into water and oxygen to prevent oxidative stress and in maintaining cell homeostasis. Administration of $AlCl_3$ reduced the activity of antioxidant enzyme catalase in the liver tissue. The reduction

in the activity of catalase enzyme reflects the reduced synthesis of this enzyme due to higher intracellular concentrations of Al and/or accumulation of free radicals and that in agreement with Newairy *et al*.[44].

The administration of ginger extract with $AlCl_3$ repaired the oxidant/antioxidant balance as reflected by the stimulation of the antioxidants enzyme catalase in the liver. These results are in agreement with Kalaiselvi *et al*.[43] who showed that Ginger has an ability to increase the intracellular activities of catalase and have synergistically conflict oxidative stress by scavenging free radicals and boosting endogenous antioxidant activities. This may be related to its active components which motivate free radical scavenging activities[48].

Glutathione is an important biofactor produced in all living cells. It forms an important substrate for GPX, GST and several other enzymes. In addition, GSH plays an important role in hepatic antioxidation and drug metabolism. High intracellular GSH levels lessen damage and stimulate better persistence under conditions of oxidative stress[49]. Reduced glutathione (GSH) constitutes the first line of defense against free radicals. $AlCl_3$ treatment resulted in a decrease in the hepatic GSH content. These observations are similar to the data reported by Kalaiselvi *et al*.[43].The administration of ginger extract plus $AlCl_3$ the GSH content was increased. These results are in agreement with Kalaiselvi *et al*.[43] and Reddy *et al*.[50].

CONCLUSION

Based on the findings of this study, it was accomplished that ginger extract showed promising antioxidant, anti-inflammatory, hepatoprotective, hypolipidemic and nephroprotective effects against $AlCl_3$ toxicity. The previous ameliorative properties of ginger make it useful as a therapeutic candidate for the treatment of human diseases.

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REFERENCES

1. Li, Y., V.H. Tran, C.C. Duke and B.D. Roufogalis, 2011. Gingerols of *Zingiber officinale* enhance glucose uptake by increasing cell surface GLUT4 in cultured L6 myotubes. Planta Med., 78: 1549-1555.
2. Butt, M.S. and M.T. Sultan, 2011. Ginger and its health claims: Molecular aspects. Crit. Rev. Food Sci. Nutr., 51: 383-393.
3. Himesh, S., S. Sarvesh., P.S. Sharan and K. Mishra, 2011. Preliminary phytochemical screening and HPLC analysis of flavonoid from methanolic extract of leaves of *Annona squamosa*. Int. Res. J. Pharm., 5: 242-246.
4. Pal, A., M. Choudhary, D.K. Joshi, S. Tripathi and D.R. Modi, 2012. Alteration in thyroid hormones and vitamins as early markers of aluminum induced neurodegeneration in rats. Int. J. Res. Pharm. Sci., 2: 137-150.
5. Lukyanenko, L.M., A.S. Skarabahatava, E.I. Slobozhanina, S.A. Kovaliova, M.L. Falcioni and G. Falcioni, 2013. *In vitro* effect of AlCl3 on human erythrocytes: changes in membrane morphology and functionality. J. Trace. Elem. Med. Biol., 27: 160-167.
6. Bouasla, I., A. Bouasla, A. Boumendjel, A. El Feki and M. Messarah, 2014. Antioxidant effect of alpha lipoic acid on hepatotoxicity induced by aluminium chloride in rats. Int. J. Pharm. Sci. Rev. Res., 29: 19-25.
7. Barbier, O., G.T. Jacquille, M. Tauc, M. Cougnan and P. Poujeol, 2005. Effect of heavy metals on and handling by, the kidney. Nephron Physiol., 99: 105-110.
8. Ajith, T.A., U. Hema and M.S. Aswathy, 2007. *Zingiber officinale* roscoe prevents acetaminophen-induced acute hepatotoxicity by enhancing hepatic antioxidant status. Food Chem. Toxicol., 45: 2267-2272.
9. Harborne, J.B., 1984. Phytochemical Methods a Guide to Modern Technique of Plant Analysis. 2nd Edn., Chapman and Hall, London, pp: 282-311.
10. Trease, G.E. and W.C. Evans, 1989. Phenols And Phenolic Glycosides. In: Textbook of Pharmacognosy, Trease, G.E. and W.C. Evans, Balliese, Tindall and Co Publishers, London, pp: 338-343.
11. Prieto, P., M. Pineda and M. Aguilar, 1999. Spectrophotometric quantitation of antioxidant capacity through the formation of a phosphomolybdenum complex: Specific application to the determination of vitamin E. Anal. Biochem., 269: 337-341.
12. Oyaizu, M., 1986. Studies on products of browning reaction. Antioxidative activities of products of browning reaction prepared from glucosamine. Jpn. J. Nutr. Dietetics, 44: 307-315.
13. Krasovskii, G.N., L.Y. Vasukovich and O.G. Chariev, 1979. Experimental study of biological effects of leads and aluminum following oral administration. Environ. Health Perspect., 30: 47-51.
14. Cohen, G., D. Dembiec and J. Marcus, 1970. Measurement of catalase activity in tissue extracts. Ann. Biochem., 34: 30-38.
15. Sedlak, J. and R.H. Lindsay, 1968. Estimation of total, protein-bound and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal. Biochem., 86: 271-278.
16. Patton, C.J. and S.R. Crouch, 1977. Spectrophotometric and kinetics investigation of the Berthelot reaction for the determination of ammonia. Anal. Chem., 49: 464-469.

17. Henry, R.J., 1974. Determination of Serum Creatinine: Clinical Chemistry Principles and Technics. 2nd Edn., Harper and Row, USA., Pages: 525.
18. Allain, C.C., L.S. Poon, C.S.G. Chan, W. Richmond and P.C. Fu, 1974. Enzymatic determination of total serum cholesterol. Clin. Chem., 20: 470-475.
19. Jacobs, N.J. and P.J. van Denmark, 1960. Enzymatic determination of serum triglyceride. J. Arch. Biochem., 88: 250-255.
20. Gordon, T. and M. Gordon, 1977. Enzymatic method to determine the serum HDL-cholesterol. Am. J. Med., 62: 707-708.
21. Friedewald, W.T., R.I. Levy and D.S. Fredrickson, 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem., 18: 499-502.
22. Tietz, N.W., 1995. Clinical Guide to Laboratory Tests. Saunders Co., USA.
23. Patel, R.V., P.R. Patel and S.S. Kajal, 2010. Antioxidant activity of some selected medicinal plants in Western Region of India. Adv. Biol. Res., 4: 23-26.
24. Morales, G., A. Paredes, P. Sierra and L.A. Loyola, 2008. Antioxidant activity of 50% aqueous-ethanol extract from *Acantholippia deserticola*. Biol. Res., 41: 151-155.
25. Bhargava, S., K. Dhabhai, A. Batra, A. Sharma and B. Malhotra, 2012. *Zingiber officinale*: Chemical and phytochemical screening and evaluation of its antimicrobial activities. J. Chem. Pharm. Res. 4: 360-364.
26. Osabor, V.N., F.I. Bassey and U.U. Umoh, 2015. Phytochemical screening and quantitative evaluation of nutritional values of *zingiber officinale* (Ginger). Am. Chem. Sci. J., 8: 1-6.
27. Turkmen, N., F. Sari and Y.S. Velioglu, 2006. Effects of extraction solvents on concentration and antioxidant activity of black and black mate tea polyphenols determined by ferrous tartrate and Folin-Ciocalteu methods. Food Chem., 99: 835-841.
28. Maizura, M., A. Aminah and W.M.W. Aida, 2011. Total phenolic content and antioxidant activity of kesum (*Polygonum minus*), ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) extract. Int. Food Res. J., 18: 529-534.
29. Eleazu, C.O., C.O. Amadi, G. Iwo, P. Nwosu and C.F. Ironua, 2013. Chemical composition and free radical scavenging activities of 10 elite accessions of ginger (*Zingiber officinale* Roscoe). J. Clin. Toxicol., Vol. 3. 10.4172/2161-0495.1000155.
30. Shiddhuraju, P., P.S. Mohan and K. Becker, 2002. Studies on the antioxidant activity of Indian Laburnum (*Cassia fistula* L.): A preliminary assessment of crude extracts from stem bark, leaves, flowers and fruit pulp. Food Chem., 79: 61-67.
31. Sallie, R., J.M. Tredger and R. Williams, 1991. Drugs and the liver. Part 1: Testing liver function. Biopharm. Drug. Dispos., 12: 251-259.
32. Ahmed, M.B., N.A. Hasona and A.H. Selemain, 2008. Protective effects of extract from dates (*Phoenix dactylifera* L.) and ascorbic acid on thioacetamide-induced hepatotoxicity in rats. Iran. J. Pharm. Res., 7: 193-201.
33. Geyikoglu, F., H. Turkez, T.O. Bakir and M. Cicek, 2013. The genotoxic, hepatotoxic, nephrotoxic, haematotoxic and histopathological effects in rats after aluminium chronic intoxication. Toxicol. Ind. Health, 29: 780-791.
34. Ighodaro, O.M., J.O. Omole, O.A. Ebuehi and F.N. Salawu, 2012. Aluminium-induced liver and testicular damage: effects of Piliostigma thonningii methanolic leaf extract. Nig. Q. J.Hosp. Med., 22: 158-166.
35. Attyah, A.M. and S.H. Ismail, 2012. Protective effect of ginger extract against cisplatin-induced hepatotoxicity and cardiotoxicity in rats. Iraqi. J. Pharm. Sci., 21: 27-33.
36. Thomson, M., K.K. Al-Qattan, S.M. Al-Sawan, M.A. Alnaqeeb, I. Khan and M. Ali, 2002. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostaglandins Leukotrienes Essent. Fatty Acids, 67: 475-478.
37. Adebisi, S.A., P.O. Oluboyo and A.B. Okesina, 2000. Effect of drug-induced hyperuricaemia on renal function in Nigerians with pulmonary tuberculosis. Afr. J. Med. Med. Sci., 29: 297-300.
38. Rached, E., D. Hoffmann, K. Blumbach, K. Weber, W. Dekant and A. Mally, 2008. Evaluation of putative biomarkers of nephrotoxicity after exposure to ochratoxin A *in vivo* and *in vitro*. Toxicol. Sci., 103: 371-381.
39. Gehan, A.E.E. and A.Y. Amin, 2009. Cadmium-ginger two way antagonistic relationship. Arab J. Biotech., 13: 115-124.
40. Abdalla, O., F. Abdelhamid, M. El-Boshy and H. Samir, 2014. Studies on the protective effects of ginger extract and in combination with ascorbic acid against aluminum toxicity induced hematological disorders, oxidative stress and hepatorenal damage in rats. Ann. Vet. Anim. Sci., 1: 136-150.
41. Araujo, L.P., R.R. Truzzi, G.E.F. Mendes, M.A.M. Luz, E.A. Burdmann and S.M. Oliani, 2012. Annexin A1 protein attenuates cyclosporine-induced renal hemodynamics changes and macrophage infiltration in rats. Inflamm. Res., 61: 189-196.
42. Naderi, Z., H. Mozaffari-Khosravi, A. Dehghan, A. Nadjarzadeh and H.F. Huseini, 2016. Effect of ginger powder supplementation on nitric oxide and C-reactive protein in elderly knee osteoarthritis patients: A 12-week double-blind randomized placebo-controlled clinical trial. J. Tradit. Complement. Med., 6: 199-203.

43. Kalaiselvi, A., G.A. Reddy and V. Ramalingam, 2015. Ameliorating effect of ginger extract (*Zingiber officinale Roscoe*) on liver marker enzymes, lipid profile in aluminium chloride induced male rats. Int. J. Pharm. Sci. Drug Res., 7: 52-58.
44. Newairy, A.A., A.F. Salama, H.M. Hussien and M.I. Yousef, 2009. Propolis alleviates aluminium-induced lipid peroxidation and biochemical parameters in male rats. Food Chem. Toxicol., 47: 1093-1098.
45. Hasona, N.A., M.Q. Ahmed, T.A. Alghassab, M.A. Alghassab and A.A. Alghabban, 2016. Antihyperlipidemic effect of pomegranate peel and Iranian fenugreek extracts on cholesterol-rich diet induced hypercholesterolemia in guinea pigs. Merit Res. J. Med. Med. Sci., 4: 196-203.
46. Abdel-Wahab, W.M., 2012. AlCl3-induced toxicity and oxidative stress in liver of male rats: Protection by melatonin. Life Sci., 9: 1173-1182.
47. Halliwell, B., 1994. Free radicals, antioxidants and human disease: curiosity, cause, or consequence? Lancet, 344: 721-724.
48. Bashandy, S.A., I.M. Alhazza, G.E. El-Desoky and Z.A. Al-Othman, 2011. Hepatoprotective and hypolipidemic effects of Spirulina platensis in rats administered mercuric chloride. Afr. J. Pharm. Pharmacol., 5: 175-182.
49. Dickinson, D.A., D.R. Moellering, K.E. Iles, R.P. Patel and A.L. Levonen *et al*., 2003. Cytoprotection against oxidative stress and the regulation of glutathione synthesis. Biol. Chem., 384: 527-537.
50. Reddy, A.Y., M. Chalamaiah, B. Ramesh, G. Balaji and P. Indira, 2014. Ameliorating activity of ginger (*Zingiber officinale*) extract against lead induced renal toxicity in male rats. J. Food Sci. Technol., 51: 908-914.