

# Nephroprotective Effect of Essential Oils from Ginger (*Zingiber officinale*) and Turmeric (*Curcuma longa*) Rhizomes against Cadmium-induced Nephrotoxicity in Rats

Ayodele Jacob Akinyemi<sup>1\*</sup>, Oluwabamise Lekan Faboya<sup>2</sup>, Awonegan Ayodeji Paul<sup>3</sup>, Israel Olayide<sup>1</sup>, Opeyemi Ayodeji Faboya<sup>4</sup>, and Titus Ademola Oluwasola<sup>5</sup>

<sup>1</sup> Department of Chemical Sciences, Biochemistry Unit, Afe Babalola University, Ado-Ekiti, NIGERIA

<sup>2</sup> Department of Chemical Sciences, Chemistry Unit, Afe Babalola University, Ado-Ekiti, NIGERIA

<sup>3</sup> Department of Science Technology, The Federal Polytechnic, Ado-Ekiti, Ekiti State, NIGERIA

<sup>4</sup> Department of Medical Biochemistry, Ekiti State University, Ado-Ekiti, Ekiti State, NIGERIA

<sup>5</sup> Department of Animal Production and Health Sciences, Ekiti State University, Ado-Ekiti, Ekiti State, NIGERIA

**Abstract:** Several studies have shown that cadmium (Cd) induces nephrotoxicity and many plant foods phytochemicals have been found useful but their possible mechanism of action still remains unexplored. Hence, this study aimed to investigate the nephroprotective effect of essential oils from Nigeria ginger and turmeric rhizomes in cadmium-treated rats by examining their effect on renal function biomarkers (creatinine, urea and BUN), inflammatory cytokines (IL-6, IL-10 and TNF-Alpha) and renal adenosine deaminase (ADA) activity. The result revealed that essential oils from ginger and turmeric rhizomes exert anti-inflammatory effect by preventing alterations of renal function markers and cytokines (IL-6, IL-10 and TNF-Alpha) levels in Cd-treated rats. In addition, the essential oils inhibited renal ADA activity in Cd-treated rats. In conclusion, inhibition of ADA activity and modulation of inflammatory cytokines could be suggested as the possible mechanism of action by which essential oils from ginger and turmeric rhizomes exert their nephroprotective activities.

**Key words:** essential oil, nephrotoxicity, cytokines, ADA

## 1 Introduction

Cadmium (Cd) is a widespread environmental pollutant that poses a significant health risk to humans. It has been found that Cd<sup>2+</sup> can produce both acute and chronic tissue injury and can damage various organs including the lung, liver, kidney, bone, testis, and placenta, depending on the dose, route and duration of exposure<sup>1,2</sup>. Cd intoxication is associated with several adverse health effects such as carcinogenesis, hepatotoxicity, renal impairment as well as disruption of normal endocrine and reproductive function<sup>2</sup>.

Nephropathy is one of the most extensively recognized disorders caused by Cd intoxication<sup>3</sup>. It has been proposed that Cd mediates its toxicity via several mechanisms including induction of apoptosis, ischemia, inflammation, oxidative stress, displacement of divalent metals ions from

their binding site, mimic the action of essential metal ions which are required for normal functioning of key enzymes and several biological activities<sup>4-6</sup>.

Several studies have investigated a number of agents which have potentials to counteract cadmium-mediated toxicity. Some of these agents including functional foods and nutraceuticals have been shown to be effective in preventing cadmium toxicity.

Ginger, the rhizome of *Zingiber officinale* Roscoe, is one of the most widely used spices, belonging to the family Zingiberaceae<sup>7</sup>. It is a common condiment in various foods and beverages and mainly used to impart aroma and flavour<sup>7</sup>. It has been reported that ginger presents some pharmacological activities including anti-inflammation, anti-tumour and antioxidant properties<sup>8-10</sup>. Essential oil from ginger can be obtained by steam distillation of the

\*Correspondence to: Ayodele Jacob Akinyemi, Department of Chemical Sciences, Biochemistry Unit, Afe Babalola University, Ado-Ekiti, NIGERIA

E-mail: ajakinyemi2010@yahoo.co.uk; akinyemij@abuad.edu.ng

Accepted August 31, 2018 (received for review June 25, 2018)

Journal of Oleo Science ISSN 1345-8957 print / ISSN 1347-3352 online

<http://www.jstage.jst.go.jp/browse/jos/> <http://mc.manuscriptcentral.com/jjocs>

rhizome, a product that possesses the aroma and flavour of the spice. Until recently, essential oils have been studied mostly for their flavour and fragrance. Essential oils and their components are now gaining worldwide interest because of their potential multipurpose functional use<sup>11</sup>. Essential oils and some of their components are also used as food preservers and for nutraceutical applications. A number of studies have been reported on the pharmacological properties of ginger essential oil<sup>8-10</sup>.

Another notable member of the family of Zingiberaceae is turmeric (*Curcuma longa* Linn). It is mainly used as spices and valued as a functional food because of its health-promoting potentials<sup>12</sup>. It is comprised of a group of three curcuminoids: curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins<sup>12</sup>. Essential oil from turmeric consists of a unique set of sesquiterpenoids considered to have significant biological activities including antifungal, insect repellent, antibacterial, antimutagenic, anticarcinogenic, antioxidant, anti-inflammatory and antinociceptive properties<sup>13-15</sup>.

Hence, the present study sought to investigate the effect of essential oil from ginger and turmeric rhizomes on renal biomarkers, inflammatory cytokines and renal adenosine deaminase activity in cadmium-induced nephrotoxicity in rats in order to provide some possible mechanism of action for their nephroprotective potential.

## 2 Materials and methods

### 2.1 Chemicals

Cadmium sulfate was obtained from Oxford Laboratory, Mumbai, India and solubilized in normal saline. Adenosine, bovine serum albumin, Dimethyl sulfoxide (DMSO) and Tris-HCl were purchased from Sigma-Aldrich, St. Louis, MO, USA. All other reagents were of analytical grade and the water was glass distilled.

### 2.2 Plant materials

Fresh ginger (*Zingiber officinale* Roscoe) and turmeric (*Curcuma longa* Linn) rhizomes were purchased from the local market of Ado-Ekiti, Nigeria. The rhizomes were identified and a voucher specimen was deposited with the Herbarium at the Department of Plant Science Laboratory, Faculty of science, Ekiti State University, Ado-Ekiti, Nigeria.

### 2.3 Extraction of essential oils

Fresh ginger and turmeric rhizomes (100 g of each) were subjected to hydrodistillation in a Clevenger apparatus for 3 h. The obtained oils were dried over anhydrous sodium sulfate. The oils were stored at 4°C in a refrigerator. The extraction yields obtained were 5.8 and 7% for ginger and

turmeric rhizomes respectively.

### 2.4 Animals

Forty-eight adult male albino rats of twelve weeks old were obtained from the animal breeding unit at College of Medicine, Afe Babalola University, Nigeria and were housed in cages, at room temperature 25–28°C, relative humidity 60–70%, and 12 h light/dark cycle. Food (pellet rat chow) and water were available *ad libitum*. Animals were cared according to US National Institute of Health (NIH) ethical guidelines. The treatment protocol was in accordance with the ethical requirement of the Animal Use and Care Committee of Afe Babalola University, Ado - Ekiti, Nigeria.

### 2.5 Experimental design

After two weeks of acclimatization, animals were divided randomly into six groups of 8 animals each.

- Group 1 – serve as the control and received daily injections of saline (1 mL/kg) i.p. plus vehicle (0.3% DMSO)
- Group 2 – received daily injections of saline (1 mL/kg) i.p. plus oral administration of essential oil from turmeric (50 mg/kg),
- Group 3 – received daily injections of saline (1 mL/kg) i.p. plus oral administration of essential oil from ginger (50 mg/kg),
- Group 4 – received daily injections of cadmium (1.0 mg/kg) i.p. plus vehicle (0.3% DMSO)
- Group 5 – received daily injections of cadmium (1.0 mg/kg) i.p. plus essential oil from turmeric (50 mg/kg) and
- Group 6 – received daily injections of cadmium (1.0 mg/kg) i.p. plus essential oil from ginger (50 mg/kg).

The Cd dosage for the bioassay was according to<sup>16</sup> where it induces toxicity in rats. The choice of the essential oil dosage (50 mg/kg) was made based on a preliminary acute toxicity study where we obtained beneficial results of this compound in the kidney of rats (Data not showed). Cd and essential oil were administered daily and the solutions were freshly prepared. The essential oil was prepared in DMSO (0.3%) and administered orally 30 min before Cd injection i.p.

At the end of the experiment (15<sup>th</sup> day), animals were euthanized by decapitation under ketamine-xylazine anaesthesia according to the approved protocol. Blood was collected for serum preparation while the kidney was quickly isolated and homogenized in 0.1 M Tris-HCl buffer, pH 7.4. The homogenates were centrifuged at 14,000 × g for 10 min at 4°C, and the supernatant was used for the subsequent analysis.

### 3 Determination of renal function markers

The levels of serum urea and creatinine were measured according to supplier's directions from commercial kits (RANDOX Laboratories Ltd, Crumlin, County Antrim, UK). Blood urea nitrogen (BUN) was determined by calculation (where  $BUN = Urea/2.14$ ).

#### 3.1 Quantification of cytokine levels

Serum cytokine (TNF- $\alpha$ , IL-6 and IL-10) levels were determined by ELISA using Quantikine Immunoassay kits (R&D systems) according to the manufacturer's instructions. Briefly, 96-well microplates were sensitized with primary antibody at room temperature for 30 min. Then, the sample was added and incubated for another 30 min and wash. After washing, secondary antibody conjugated with peroxidase was added and incubated. Thereafter, the cytokine concentration was measured by the intensity of the colour determined by spectrometry in an ELISA plate reader.

#### 3.2 Adenosine deaminase (ADA) activity assay

ADA activity determination was performed as described by<sup>17</sup> which is based on the direct measurement of the formation of ammonia, produced when adenosine deaminase acts in excess of adenosine. In brief, 50  $\mu$ L of tissue homogenate, followed by 50  $\mu$ L of 21 mM of adenosine, pH 6.5, and was incubated at 37°C for 60 min. Absorbance was measured at 630 nm using a Microplate Spectrophotometer (Molecular Devices, Sunnyvale, CA). Enzyme activity was calculated in units per litre (U/L). One unit (1 U) of ADA is defined as the amount of enzyme required to release 1 mmol of ammonia per minute from adenosine at standard assay conditions.

#### 3.3 Gas chromatography-mass spectrometry (GC/MS) analysis

The samples were analyzed for volatile compounds using 7820A gas chromatograph coupled to 5975C inert mass spectrometer (with triple axis detector) with electron-impact source (Agilent Technologies). The stationary phase of separation of the compounds was HP-5 capillary column coated with 5% Phenyl Methyl Siloxane (30 m length  $\times$  0.32 mm diameter  $\times$  0.25  $\mu$ m film thickness) (Agilent Technologies). The carrier gas was Helium (He) used at constant flow rate of 1.6 mL/min at an initial nominal pressure of 2.84 psi and average velocity of 46 cm/sec. 1  $\mu$ L of the samples were injected in split less mode at an injection temperature of 260°C. Purge flow was 21.5 mL/min at 0.50 min with a total flow of 25.8 mL/min; gas saver mode was switched on. Oven was initially programmed at 60°C (1 min) then ramped at 4°C/min to 110°C (3 min) then 8°C/min to 260°C (5 min) and 10°C/min to 300°C (12 min). Run time was 56.25 min with a 3 min solvent delay. The mass spectrometer was operated in electron-impact ionization mode

at 70 eV with ion source temperature of 230°C, quadrupole temperature of 150°C and transfer line temperature of 280°C.

The identification of the compounds was achieved on the basis of retention time, Kovats Index, literature reported retention index using a homologous series of n-alkanes (C8–C25 hydrocarbons, Polyscience Corp., Niles, IL), co-injection with standards (Sigma Aldrich, St. Louis, MO), mass spectra library search (NIST, Wiley, and Nbs), and by comparing with the mass spectral literature data.

#### 3.4 Protein concentration

Protein content was determined by the Coomassie blue method according to<sup>18</sup> using serum albumin as standard.

#### 3.5 Statistical analysis

All the results were represented as mean  $\pm$  SEM performed in triplicate. Statistical analysis used was software of GraphPad Prism 4.0 (GraphPad Software, Inc., San Diego, CA). One-way analysis of variance (ANOVA), followed by Duncan's multiple range tests was used and a probability of  $p < 0.05$  was considered to be statistically significant.

## 4 Results

### 4.1 Renal function biomarkers

The effects of essential oil from ginger and turmeric rhizomes on some serum renal biomarkers (urea, creatinine and BUN) in cadmium-treated rats were examined. As presented in **Table 1**, cadmium administration caused a significant ( $p < 0.05$ ) increase in urea, creatinine and BUN level when compared to control. However, co-treatment with essential oil from ginger and turmeric rhizome prevent alteration in the level of these renal biomarkers by preventing an increase in urea, creatinine and BUN when compared with Cd untreated group (**Table 1**).

### 4.2 Inflammatory cytokine level

Furthermore, the effect of essential oil from ginger and turmeric rhizomes on some serum inflammatory cytokines [interleukin 1 (IL-1), interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF- $\alpha$ )] in cadmium-treated rats were examined. The result revealed that cadmium administration caused a significant ( $p < 0.05$ ) reduction in IL-10 level with a concomitant increase in IL-6 and TNF- $\alpha$  level when compared to control. However, co-treatment with essential oil from ginger and turmeric rhizome modulates the level of these inflammatory cytokines by preventing a decrease in IL-10 and causing a reduction in IL-6 and TNF- $\alpha$  levels when compared with Cd untreated group (**Table 2**).

**Table 1** Effect of essential oil from ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) on some renal function biomarkers in cadmium treated rats.

Group	Urea (mg/dL)	Creatinine (mg/dL)	Blood urea nitrogen (BUN) (mg/dL)
Control	20.9 ± 1.0 <sup>a</sup>	0.95 ± 0.08 <sup>a</sup>	9.76 ± 0.024 <sup>a</sup>
Tur Oil only	23.3 ± 1.8 <sup>a</sup>	1.06 ± 0.05 <sup>a</sup>	10.89 ± 0.010 <sup>a</sup>
Ging Oil only	24.4 ± 1.6 <sup>a</sup>	1.03 ± 0.07 <sup>a</sup>	11.40 ± 0.001 <sup>a</sup>
Cd alone	82.1 ± 4.1 <sup>b</sup>	3.33 ± 0.91 <sup>b</sup>	38.36 ± 0.18 <sup>b</sup>
Tur Oil + Cd	20.6 ± 2.1 <sup>a</sup>	1.64 ± 0.34 <sup>a</sup>	9.62 ± 0.018 <sup>a</sup>
Ging Oil + Cd	22.7 ± 1.5 <sup>a</sup>	1.78 ± 0.56 <sup>a</sup>	10.61 ± 0.36 <sup>a</sup>

Values represent the mean ± SEM (n=8). Values with different superscript letters in the same column are statistically significance at  $p < 0.05$

**Key:**

Control: received normal saline + vehicle

Tur Oil only: received normal saline + turmeric essential oil (50 mg/kg)

Ging Oil only: received normal saline + ginger essential oil (50 mg/kg)

Cd alone: received Cd + vehicle

Tur Oil + Cd: received Cd + turmeric essential oil (50 mg/kg)

Ging Oil + Cd: received Cd + ginger essential oil (50 mg/kg)

**Table 2** Effect of essential oil from ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) on some inflammatory cytokines in cadmium treated rats.

Group	IL-10 (pg/mL)	IL-6 (pg/mL)	TNF- $\alpha$ (pg/mL)
Control	49.4 ± 2.6 <sup>a</sup>	18.6 ± 1.0 <sup>a</sup>	45.3 ± 2.2 <sup>a</sup>
Tur Oil only	42.1 ± 2.4 <sup>a</sup>	21.1 ± 1.6 <sup>a</sup>	55.1 ± 3.1 <sup>a</sup>
Ging Oil only	41.2 ± 2.4 <sup>a</sup>	22.1 ± 1.4 <sup>a</sup>	47.6 ± 1.6 <sup>a</sup>
Cd alone	19.3 ± 1.0 <sup>b</sup>	74.1 ± 2.8 <sup>b</sup>	152.1 ± 6.7 <sup>b</sup>
Tur Oil + Cd	44.2 ± 1.7 <sup>a</sup>	18.7 ± 2.0 <sup>a</sup>	71.5 ± 2.1 <sup>c</sup>
Ging Oil + Cd	36.1 ± 1.4 <sup>c</sup>	23.7 ± 4.1 <sup>a</sup>	61.9 ± 1.9 <sup>c</sup>

Values represent the mean ± SEM (n=8)

Values with different superscript letters in the same column are statistically significance at  $p < 0.05$

**Key:**

Control: received normal saline + vehicle

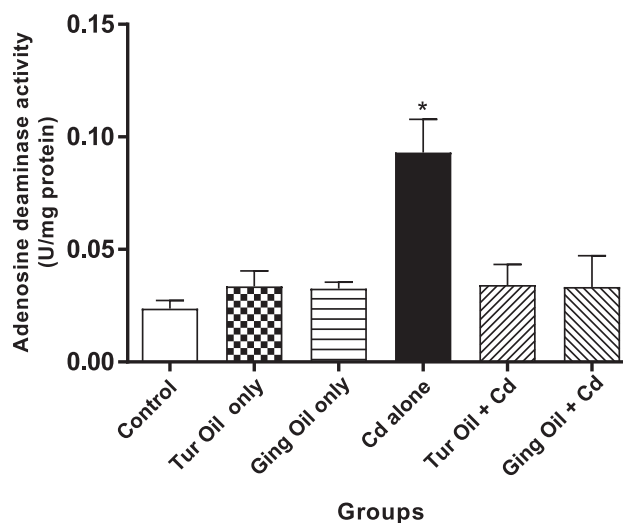
Tur Oil only: received normal saline + turmeric essential oil (50 mg/kg)

Ging Oil only: received normal saline + ginger essential oil (50 mg/kg)

Cd alone: received Cd + vehicle

Tur Oil + Cd: received Cd + turmeric essential oil (50 mg/kg)

Ging Oil + Cd: received Cd + ginger essential oil (50 mg/kg)



**Fig. 1** Effect of essential oil from ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) on kidney adenosine deaminase (ADA) activity in cadmium treated rats. Data represent the mean ± SEM of a group of eight rats (\* $p < 0.05$  vs control).

**Key:**

Control: received normal saline + vehicle

Tur Oil only: received normal saline + turmeric essential oil (50 mg/kg)

Ging Oil only: received normal saline + ginger essential oil (50 mg/kg)

Cd alone: received Cd + vehicle

Tur Oil + Cd: received Cd + turmeric essential oil (50 mg/kg)

Ging Oil + Cd: received Cd + ginger essential oil (50 mg/kg)

**Table 3** Chemical composition found in the essential oils from Nigeria ginger and turmeric rhizomes.

Compound name	Ginger		Turmeric	
	Retention time (min)	Percent total of compound (%)	Retention time (min)	Percent total of compound (%)
exo-Norborneol	3.663	0.27	–	–
Eucalyptol	5.194	2.75	5.200	76.46
Linaloloxide	6.511	0.06	–	–
endo-Borneol	8.589	1.31	–	–
Furfural	9.135	1.76	–	–
$\alpha$ -Terpineol	9.343	1.35	9.331	0.62
Limonene	12.625	1.21	–	–
p-Cymene	–	–	13.061	1.31
$\gamma$ -Terpinene	–	–	14.350	3.32
Oxirane	18.358	0.45	–	–
Citral	18.869	0.56	–	–
$\alpha$ -Terpinene	–	–	19.151	4.41
cis-Verbenol	23.368	0.12	–	–
Thunbergol	23.961	0.84	–	–
Squalene	25.220	0.02	–	–
Caryophyllene oxide	25.504	0.42	–	–
Nerolidol	28.205	0.31	–	–
$\alpha$ -Zingiberene	43.08	17.4	–	–
$\beta$ -Sesquiphellandrene	44.85	3.10	–	–
Other components	–	100%	–	100%

#### 4.3 Adenosine deaminase (ADA) activity

As presented in Fig. 1, cadmium administration caused a significant ( $p < 0.05$ ) increase in renal ADA activity when compared to control. However, co-treatment with essential oil from ginger and turmeric rhizome respectively prevents an increase in ADA activity when compared with Cd untreated group (Fig. 1).

#### 4.4 Volatile compounds analysis

In order to justify the efficacy of the essential oils, we characterized the oils for volatile/essential oil components using gas chromatography analysis according to their retention indices (RI) on a HP-5MS column and the observed results are listed in Table 3. The result revealed that the major essential oils from turmeric rhizomes are Eucalyptol (76.46%),  $\alpha$ -Terpinene (4.41%),  $\gamma$ -Terpinene (3.32%), p-Cymene (1.31%) and  $\alpha$ -Terpineol (0.62%) whereas  $\alpha$ -Zingiberene (17.43%),  $\beta$ -Sesquiphellandrene (3.10%), Eucalyptol (2.75%), Furfural (1.76%),  $\alpha$ -Terpineol (1.35%), endo-Borneol (1.31%), Limonene (1.21%), Thunbergol (0.84%), Citral (0.56%), Oxirane (0.45%), Caryophyllene oxide (0.42%), Nerolidol (0.31%), exo-Nor-

borneol (0.27%), cis-Verbenol (0.12%), Linaloloxide (0.06%) and Squalene (0.02%) are the major essential oil compounds detected in ginger rhizomes.

#### 5 Discussion

The kidneys have been identified as the major focus in many studies due to their importance in the body, their role as a target organ for toxic substances, the detrimental effects of toxic substances on the kidneys and changes in renal function<sup>19, 20</sup>. In this study, cadmium (Cd) administration caused a significant increase in some renal function biomarkers (urea, creatinine and BUN). The significant elevation in renal function biomarkers observed in our study (Table 1) reaffirms the nephrotoxicity of Cd. The significant alterations in the renal function parameters of Cd-exposed animals (Table 1) are in line with the renal toxicity of Cd<sup>20, 21</sup>. It has been proposed that Cd-induced renal damage is associated with degeneration and hypertrophy of epithelial cells and dialation of glomeruli and massive local haemorrhage of the renal tissues in kidney tubules<sup>22, 23</sup>.



In the present study, treatment with essential oil from ginger and turmeric rhizome prevent alteration in the level of these renal biomarkers by preventing an increase in urea, creatinine and BUN when compared with Cd group (Table 1). This is an indication the essential oils exert nephroprotective potential in Cd-treated rats. Previous studies have established the nephroprotective potential of ginger and turmeric rhizomes<sup>24-26</sup>. However, the mechanism of action against nephrotoxicity remains unclear.

In attempt to suggest possible mechanism of action of the oils as renoprotective agent against Cd induced nephrotoxicity, their effect on inflammatory cytokine and adenosine deaminase (ADA) activity were evaluated.

As observed from our result, Cd administration induces inflammatory mediated response via a reduction in IL-10 with a concomitant increase in IL-6 and TNF- $\alpha$  level when compared to control. The previous study by Min *et al.*<sup>2)</sup> reported that Cd-induced inflammatory response is associated with its nephrotoxicity. It is interesting to note that administration of pharmacological doses of essential oil from ginger and turmeric rhizomes appears to increase the endogenous release of anti-inflammatory cytokine IL-10. Thus, the nephroprotective effect of the oils could be linked to suppression of the inflammation mediated tolerance to Cd. This activity could be attributed to the volatile compounds present that have been extensively studied for their anti-inflammatory properties and their ability to inhibit inflammatory mediators<sup>9, 15, 27, 28)</sup>. The bioactive volatile compounds such as terpenes act by inhibiting the release of histamine or reducing the production of inflammation mediators. In addition, the anti-inflammatory activity of essential oils have been attributed to their interactions with signaling cascades involving cytokines and regulatory transcription factors, and on the expression of pro-inflammatory genes<sup>29)</sup>.

Furthermore, our result revealed that administration of Cd activates renal adenosine deaminase (ADA) activity. ADA represents a critical checkpoint in the regulation of extracellular adenosine levels and, thus implicated to play a vital role in the modulation of purinergic responses to several pathophysiological events<sup>30, 31)</sup>. This enzyme has been implicated in renal function such that an alteration has been linked to several kidney diseases<sup>30, 31)</sup>. The adenosine pathway has been suggested as an important mechanism that plays a vital role in the modulation of inflammatory responses and protection of renal injuries<sup>32)</sup>. Adenosine exerts its modulatory effects via interaction with G protein-coupled receptors, designated as A1, A2A, A2B and A3<sup>30, 31)</sup>. However, treatment with essential oil from ginger and turmeric rhizome respectively prevents an increase in ADA activity when compared with Cd untreated group (Fig. 1). This action may lead to an increased extracellular adenosine level and offers renoprotection during Cd induce renal damage.

## 6 Conclusion

In the current study, oral administration of essential oil from ginger and turmeric rhizomes exerts nephroprotective activity in Cd-treated rats. According to our findings, the inhibition of ADA activity and modulation of inflammatory cytokine by the oils could be suggested as a possible mechanism of action for their nephroprotective activity. However, the observed effect could be due to the volatile compounds identified.

## 7 Conflict of interest

The authors declare no conflict of interest.

## 8 Acknowledgement

The corresponding author is grateful to The World Academy of Sciences (TWAS) for financial support through the individual TWAS research grant FR3240293337 for timely completion of this research.

## References

- 1) Jarup, L.; Berglund, M.; Elinder, C.G.; Nordberg, G.; Vahter, M. Health effects of cadmium exposure: A review of the literature and a risk estimate. *Scand. J. Work Environ. Health* **24**, 1-51 (1998).
- 2) Min, K.S.; Kim, H.; Fujii, M.; Tetsuchikawahara, N.; Onosaka, S. Glucocorticoids suppress the inflammation-mediated tolerance to acute toxicity of cadmium in mice. *Toxicol. Appl. Pharmacol.* **178**, 1-7 (2002).
- 3) Erboga, M.; Kanter, M.; Aktas, C.; Sener, U.; Erboga, Z.F.; Donmez, Y.B.; Gurel, A. Thymoquinone ameliorates cadmium-induced nephrotoxicity, apoptosis, and oxidative stress in rats is based on its anti-apoptotic and anti-oxidant properties. *Biol. Trace Elem. Res.* **170**, 165-172 (2016).
- 4) Agirdir, B.V.; Bilgen, I.; Dinc, O.; Ozcağlar, H.U.; Fişenk, F.; Turhan, M.; Oner, G. (2002) Effect of zinc ion on cadmium induced auditory changes. *Biol. Trace Elem. Res.* **88**, 153-163 (2002).
- 5) Thijssen, S.; Cuypers, A.; Maringwa, J.; Smeets, K.; Horemans, N.; Lambrichts, I.; van Kerkhove, E. Low cadmium exposure triggers a biphasic oxidative stress response in mice kidneys. *Toxicology* **236**, 29-41 (2007).
- 6) Go, Y.M.; Roede, J.R.; Orr, M.; Liang, Y.; Jones, D.P. Integrated redox proteomics and metabolomics of mitochondria to identify mechanisms of Cd toxicity. *Toxicol. Sci.* **139**, 59-73 (2014).
- 7) Geiger, L.J. The essential oil of ginger, *Zingiber officinale*.

- nale, and anaesthesia. *Int. J. Aromather.* **15**, 7-14 (2005).
- 8) Masuda, Y.; Kikuzaki, H.; Hisamoto, M.; Nakatani, N. Antioxidant properties of gingerol related compounds from ginger. *Biofactors* **21**, 293-296 (2004).
  - 9) Zhou, H.L.; Deng, Y.M.; Xie, Q.M. The modulatory effects of the volatile oil of ginger on the cellular immune response in vitro and in vivo in mice. *J. Ethnopharmacol.* **105**, 301-305 (2006).
  - 10) Biapa Nya Prosper, C.; Kuate Jules, R.; Wankeu Modeste, Ntiokam D. Acute and subacute toxicity studies of *Zingiber officinalis* Roscoe essential oil on mice (Swiss) and rats (Wistar). *Afr. J. Pharmaceutical Sci. Pharmacy* **1**, 39-49 (2010).
  - 11) Sawamura, M. Aroma and functional properties of Japanese yuzu (*Citrus junos* Tanaka) essential oil. *Aroma Res.* **1**, 14-19 (2000).
  - 12) Jayaprakasha, G.K.; Jagan Rao, L.; Sakariah, K.K. Chemistry and biological activities of *C. longa*. *Trends Food Sci. Tech.* **16**, 533-548 (2005).
  - 13) Hastak, K.; Lubri, N.; Jakhi, S.D.; More, C.; John, A.; Ghaisas, S.D. Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from oral submucous fibrosis. *Cancer Lett.* **116**, 265-269 (1997).
  - 14) Norajit, K.; Laohakunjit, N.; Kerdchoechuen, O. Antibacterial effect of five Zingiberaceae essential oils. *Molecules* **12**, 2047-2060 (2007).
  - 15) Liju, V.B.; Jeena, K.; Kuttanet, R. Antioxidant, anti-inflammatory, and antinociceptive activities of essential oil from *Curcuma longa*. *L. Indian J. Pharmacol.* **43**, 526-531 (2011).
  - 16) Aktoz, T.; Kanter, M.; Uz, Y.H.; Aktas, C.; Erboa, M.; Atakan, I.H. Protective effect of quercetin against renal toxicity induced by cadmium in rats. *Balkan Med. J.* **29**, 56-61 (2012).
  - 17) Guisti, G.; Galanti, B. Colorimetric method. in *Methods of Enzymatic Analysis* (Bergmeyer, H.U. ed.). Verlag Chemie, Weinheim, pp. 315-323 (1984).
  - 18) Bradford, M.M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal. Biochem.* **72**, 248-254 (1976).
  - 19) Prozialeck, W.C.; Edwards, J.R. Cell adhesion molecules in chemically induced renal injury. *Pharmacol. Ther.* **114**, 74-93 (2007).
  - 20) Boroushaki, M.T.; Mollazadeh, H.; Rajabian, A.; Dolati, K.; Hoseini, A.; Paseban, M.; Farzadnia, M. Protective effect of pomegranate seed oil against mercuric chloride-induced nephrotoxicity in rat. *Ren. Fail.* **36**, 1581-1586 (2014).
  - 21) Obianime, A.W.; Roberts, II. Antioxidants, cadmium-induced toxicity, serum biochemical and the histological abnormalities of the kidney and testes of the male wistar rats. *Niger. J. Physiol. Sci.* **24**, 177-185 (2009).
  - 22) Renugadevi, J.; Milton Prabu, S. Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. *Toxicology* **256**, 128-134 (2009).
  - 23) Jung, H.Y.; Seo, D.W.; Hong, C.O.; Kim, J.Y.; Yang, S.Y.; Lee, K.W. Nephroprotection of plantamajoside in rats treated with cadmium. *Environ. Toxicol. Pharmacol.* **39**, 125-136 (2015).
  - 24) Ajith, T.A.; Aswathy, M.S.; Hema, U. Protective effect of *Zingiber officinale* roscoe against anticancer drug doxorubicin-induced acute nephrotoxicity. *Food Chem. Toxicol.* **46**, 3178-3181 (2008).
  - 25) Jeena, K.; Liju, V.B.; Kuttan, R. A preliminary 13-week oral toxicity study of ginger oil in male and female Wistar rats. *Int. J. Toxicol.* **30**, 662-670 (2011).
  - 26) Ademiluyi, A.O.; Oboh, G.; Ogunsuyi, O.B.; Akinyemi, A.J. Attenuation of gentamycin-induced nephrotoxicity in rats by dietary inclusion of ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) rhizomes. *Nutr. Health* **21**, 209-218 (2012).
  - 27) Jurenka, J. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. *Altern. Med. Rev.* **14**, 141-153 (2009).
  - 28) Bagad, A.S.; Joseph, J.A.; Bhaskaran, N.; Agarwal, A. Comparative evaluation of anti-inflammatory activity of curcuminoids, turmerones, and aqueous extract of *Curcuma longa*. *Adv. Pharmacol. Sci.* **2013**, 805756 (2013).
  - 29) Hart, P.H.; Brand, C.; Carson, C.F.; Riley, T.V.; Prager, R.H.; Finlay-Jones, J.J. Terpinen-4-ol, the main component of the essential oil of *Malaleuca altemifolia* (tea tree oil), suppresses inflammatory mediator production by activated human monocytes. *Inflamm. Res.* **49**, 619-626 (2000).
  - 30) Burnstock, G. Historical review: ATP as a neurotransmitter. *Trends Pharmacol. Sci.* **27**, 166-176 (2006).
  - 31) Rial, D.; Lara, D.R.; Cunha, R.A. The adenosine neuromodulation system in schizophrenia. *Int. Rev. Neurobiol.* **119**, 395-449 (2014).
  - 32) Antonioli, L.; Colucci, R.; La Motta, C.; Tuccori, M.; Awwad, O.; Da Settimo, F.; Blandizzi, C.; Fornai, M. Adenosine deaminase in the modulation of immune system and its potential as a novel target for treatment of inflammatory disorders. *Curr. Drug Targets* **13**, 842-862 (2012).