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Research Article

Gallic and Hesperidin Ameliorate Electrolyte Imbalances in $AlCl_3$-Induced Nephrotoxicity in Wistar Rats

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Nephrotoxicity is usually characterized by inefficiency of the kidney, thereby causing disruptions to electrolyte balance and blood acidity. This study aimed to evaluate the effect of hesperidin and gallic acid on serum electrolytes and ion pumps in Wistar rats subjected to aluminum chloride ($AlCl_3$)-induced nephrotoxicity. Thirty Wistar rats were randomly divided into six groups of five animals apiece. Group one served as the negative control and received distilled water while the study lasted. Animals in groups 2–4 received 100 mg/kg/day $AlCl_3$ throughout the study. Animals in groups 3 and 4 were also administered 100 mg/kg/day gallic acid and 100 mg/kg/day hesperidin, respectively. Groups 5 and 6 were treated with 100 mg/kg/day gallic acid only and 100 mg/kg/day hesperidin only, respectively. Treatments were administered orally via gavage for 28 days with distilled water as the vehicle. Animals were sacrificed after which levels of potassium, calcium, magnesium, phosphate, chloride, and bicarbonate ions were evaluated in the serum, while activities of Na^+/K^+ and Ca^{2+}/Mg^{2+} ATPases were determined in kidney homogenate. Results showed that $AlCl_3$ significantly ($p < 0.05$) inhibited activities of Na^+/K^+ and Ca^{2+}/Mg^{2+} ATPases in addition to increasing serum levels of potassium, calcium, phosphate, and chloride, with concomitant decrease in serum levels of magnesium and bicarbonate. However, coadministration of $AlCl_3$ with either gallic acid or hesperidin ameliorated all the disruptions caused by $AlCl_3$. It could be concluded that gallic acid and hesperidin could be relevant in managing electrolyte imbalances and acidosis occasioned by kidney dysfunction.

1. Introduction

Nephrotoxicity is a condition in which detoxification and excretion functions of the kidney are impaired as a result of damage or destruction to the kidney by toxicants or drugs. Nephrotoxicity is usually implicated in the aetiology of acute kidney injury (AKI) [1]. Acute kidney injury is a health challenge of global dimension, annually affecting about 13.3% of people worldwide. AKI is in turn a risk factor for chronic kidney disease (CKD) [2, 3]. Both experimental and clinical data support the existence of a bidirectional relationship between AKI and CKD [4]. Due to the critical role of the kidney in maintenance of homeostasis, detoxification, and excretion of both drugs and toxic metabolites, the kidney is apparently a major target organ for toxicants [5].

In the course of daily interaction with the environment, humans and animals get exposed to various chemicals and heavy metals, which have the tendency to bioaccumulate in body tissues. Among the metallic elements in the Earth crust, aluminum has the third highest occurrence [6]. Exposure to aluminum mostly occurs via several of its compounds including aluminum chloride [7]. Sources of exposure of humans to aluminum include common household products such as shampoo, water treatment products, wood preservation products, food additives, and toothpaste. Non-household sources of aluminum include particulate matters from cement factories and waste waters from industries [6, 7]. In spite of its low gastrointestinal absorption rate, aluminum has the tendency to accrue in essential organs such as the brain, kidney, and liver, and it over time causes cytotoxicity [8]. Moreover, the aluminum level has been

reported to increase in both tissues and organs, with age [9]. An important reason for aluminum bioaccumulation is protein binding that constrains its ultrafiltration [9, 10]. Due to its limited excretion, primarily via urine, high doses of aluminum may lead to its renal retention and cause nephrotoxicity [11].

Maintenance of electrolyte levels within normal ranges is important for proper functioning of organs as well as several metabolic processes. The kidneys play an important role in maintaining electrolyte homeostasis. Thus, diseases and dysfunctions affecting the kidneys disturb their regulatory functions, thereby leading to imbalances in electrolyte level, with attendant life-threatening implications [12].

Hesperidin belongs to the flavanone class of flavonoids. Its antioxidant and anti-inflammatory effects in acute renal damage were earlier reported [13]. Gallic acid (3, 4, 5-trihydroxy benzoic acid) is a phenolic acid that has protective effect against oxidative stress-induced damage in tissues. Moreover, an earlier study reported its ability to prevent nephrotoxicity [14, 15]. A search through literature suggests that aluminum chloride is more often studied for its neurotoxicity compared with its nephrotoxicity. This study aimed to study and aimed to evaluate the protective effect of gallic acid and hesperidin, which are phytochemicals with proven pharmacological effects, against electrolyte imbalance in $AlCl_3$-induced nephrotoxicity in Wistar rats.

2. Materials and Methods

2.1. Chemicals. Hesperidin and gallic acid were obtained from SantaCruz Biotechnology Inc, Heidelberg Germany. Kits for evaluating serum levels of potassium, calcium, and magnesium were obtained from Atlas Medical, Blankenfelde-Mahlow, Berlin, Germany. Kits for estimating serum levels of phosphate, chloride, and bicarbonate were purchased from Teco Diagnostics, Anaheim, USA. ELISA kits for evaluating Na^+/K^+ ATPase and Ca^{2+}/Mg^{2+} ATPase were purchased from MyBiosource, Inc, San Diego, USA. All other chemicals and reagents used were of analytical grade.

2.2. Experimental Design. Thirty male rats of Wistar strain (180–200 g) were obtained from the animal research facility of Afe Babalola University, Ado-Ekiti, Nigeria. They were allowed to acclimatize for 10 days under standard conditions before commencement of the study. The experimental animals were randomly distributed into six groups ($n = 5$). Group 1 was the control and was administered distilled water only throughout the study. Animals in groups 2–4 were administered 100 mg/kg $AlCl_3$ while the study lasted. Animals in groups 3 and 4 also received 100 mg/kg gallic acid and 100 mg/kg hesperidin, respectively, in addition to $AlCl_3$. Groups 5 and 6 animals received 100 mg/kg gallic acid only and 100 mg/kg hesperidin only, respectively. All treatments were orally administered. Experimental animals were allowed access to food and water without restriction throughout the acclimatization and study periods. Animals were treated for 28 days. Doses of $AlCl_3$, gallic acid, and hesperidin used in this study were as reported in previous studies [14, 16, 17].

2.3. Sample Preparation. Experimental animals were sacrificed under mild anaesthesia with diethyl ether 24 h after administration of the last doses of treatment. Blood was obtained via cardiac puncture and spun for 5 min at 3000 rpm to obtain serum for evaluating levels of potassium, calcium, phosphate, magnesium, chloride, and bicarbonate. Kidneys were dissected out and trimmed of excess fat, after which they were rinsed in isotonic saline. The kidneys were homogenized in chilled 50 mmol/l Tris-HCl buffer (pH 7.4). The homogenates were centrifuged at 3000 rpm for 10 min at 4°C after which the supernatant was used for evaluation of activities of Na^+/k^+ ATPase and Ca^{2+}/Mg^{2+} ATPase. All animal studies complied with the Principle of Laboratory Animal Care [18]. Ethical approval (No : ABUAD/COS/2022/023) was obtained for the study from the Ethical Committee of the Afe Babalola University Research Directorate.

2.4. Biochemical Analyses. Serum levels of potassium, sodium, calcium, magnesium, phosphate, chloride, and bicarbonate were estimated spectrophotometrically by following instructions provided by kit manufacturers. Activities of Na^+/K^+ ATPase and Ca^{2+}/Mg^{2+} were evaluated using ELISA according to kit manufacturers' instructions.

2.5. Statistical Analyses. Data were expressed as mean ± standard deviation. Data was analyzed with one-way ANOVA using using Graphpad prism 5 software. Mean comparison was done with the Tukey test. The level of statistical significance was held at $p < 0.05$.

3. Results

Figure 1 shows that administration of $AlCl_3$ only to rats occasioned a significant decrease in renal Na^+/K^+ ATPase activity while gallic acid and hesperidin prevented such decrease when they were coadministered with $AlCl_3$. As presented in Figure 2, coadministration of $AlCl_3$ with either gallic acid or hesperidin to experimental animals significantly ($p < 0.05$) increased Ca^{2+}/Mg^{2+} ATPase activity, when compared with administration of $AlCl_3$ only. In Figures 3–6, it was observed that administration of $AlCl_3$ only to rats caused a significantly ($p < 0.05$) higher serum potassium, calcium, phosphate, and chloride levels, respectively. However, coadministration of gallic and hesperidin with $AlCl_3$ prevented such an increase in all the electrolytes. Figures 7 and 8 showed that $AlCl_3$ significantly ($p < 0.05$) lowered serum levels of magnesium and bicarbonate, respectively. This decrease was however prevented in rats administered with either gallic acid or hesperidin, in addition to $AlCl_3$. Results from our study indicated that administration of gallic acid only and hesperidin only did not have adverse effects on the biochemical indices evaluated in this study.

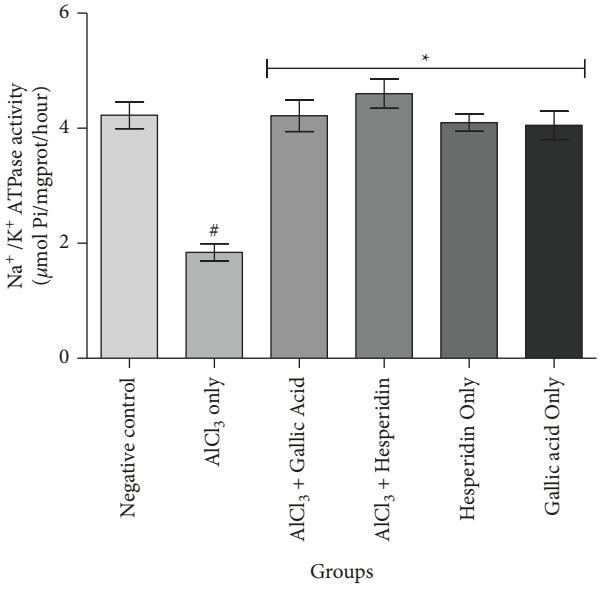

Figure 1: Effect of gallic acid and hesperidin on renal Na^+/K^+ ATPase activity in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as the mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

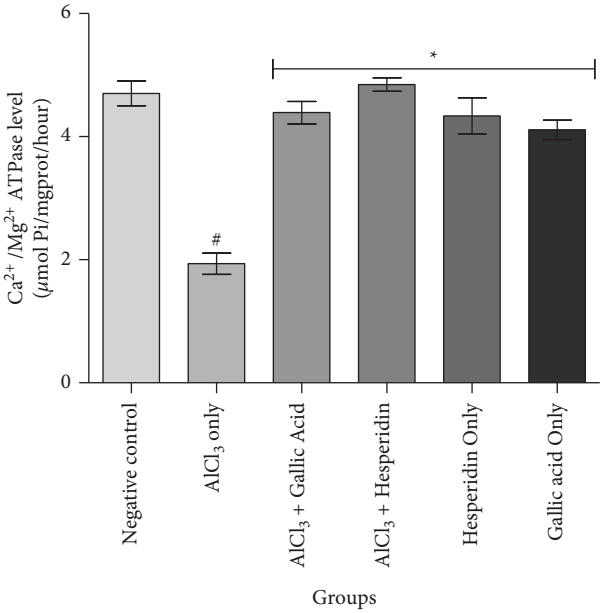

Figure 2: Effect of gallic acid and hesperidin on renal Ca^{2+}/Mg^{2+} ATPase activity in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

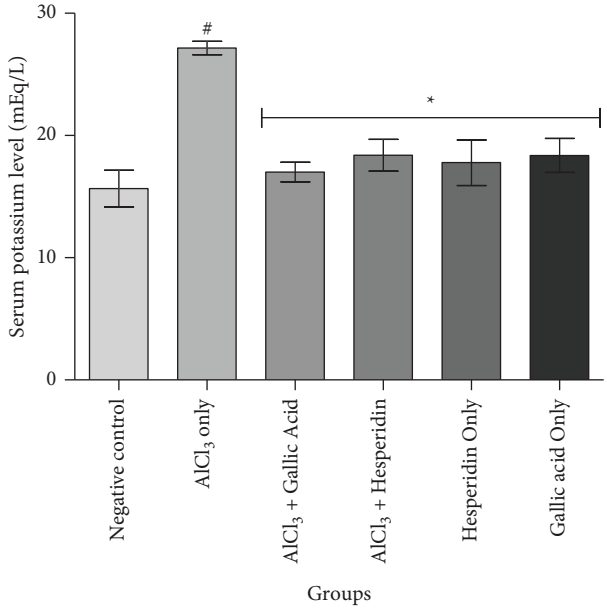

Figure 3: Effect of gallic acid and hesperidin on the serum potassium level in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as the mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

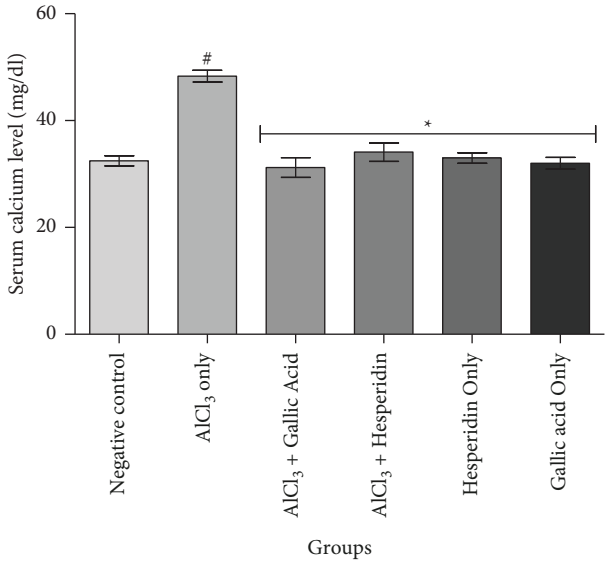

Figure 4: Effect of gallic acid and hesperidin on the serum calcium level in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as the mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

4. Discussion

Nephrotoxicity is one of the commonest kidney disorders. It can be caused by several therapeutic and nontherapeutic chemicals that have toxic effects on various anatomical components of the kidney. These toxic effects eventually culminate in degeneration of morphology and function of the kidney [19]. Nephrotoxicity is capable of leading to both acute and chronic kidney diseases via tubular and glomerular damage [20]. Even though change in renal function, which is usually assessed by the glomerular filtration rate, blood urea nitrogen, serum creatinine, or urine output, is an important indication of nephrotoxicity, nephrotoxicants can cause kidney damage without causing alterations in these traditional biomarkers of kidney function [21]. *In vivo* and *in* vitro studies have established that aluminum is a prooxidant, whose basis of toxicity is oxidative stress and apoptosis,

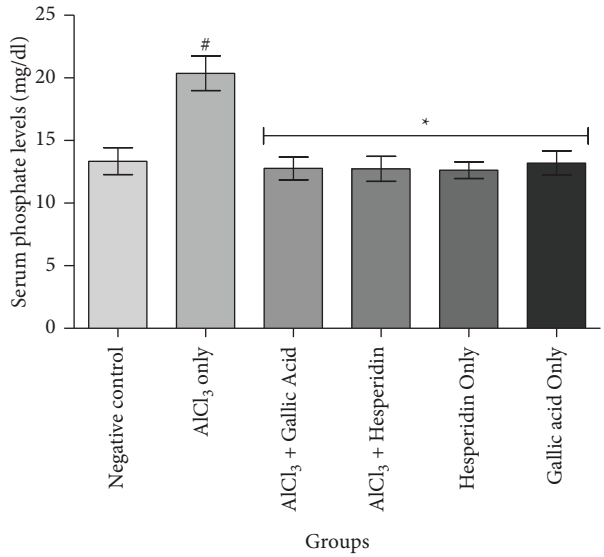

Figure 5: Effect of gallic acid and hesperidin on the serum phosphate level in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as the mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

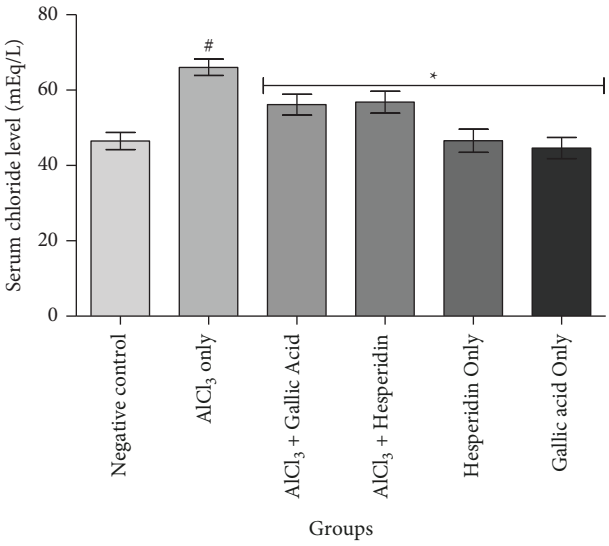

Figure 6: Effect of gallic acid and hesperidin on the serum chloride level in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as the mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

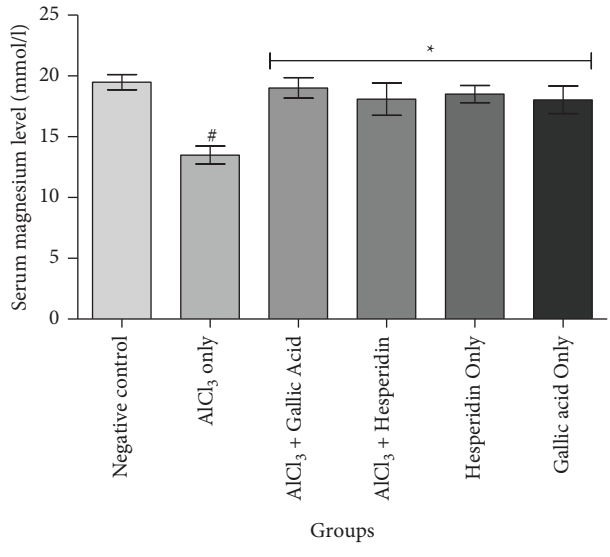

Figure 7: Effect of gallic acid and hesperidin on the serum magnesium level in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as the mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

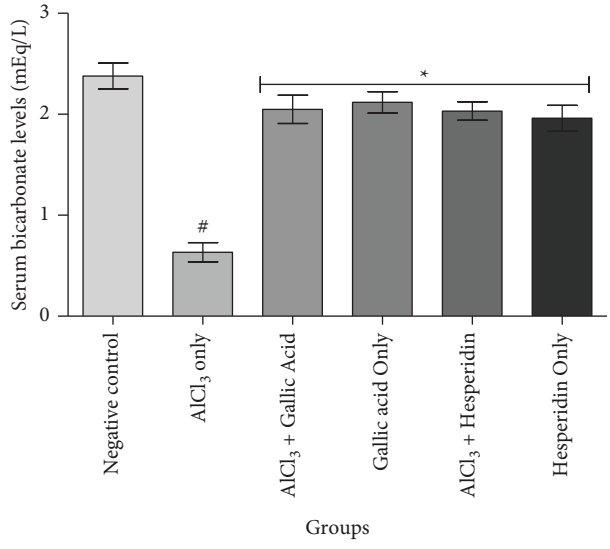

Figure 8: Effect of gallic acid and hesperidin on the serum bicarbonate level in $AlCl_3$-induced nephrotoxicity in Wistar rats. Values are expressed as the mean ± standard deviation of six determinations. $^{\#}p < 0.05$ vs negative control, $^{*}p < 0.05$ vs. $AlCl_3$ only.

characterized by degeneration of the renal-tubular cells to [22, 23].

Electrolyte homeostasis is essential for proper functioning of numerous biological processes in the body. Consequently, dysfunctions of the kidney disrupt the electrolyte balance and may lead to life-threatening health conditions [24]. Na^+/K^+ ATPase and Ca^{2+}/Mg^{2+} ATPase are enzymes found in all living organisms. They are involved in generating and maintaining ion gradients across biological membranes. Na^+/K^+ ATPase is highly expressed in the kidney, with the distal convoluted tubules having up to 50 million pumps per cell. The ion gradient generated by the enzyme is utilized by the kidney to filter the blood, maintain pH, and regulate levels of electrolytes in the blood [25]. Ca^{2+}/Mg^{2+} ATPase is expressed in the basolateral membranes of the kidney where it contributes to the intracellular calcium concentration essential for kidney function and also contributes to maintenance of Ca^{2+} and Mg^{2+} homeostasis [26]. Chemical-induced inhibition of these enzymes might contribute to the disruption of electrolytes, a condition usually associated with nephrotoxicity and other kidney dysfunctions [12, 27]. Moreover, it has been reported that the action of Na^+/K^+ ATPase can be inhibited by aluminum in the

kidney and liver, both *in vivo* and *in vitro* [24, 28]. In this study, it was observed that $AlCl_3$ only significantly inhibited the activity of Na^+/K^+ ATPase and Ca^{2+}/Mg^{2+} ATPase in the kidney of Wistar rats. However, when gallic acid and hesperidin were coadministered with $AlCl_3$, inhibition of the enzymes was prevented. This observation is an indication that both gallic acid and hesperidin might be relevant in maintaining electrochemical gradients across membranes and thereby ameliorate imbalances in concentration of the electrolytes specific to these enzymes, thereby improving aluminum chloride-induced nephrotoxicity.

About 98% of potassium, which is the most abundant intracellular cation, is sequestered in the intracellular fluid. The electrochemical gradient of potassium is maintained by the action of Na^+/K^+ ATPase in the kidney [28]. Hyperkalemia is a serious health disorder that can lead to alterations in cardiac electrophysiology and ultimately death. Rise in serum levels of potassium is due to loss of nephron function and is an indication of deterioration of kidney functions [29]. In the present study, it was observed that $AlCl_3$ caused hyperkalemia. However, coadministration of hesperidin and gallic acid reversed the high serum level observed in the group which administered $AlCl_3$ only. This suggests that both gallic acid and hesperidin might be relevant in preventing cardiovascular events associated with impaired kidney function as hyperkalemia is an important link between both health conditions [30].

Calcium ion plays an important role in the regulation of several physiological processes including muscle contraction, secretory mechanisms, and excitation of neurons [31]. One of the causes of hypercalcemia is renal dysfunction characterized by decreased glomerular filtration and renal excretion. Hypercalcemia is usually associated with acute kidney disease [32, 33]. We report that $AlCl_3$ caused a significant increase in serum calcium levels, a situation that was prevented with coadministration of $AlCl_3$ with either gallic acid or hesperidin. It should however be noted that hypercalcemia arising from renal dysfunctions constitutes only a small fraction of all hypercalcemia cases [31, 33].

The kidneys play an important role in phosphorus homeostasis, and hence, renal dysfunctions can significantly disrupt phosphorus homeostasis. It was reported that the risk of death increases by 20% for every 1 mg/dl increase in serum phosphorus among CKD patients [34]. Even though phosphorus comes after calcium in order of abundance in the body, about 85% of phosphorus is found in bone and teeth as hydroxyapatite, while only 1% is located in the vascular space as inorganic phosphate. Hyperphosphatemia is predominantly observed in reduced renal functions, even though other probable causes exist [35]. Renal failure, presented as the reduced glomerular filtration rate, was reported to be the commonest cause of hyperphosphatemia [36]. In the present study, it was observed that the serum phosphate level was significantly higher in rats administered $AlCl_3$ only. This is in contrast to the observation in rats coadministered $AlCl_3$ with either gallic acid or hesperidin. Hyperphosphatemia increases the risk of mortality due to cardiovascular events in CKD patients mainly due to calcification of the vascular system [37]. Findings from this study suggest that gallic acid and hesperidin could prevent vascular calcification and its deleterious implications.

Magnesium is one of the most abundant intracellular divalent cations. It serves various essential roles in the body such as DNA synthesis, oxidative phosphorylation, cardiovascular tone, cofactor for enzymes, bone formation, and neuromuscular excitability [38]. Maintenance of the serum magnesium level is via an interaction between intestinal transport, renal transport, and bone exchange [32]. Thus, imbalances in the serum magnesium level are usually followed by serious clinical consequences. About of 95% of plasma magnesium is filtered by the glomerulus, followed by almost complete tubular reabsorption by the proximal and distal tubules and ascending loop of Henle. Thus, disruption in the tubular reabsorption processes could lead to hypomagnesemia as a result of increased renal loss [39]. In the present study, nephrotoxicity due to $AlCl_3$ was observed to significantly lower the serum magnesium level in Wistar rats. Nevertheless, coadministration of $AlCl_3$ with gallic acid and hesperidin to Wistar rats significantly increased the serum magnesium level, when compared with the $AlCl_3$ only group. This observation implies that the ability of gallic acid and hesperidin to prevent hypomagnesemia could be due to improvement of tubular reabsorption of magnesium.

Chloride is a critical driver of several biological processes such as rennin secretion, renal sodium handling, blood pressure, and tubuloglomerular feedback [40]. A previous study identified an association between hyperchloremia and acute kidney injury [41], while another study correlated hyperchloremia with a worsened estimated glomerular filtration rate, which is an indication of nephrotoxicity [21, 40]. In our study, $AlCl_3$ induced hyperchloremia in rats. However, gallic acid and hesperidin significantly lowered serum chloride levels when coadministered $AlCl_3$. Our result suggests that gallic acid and hesperidin might have ameliorated the damaging effect of $AlCl_3$ on the glomerular filtration rate in experimental animals.

In order to maintain regular acid-base balance, renal tubules reabsorb filtered HCO_3^-, in addition to synthesizing adequate HCO_3^- in order to neutralize the intrinsic acid load [42]. The proximal convoluted tubule reabsorbs the bulk (80–85%) of filtered HCO_3^-, while the thick ascending limb of the loop of Henle reabsorbs the balance [43]. Failure of renal-tubular reabsorption of HCO_3^- eventually leads to a reduction of serum bicarbonate concentration which ultimately contributes to metabolic acidosis [44]. Moreover, inability of residual nephrons to expel the daily acid load sequel to reduced renal mass is also known to lead to metabolic acidosis [45]. Both acute kidney injury and CKD are associated with metabolic acidosis [46]. In the present study, it was discovered that $AlCl_3$ prompted metabolic acidosis by significantly lowering serum bicarbonate levels. Nonetheless, coadministration of gallic acid and hesperidin prevented metabolic acidosis possibly by preventing reduced renal mass and maintaining tubular reabsorption function of the kidneys.

5. Conclusion

This study corroborates the disruptive effect of aluminum on electrolyte homeostasis due to its nephrotoxic effects on renal functions. Apart from its effect on the serum levels of individual electrolytes, aluminum was also found to disrupt the activities of two enzymes involved in generation and maintenance of electrochemical gradients across membranes. Coadministration of gallic acid and hesperidin however prevented these biochemical alterations, an observation that further underlines the relevance of plant-derived bioactive compounds in health promotion. This study did not also discover a significant difference in the ability of gallic acid and hesperidin as far as maintenance of serum electrolyte levels was concerned.

Data Availability

All data for this study are available on request.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this article.

References

[1] E. J. Weber, J. Himmelfarb, and A. J. Kelly, "Concise review: current and emerging biomarkers of nephrotoxicity," *Current Opinion in Toxicology*, vol. 4, pp. 16–21, 2017.

[2] E. Kwiatkowska, L. Domanski, V. Dziedziejko, A. Kajdy, K. Stefanska, and S. Kwiatkowski, "The mechanism of drug nephrotoxicity and the methods for preventing kidney damage," *International Journal of Molecular Sciences*, vol. 22, Article ID 6106, 2021.

[3] S. Verma, P. Singh, S. Khurana et al., "Implications of oxidative stress in chronic kidney disease: a review on current concepts and therapies," *Kidney Research and Clinical Practice*, vol. 40, no. 2, pp. 183–193, 2021.

[4] L. S. Chawla and P. L. Kimmel, "Acute kidney injury and chronic kidney disease: an integrated clinical syndrome," *Kidney International*, vol. 82, no. 5, pp. 516–524, 2012.

[5] S. Y. Kim and A. R. Moon, "Drug-induced nephrotoxicity and its biomarkers," *Biomolecules and Therapeutics*, vol. 20, pp. 268–272, 2012.

[6] H. S. A. Dera, "Protective effect of resveratrol against aluminum chloride induced nephrotoxicity in rats," *Saudi Medical Journal*, vol. 37, no. 4, pp. 369–378, 2016.

[7] I. O. Igbokwe, E. Igwenagu, and N. A. Igbokwe, "Aluminium toxicosis: a review of toxic actions and Effects," *Interdisciplinary Toxicology*, vol. 12, no. 2, pp. 45–70, 2019.

[8] A. E. Abdel Moneim, M. S. Othman, S. M. Mohmoud, and K. M. El-Deib, "Pomegranate peel attenuates aluminum-induced hepatorenal toxicity," *Toxicology Mechanisms and Methods*, vol. 23, no. 8, pp. 624–633, 2013.

[9] D. Krewski, R. A. Yokel, E. Nieboer et al., "Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide," *Journal of Toxicology and Environmental Health, Part B*, vol. 10, pp. 1–269, 2007.

[10] G. Berthon, "Aluminium speciation in relation to aluminium bioavailability, metabolism and toxicity," *Coordination Chemistry Reviews*, vol. 228, no. 2, pp. 319–341, 2002.

[11] G. Stoehr, K. Luebbers, M. Wilhelm, J. Hoelzer, and C. Ohmann, "Aluminum load in ICU patients during stress ulcer prophylaxis," *European Journal of Internal Medicine*, vol. 17, no. 8, pp. 561–566, 2006.

[12] T. Dhondup and Q. Qian, "Acid-base and electrolyte disorders in patients with and without chronic kidney disease: an update," *Kidney Disease*, vol. 3, no. 4, pp. 136–148, 2017.

[13] B. Hanedan, M. Ozkaraca, A. Kirbas et al., "Investigation of the effects of hesperidin and chrysin on renal injury induced by colistin in rats," *Biomedicine and Pharmacotherapy*, vol. 108, pp. 1607–1616, 2018.

[14] M. A. Dehghani, N. Shakiba Maram, E. Moghimipour, L. Khorsandi, M. Atefi khah, and M. Mahdavinia, "Protective effect of gallic acid and gallic acid-loaded Eudragit-RS 100 nanoparticles on cisplatin-induced mitochondrial dysfunction and inflammation in rat kidney," *Biochimica et Biophysica Acta—Molecular Basis of Disease*, vol. 1866, no. 12, pp. 165911–165914, 2020.

[15] B. Gholamine, G. Houshmand, A. Hosseinzadeh, M. Kalantar, S. Mehrzadi, and M. Goudarzi, "Gallic acid ameliorates sodium arsenite-induced renal and hepatic toxicity in rats," *Drug and Chemical Toxicology*, vol. 44, no. 4, pp. 341–352, 2021.

[16] G. M. Hammoud and R. A. Shalaby, "Experimental evaluation of protective action of resveratrol against aluminum-induced toxicity in male rats," *International Journal of Advanced Research in Biological Sciences*, vol. 6, no. 1, pp. 11–24, 2019.

[17] A. Justin-Thenmozhi, M. Dhivya Bharathi, R. Kiruthika, T. Manivasagam, A. Borah, and M. M. Essa, "Attenuation of aluminum chloride-induced neuroinflammation and caspase activation through the AKT/GSK-3β pathway by hesperidin in wistar rats," *Neurotoxicity Research*, vol. 34, no. 3, pp. 463–476, 2018.

[18] National Research Council, *Guide for the Care and Use of Laboratory Animals*, The National Academic Press, Washington, DC, 8th edition, 2011.

[19] J. Jose and R. Ahmed, "A brief study of nephrotoxicity and nephroprotective agents," *Indian Journal of Pharmaceutical and Biological Research*, vol. 8, no. 01, pp. 09–13, 2020.

[20] L. M. A. Barnett and B. S. Cummings, "Nephrotoxicity and renal pathophysiology: a contemporary perspective," *Toxicological Sciences*, vol. 164, no. 2, pp. 379–390, 2018.

[21] Y. Zhou, V. S. Vaidya, R. P. Brown et al., "Comparison of kidney injury molecule-1 and other nephrotoxicity biomarkers in urine and kidney following acute exposure to gentamicin, mercury, and chromium," *Toxicological Sciences*, vol. 101, no. 1, pp. 159–170, 2008.

[22] C. Exley, "The pro-oxidant activity of aluminum," *Free Radical Biology and Medicine*, vol. 36, no. 3, pp. 380–387, 2004.

[23] M. S. Othman, M. A. Fareid, R. S. Abdel Hameed, and A. E. Abdel Moneim, "The protective effects of melatonin on aluminum-induced hepatotoxicity and nephrotoxicity in rats," *Oxidative Medicine and Cellular Longevity*, vol. 2020, Article ID 7375136, 12 pages, 2020.

[24] M. R. Rahimzadeh, M. R. Rahimzadeh, S. Kazemi, R. J. Amiri, M. Pirzadeh, and A. A. Moghadamnia, "Aluminum poisoning with emphasis on its mechanism and treatment of intoxication," *Emergency Medicine International*, vol. 2022, 13 pages, 2022.

[25] Y. Pirahanchi, R. Jessu, and N. R. Aeddula, *Physiology, Sodium Potassium Pump*, StatPearls Publishing LLC, Treasure Island FL, USA, 2022.

[26] Q. M. Abd and S. J. Ali, "Biochemical Characterization of (Ca^{2+}-Mg^{2+})-Atpase and ionic imbalance in patient with chronic renal failure," *European Journal of Molecular and Clinical Medicine*, vol. 7, pp. 4325–4334, 2020.

[27] A. Sahai and P. K. Ganguly, "(Ca^{2+} + Mg^{2+}) ATPase activity in kidney basolateral membrane in diabetes: role of atrial natriuretic peptide," *Molecular and Cellular Biochemistry*, vol. 105, no. 1, pp. 15–20, 1991.

[28] A. G. Therien and R. Blostein, "Mechanisms of sodium pump regulation," *American Journal of Physiology—Cell Physiology*, vol. 279, no. 3, pp. C541–C566, 2000.

[29] NKF, *Clinical Update on Hyperkalemia: A Chronic Risk for CKD Patients and a Potential Barrier to Recommended CKD Treatment*, National Kidney Foundation, Inc, New York, NY, USA, 2014.

[30] P. H. Pun, B. A. Goldstein, J. A. Gallis, J. P. Middleton, and L. P. Svetkey, "Serum potassium levels and risk of sudden cardiac death among patients with chronic kidney disease and significant coronary artery disease," *Kidney International Reports*, vol. 2, no. 6, pp. 1122–1131, 2017.

[31] M. Moysés-Neto, F. M. Guimarães, F. H. Ayoub, O. M. Vieira-Neto, J. A. C. Costa, and M. Dantas, "Acute renal failure and hypercalcemia," *Renal Failure*, vol. 28, no. 2, pp. 153–159, 2006.

[32] J. Blaine, M. Chonchol, and M. Levi, "Renal control of calcium, phosphate, and magnesium homeostasis," *Clinical Journal of the American Society of Nephrology*, vol. 10, no. 7, pp. 1257–1272, 2015.

[33] N. A. Bhat, F. Mustafa, R. Y. Sheikh, and I. Wani, "Incidence, etiology, and course of hypercalcemia-induced AKI in a tertiary care center from northern India," *The Egyptian Journal of Internal Medicine*, vol. 33, no. 1, 2021.

[34] H. Moon, H. J. Chin, K. Y. Na et al., "Hyperphosphatemia and risks of acute kidney injury, end-stage renal disease, and mortality in hospitalized patients," *BMC Nephrology*, vol. 20, no. 1, pp. 362–367, 2019.

[35] A. M. Shaman and S. R. Kowalski, "Hyperphosphatemia management in patients with chronic kidney disease," *Saudi Pharmaceutical Journal*, vol. 24, no. 4, pp. 494–505, 2016.

[36] R. Goyal and I. Jialal, *Hyperphosphatemia*, StatPearls Publishing, Treasure Island, FL, USA, 2022.

[37] A. M. Askar, "Hyperphosphatemia: The hidden killer in chronic kidney disease," *Saudi Medical Journal*, vol. 36, no. 1, pp. 13–19, 2015.

[38] J. Ayuk and N. J. L. Gittoes, "How should hypomagnesaemia be investigated and treated," *Clinical Endocrinology*, vol. 75, no. 6, pp. 743–746, 2011.

[39] E. P. Gonzalez, F. Santos, and E. Coto, "Magnesium homeostasis. Etiopathogeny, clinical diagnosis and treatment of hypomagnesaemia. a case study," *Nefrologia*, vol. 29, no. 6, pp. 518–524, 2009.

[40] M. Khatri, J. Zitovsky, D. Lee, K. Nayyar, M. Fazzari, and C. Grant, "The association between serum chloride levels and chronic kidney disease progression: a cohort study," *BMC Nephrology*, vol. 21, no. 1, p. 165, 2020.

[41] B. Suetrong, C. Pisitsak, J. H. Boyd, J. A. Russell, and K. R. Walley, "Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients," *Critical Care*, vol. 20, no. 1, pp. 315–318, 2016.

[42] C. A. Wagner, O. Devuyst, S. Bourgeois, and N. Mohebbi, "Regulated acid-base transport in the collecting duct," *Pfluegers Archiv European Journal of Physiology*, vol. 458, no. 1, pp. 137–156, 2009.

[43] M. L. Gumz, I. J. Lynch, M. M. Greenlee, B. D. Cain, and C. S. Wingo, "The renal H^+-K^+- ATPases: physiology, regulation, and structure," *American Journal of Physiology—Renal Physiology*, vol. 298, no. 1, pp. F12–F21, 2010.

[44] J. A. Kraut and N. E. Madias, "Metabolic acidosis: pathophysiology, diagnosis and management," *Nature Reviews Nephrology*, vol. 6, no. 5, pp. 274–285, 2010.

[45] L. M. Ortega and S. Arora, "Metabolic acidosis and progression of chronic kidney disease: incidence, pathogenesis, and therapeutic options," *Nefrologia*, vol. 32, no. 6, pp. 724–730, 2012.

[46] J. A. Kraut and I. Kurtz, "Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment," *American Journal of Kidney Diseases*, vol. 45, no. 6, pp. 978–993, 2005.