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Research Article

Effect of *Ficus carica* extract on hematological parameters and antioxidant defense system in erythrocytes of albino rats exposed to nickel chloride

Souhila NEMICHE[1]*, Nadia AIT HAMADOUCHE[1], Saïd NEMMICHE[2]

[1]*University of Oran 1 Ahmed Ben Bella, Faculty of Nature and Life Sciences, Department of Biology, Oran 31000, Algeria; sbiochimie@outlook.fr (*corresponding author); naithamadouche@live.fr*
[2]*University of Mostaganem, Faculty of Nature and Life Sciences, Department of Biology, Mostaganem 27000, Algeria; snemiche@hotmail.com*

Abstract

Heavy metals including nickel have adverse effects on hematological system and red blood cells antioxidant defense. The purpose of the study is to examine the possible corrective effect of fig (*Ficus carica* L.) extract (FCE) on hematological parameters and antioxidant enzyme activities in red blood cells of rats exposed to sub-lethal concentration of nickel. Male Wistar rats were exposed to nickel chloride (10 mg/kg) and then treated or no with FCE (350 mg/kg) for 4-weeks. The intoxication induces alteration of haematological parameters and enhances blood haemolysis, generates oxidative stress induced decrease in the antioxidant enzyme activities and depletion in reduced glutathione levels in intoxicated group compared to the control group. The oral administration of FCE increase significantly hemoglobin levels (Hb), red blood cells count (RBC), hematocrit (Ht) and decreases white blood cells counts (WBC), and platelets in *F. carica* treated groups, and also the extract increase the GSH-Px and SOD antioxidant activity, GSH reserves in red blood cells, and reduces lipids peroxidation. The present study concludes that fig fruits may exhibit potent antioxidant potential for erythrocytes and have a positive effect on hematological system.

Keywords: erythrocytes; fig; haematology; nickel chloride; oxidative stress

Introduction

Humans are exposed continuously or accidentally to natural and/or synthetic chemical pollutants that may interfere with their overall health status. Nickel (Ni) is a known heavy metal potentially toxic that can affect multiple organs in living systems (Song *et al*., 2017). Humans are exposed to Ni via occupational and environmental exposure such as refining, mining, stainless steel industries, and battery manufacturing (Schmidt *et al*., 2016). Other environmental sources at low concentrations of nickel include tobacco (Harasim and Filipek, 2015) cooking utensils made of stainless steel and dental or orthopedic implants. Nickel absorption, distribution and removal are influenced by factors such as the route of exposure, the physical form of the

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material (solid or powder) and the aerodynamic size of the nickel particles (Fay *et al.*, 2005). According to Buxton *et al.* (2019) the distribution and removal of nickel depend on the route of administration and its binding to proteins. Inhaled nickel is distributed mainly to the respiratory tract (lungs, nasal sinuses) and then to the kidneys (Dunnick *et al*., 1989). Orally absorbed nickel is distributed to the kidneys and then to the liver, brain, and heart (Finke *et al*., 2015). The immediate toxic effects of Ni exposure are the development of allergies manifested by contact dermatitis, respiratory tract irritation and neurological disorders (Song *et al*., 2017). Several studies have already indicated that a long-term exposure to nickel causes various toxic effects on different organs such as the lungs, liver, kidneys and cardiovascular system (Buxton *et al*., 2019).

The toxic effects of nickel may be prevented by some exogenous supplementation of antioxidant compounds. In recent years, scientific investigations have been a growing interest in the potential use of medicinal plant extracts to cure and prevent disease and protection against the effects of various xenobiotics (Hao *et al*., 2015; Kopeć *et al*., 2016).

Ficus carica L., also known as figs, is a fruit rich in natural bioactive compounds (Nemiche *et al.,* 2022; Rodríguez-Solana *et al*., 2018) with powerful antioxidant. This potential is related to the high presence of secondary metabolites. Figs are considered as an important source of calcium and fiber, rich in sugar, iron, minerals, vitamins and amino acids. In addition, it is one of the highest sources of bioactive compounds such as phenolic acids, flavonoids, flavonols and flavanones, hydroxycinnamic acids, anthocyanins, and pro-anthocyanidins (Pereira *et al*., 2017). *F. carica* L. has been incorporated into Western pharmacopoeias and therapeutic guidelines for medicinal plants (Barolo *et al*., 2014) for a long time. It has been reported that various parts (fruit, roots and leaves) and extracts of the Fig tree can be used in the medical treatment of several diseases (Menichini *et al*., 2012). Fruits are also considered as a good laxative, expectorant and diuretic, and can be used against bleeding (Solomon *et al*., 2006) or as a dietary supplement for diabetics (Veberic *et al*., 2008).

Our study was aimed to evaluate the potential toxic effects of nickel chloride on blood components, mainly red blood cells (RBCs) and the possible corrective or protective effect of figs extract against nickel injuries.

Materials and Methods

Plant material

Fig (*Ficus carica* L.) fruits 'White' variety was collected in a coastal region of western Oran (Algeria). They were identified taxonomically and authenticated by Prof. Hadjadj-Aoul at the Herbarium of Botany Directorate in Ahmed Ben-Bella Oran 1 University (voucher specimen N° LB 0695). The fruits were dried and ground into powder. The Oliveira *et al.* (2009) method was used to prepare fig fruit extract (FCE) as follows: 50 g of powder fig were boiled for 15 minutes, filtered, and then lyophilized (Christ-Alpha 2-4 LSC D-37520).

Animals

A total of 48 male albino Wistar rats weighing (165 ± 5 g) were used for this study. The animals were housed under standard conditions photoperiod (12-h light/dark cycle), temperature (23 ± 1 °C) and humidity (50 ± 15%), and maintained with free access to standard diet and water *ad libitum*.

Experimental design

The rats were randomly divided into two lots: Control lot (24 rats) considered as negative control received an intraperitonial (i.p) injection of 0.9 % saline solution, and intoxicated lot (24 rats) received 10 mg $NiCl_2$ kg^{-1} body weight (BW) by i.p injection three times a week. After 1 month of the experiment, 8 rats of each lot which represents respectively:

"**Group C1**" from control lot and "**Group Ni1**" from intoxicated lot were sacrificed.

The rats remaining were divided into 4 groups of 8 rats each as follow:

- Two groups from control lot:
  - **Group "C2":** served as a negative control group.
  - **Group "C+FC":** served as positive control and received 350 mg kg^{-1} fig "*Ficus carica*" extract (FCE) by gavage for 4 weeks.
- Two groups from intoxicated lot:
  - **Group "Ni2":** were given free access to water and food for 4 weeks after stopping the intoxication;
  - **Group "Ni+FC":** were treated with 350 mg FCE kg^{-1} BW for 4 weeks after stopping the intoxication too.

Blood collection and hematological analysis

The blood samples were stored in anticoagulant bottles containing EDTA (ethylene diaminetetra-acetic acid-Na_2) (Sigma, St. Louis, Mo, USA) and used subsequently for hematological analysis. Red blood cells count (RBC x 10^6 mm^{-3}), white blood cells count (WBC x 10 mm^{-3}), hemoglobin concentration (Hb, $g.dL^{-1}$), haematocrit (Ht %), mean total platelet count (TPL %), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) were measured by using fully automated hematology analyzer (Biobase BK6200).

Erythrocytes separation

The erythrocyte suspension was prepared as mentioned by Beutler *et al.* (2011) for the evaluation of GSH, MDA level, SOD, GPx, and CAT activities.

Lipid peroxidation determination

Red blood cells' (RBC) lipid peroxidation was analyzed in accordance with Brown and Duthie's method (1997). Briefly, 100 µl of RBC were diluted in 900 µL of PBS buffer, added to 100 µL of H_2O_2 (1.15%) and then incubated for 60 min at 37 °C. A solution of 1 mL of 20% trichloroacetic acid (TCA) was added. After centrifuging at 2,000 x g for 10 min, the supernatant sample was mixed with 100 µL of 2% butylated hydroxy Toluene (BHT).

RBCs antioxidant capacity and Assessment of haemolysis

Antioxidant activity for catalase was estimated at 240 nm by observing the decomposition of H_2O_2 and a decrease in absorbance as described by Aebi (1984). The superoxide-dismutase (SOD) activity was determined following the procedure described by Marklund and Marklund (1974). GSH-Px (EC 1.11.1.9) activity in RBCs was assessed as described by Rotruck *et al.* (1973). The concentration of GSH was measured according to the method of Ellman (1959) and haemolysis was evaluated following the method of Khan *et al.* (2015).

Statistical analysis

The data were expressed as the Mean ± SEM in each group and analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. All statistical analysis was carried out with SPSS statistical software (ver.23.0, SPSS Inc., Chicago, IL, USA). The level of significance was set at $p < 0.05$.

Results

Hematological parameters

The effect of nickel and FCE on hematological parameters in different experimental groups is represented in Table 1. Nickel causes a significant ($p<0.001$) decrease of RBC, Hb, and Ht by -28%, -26%, -26% respectively in the Ni1 group compared to control C1, in parallel an increase in the rate of WBC and platelet by +71%, +48% respectively was also observed in this group. The administration of the fig extract after stopping nickel intoxication to the Ni+FC rat group shows a significant increase by +33%, +34%, +9% and 12% in RBC, Hb, Ht and MCV level respectively and decrease by -40% in platelet counts compared to the Ni2 group. No significant variation was observed at the other parameters level of WBC, MCH, and MCHC.

Table 1. Effect of $NiCl_2$ and FCE on hematological parameters of different experimental groups

Parameters	Experimental groups					
	C1	C2	C+FC	Ni1	Ni2	Ni+FC
RBC (x 10^6 mm^{-3})	7.58 ± 0.14	8.38 ± 0.26	8.72 ± 0.05	5.50 ± 0.22***	6.42 ± 0.07	8.58 ± 0.06$^{\#\#\#}$
HB (g/dl)	12.72 ± 0.24	14.10±0.15	13.80±0.80	9.35±0.25***	10.82±0.17	14.55±0.05$^{\#\#\#}$
Ht (%)	37.44 ± 0.74	41.26±0.56	43.15±0.68	27.53±0.12***	41.85±0.39	45.72±0.43$^{\#\#}$
MCV (fL)	49.83 ± 0.16	49.16±0.40	47.50±0.50	48.66±0.33	47.50±0.50	53.50±0.50$^{\#\#\#}$
MCH (pg)	32.08 ± 0.90	34.13±0.17	34.65±0.35	33.50±0.30	33.74±0.10	33.51±0.27
MCHC (g/dL)	16.85 ± 0.33	16.94±0.37	16.55±0.05	16.40±0.28	16.42±0.16	16.95±0.23
WBC(x$10^3$$mm^{-3}$)	3.04 ± 0.41	2.98±0.19	2.75±0.47	5.20±0.37**	4.12±0.09	3.02±0.07
Platelet (10^3 cell/µl	684 ± 31	694±17.03	643.5±11.50	1012.5±16.50***	791±47	598.33±10.91$^{\#\#}$

Each value is mean ± SEM, n = 8 (Tukey test, $p < 0.05$). The * depicts comparison with group "C1";
$^{€}$ depicts comparison with group "C2" ($^{€}p < 0.05$, $^{€€}p < 0.01$, $^{€€€}p < 0.001$); $^{\#}$depicts comparison with group "Ni2" ($^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$)

RBCs Antioxidant enzymes activities

The level of erythrocyte antioxidant activity is represented in Table 2. In the Ni1 intoxicated group, the catalase activity shows a twofold-increase compared to control C1 group, while the activity of the GSH-Px and SOD recognize a significant decrease of 44% and 48% respectively in this group compared to control C1. After 1 month of stopping the intoxication and FCE administration, a significant increase of +56% in SOD activity is observed with a twofold-increase in GSH-Px activity in rats of the Ni+FC group treated with FCE in comparison to rats of the Ni2 group. Also, in the control treated group we observe two-fold-increases in SOD activity and significant enhancements of +58% in GSH-Px activity in rate of C+FC group compared to control C1 group.

Table 2. Effect of $NiCl_2$ and FCE on antioxidant enzymes activities in RBCs of different experimental groups

Parameters	Experimental groups					
	C1	C2	C+FC	Ni1	Ni2	Ni+FC
CAT (pmol/min/mL)	419.03 ± 39.4	602.43 ± 65.6	516.7 ± 13.3	856 ± 42.8***	499.63± 10.2	417.14 ± 12.42
SOD (U/mL)	1679 ±116	1869 ± 17.5	4178± 129$^{€€€}$	928 ± 29**	1156 ± 35.6	1807 ± 33.5$^{\#}$
GSH-Px (nmol/min/mL)	25.09±0.02	32.73±1.74	51.93 ±0.68$^{€€}$	10.38 ± 0.26*	14.92 ± 2.56	36.83 ± 5.74$^{\#\#}$

Each value is mean ± SEM, n = 8 (Tukey test, $p < 0.05$). The * depicts comparison with group "C1";
$^{€}$ depicts comparison with group "C2" ($^{€}p < 0.05$, $^{€€}p < 0.01$, $^{€€€}p < 0.001$); $^{\#}$depicts comparison with group "Ni2" ($^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$).

RBCs malondialdehyde levels

The erythrocyte MDA levels of different experimental groups are represented in Figure 1. Nickel induced a lipid peroxidation justified by the three-fold increase of the erythrocytes MDA level in the rats of the Ni1 group in contrast to the C1 group. However, we notice a significant decrease by 74% in the Ni+FC group after FCE administration in comparison to Ni2 group.

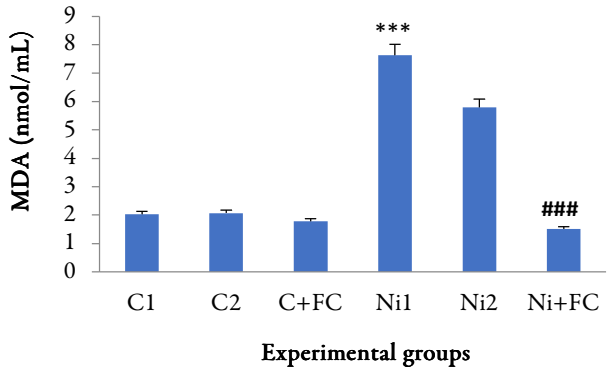

Figure 1. Effect of $NiCl_2$ and FCE extract on MDA level of different experimental groups
Each value is mean ± SEM, n = 8 (Tukey test, $p < 0.05$). The *depicts comparison with group "C1"; #depicts comparison with group "Ni2" ($^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$).

RBCs Reduced glutathione (GSH) levels

The reduced glutathione concentration in the animals of the different experimental groups is shown in Figure 2. Nickel induced a significant decrease by 49% in the erythrocyte glutathione levels in the Ni1 group rats compared to the control C1. No significant variation was observed after FCE administration in the erythrocyte glutathione reserves in the rats of the Ni+FC group against the Ni2 group

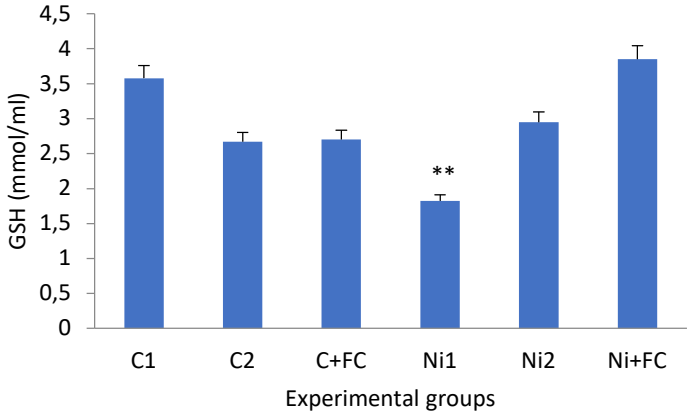

Figure 2. The effect of $NiCl_2$ and FCE on GSH levels of different experimental groups
Each value is mean ± SEM, n = 8 (Tukey test, $p < 0.05$). The * depicts comparison with group "C1

Haemolyse

The percentage haemolysis induced by nickel and Fig extract in the different experimental groups is represented in the Figure 3. In Wistar rats, nickel chloride injection caused a significant increase (+78%) in

haemolysis levels in Ni1 group compared to control C1. In contrast, the treatment with figs extracts after stopping nickel intoxication induced a significant decrease (-24%) in haemolysis in rats of Ni+FC group compared to the Ni2 group.

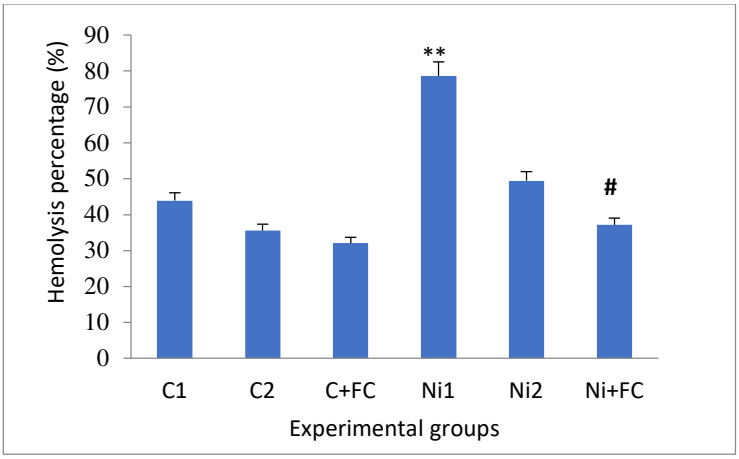

Figure 3. Effect of $NiCl_2$ and FCE on haemolysis (%) of different experimental groups
Each value is mean ± SEM, n=8 (Tukey test, $p < 0.05$). The * depicts comparison with group "C1"; #depicts comparison with group "Ni2" ($^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$).

Discussion

Blood plays a decisive role in the regulation of vital processes. Hence the need to keep its composition relatively constant and must also has the capacity to modify it in the most extreme stress situations due to the aggressions of various xenobiotics (Schulz *et al*., 2012). Heavy metals are toxic or carcinogenic elements in their nature and are considered as a danger to human health and the environment. The nickel has adversely affected peripheral white blood cells and red blood cells (Méndez-Gomez *et al*., 2008). Evaluation of the hematological and oxidative profile proved to be a sensitive index for the study of the blood toxicity process of nickel. The objective of the current study is to investigate the sub-chronic toxicity of nickel chloride on hematological parameters of adult Wistar rats and the possible corrective effects of FCE as an antioxidant agent to reduce levels of the RBC toxicity. The present data showed that after 30 days of Ni exposure, rats exposed exhibited a significant reduction in their RBC count, Hb concentrations, Ht values and increases in the rate of WBC and platelet count in Ni1 group compared to control C1 group. Adjroud (2013) reported that sub-cutaneous injection of 25 mg $NiCl_2$ kg^{-1} induced a significant decrease in the erythrocyte counts, haematocrit values, and hemoglobin concentration. Significant variations in different blood parameters were also observed by Ololade and Oginni (2010) in the experimental fish after exposure to 4-12 mg nickel sulfate kg^{-1}. Nickel accumulation in the blood may be the cause of the decline in hematological parameters (DemÎr *et al*., 2005) and seemed to be associated with decreased iron absorption in Wistar rats (Cempel and Janicka, 2002). The increase in white blood cells (WBC) count after nickel intoxication may be due to the inflammatory response as a defense mechanism. After one month of nickel stopping exposure, a slight significant improvement in hematological parameters in Ni2 group compared to Ni1 group has been noticed, but the FCE administration showed an important significant increase in RBC counts, Hb concentrations, Ht values with a decrease in the rate of WBC and platelet count. These results are in agreement with results of Said *et al.* (2017) who investigate the possible effect of *F. carica* fruit extracts against lead toxicity on hematological parameters of the fish Nile Tilapia (*Oreochromis niloticus*). In fish exposed to 38.7 mg Pb L^{-1} and received a diet supplemented with 600 mg figs kg^{-1}, we notice an improvement in erythrocyte count, Hb content, and Ht values after 60 days of treatment.

This research considers fig as chelating agent for lead ions. Our findings are in agreement with Fouad *et al*. (2019) who reported that prior to irradiation, oral administration of *F. carica* extract significantly increased WBC, PLT, lymphocyte, and neutrophil counts. Fathy *et al*. (2018) found similar results with rats treated with figs and dates extract for four weeks after exposure to Adricin® (doxorubicin hydrochloride) and / or irradiation. The heamatotoxic effect of nickel is primarily due to the over-stimulation of metallothioneins and reactive oxygen species (ROS) production that leads to erythrocyte oxidative damage. Oxidative stress alters both the activity and content of all antioxidant defense system. Our data on oxidative status indicated that exposure to nickel tends to inhibit SOD and GSH-Px activity and increases the catalase activity which prevent against H_2O_2 accumulation in the erythrocytes of Ni1 intoxicated group. The data show also a decrease in RBCs-GSH level considered as the non-enzymatic first line of defense against oxidative stress induced by heavy metals and an augmentation in MDA level in Ni1 group compared to the C1 group. These results are in accordance with the study of Gupta *et al.* (2006) who showed that nickel sulfate induced an increase in the malondialdehyde, glutathione levels and the activities of SOD, GSH-Px and CAT in erythrocytes compared to untreated control rats. According to Chen *et al*. (2003) and De Luca *et al*. (2007), $NiCl_2$ induces a decrease in the activity of erythrocyte glutathione peroxidase and consequently an increase in oxidative stress. In accordance with study of Kalahasthi *et al*. (2006) the level of MDA in the Ni-intoxicated group is the consequence of increased in RBCs lipid peroxidation. Administration of *F. carica* extract restored the GSH content to normal levels with a decrease in MDA and improved SOD, catalase and GSH-Px activities.

Many authors have already confirmed that *F. carica* have the capacity to improve the activity of antioxidant enzymes and the level of glutathione in serum and different organs. Solomon *et al*. (2010) attributes the antioxidant effect of fresh figs to the presence of a powerful antioxidant called cyanidin-3-rhamnoglucoside (C3R), identified to inhibit lipid peroxidation and reduce oxidative stress. The treatment with the *FC* leaf extract alone or combined with ascorbic acid noticeably prevented the effect of lead induced-oxidative damage in rats (Diab *et al.*, 2018). The fig extract can induce an increase of the antioxidant enzyme level and chelating heavy metal ions, and consequently decreases oxidative stress. Our results are in agreement with the work of El-Sayed *et al.* (2019) who found that administration of dried figs induced an increase in the level of reduced glutathione in animals exposed to diclofenac sodium.

Haemolysis is defined as destruction of erythrocytes with the release of their intracellular contents. Red cells can haemolyse in the presence of chemical species or toxic element (Shah *et al.*, 2011). An excessive haemolysis can cause a reduction of red blood cells count and systematically a hemolytic anaemia. Our results demonstrated that nickel has an important hemolytic power as shown by the increase in the hemolytic percentage in Ni1 exposed group compared to control C1 group. Little amelioration was observed after stopping intoxication in Ni2 group compared to Ni1 group, but an important significant decrease in hemolytic percentage was recorded after stooping intoxication and starting FCE administration in Ni+ FC group compared to Ni2 group. Our data show that fig fruits can protect from haemolysis induced by nickel chloride. According to Asadi-Samani *et al.* (2016), *F. carica species* is a medicinal plant that has been shown to be a hematopoietic agent due to its high antioxidant content, which contributes to the inhibition of the lysis of red blood cell membranes and the prevention of the harmful effects of free radicals.

Conclusions

On the basis of obtaining results, nickel ions induce haematotoxicity and changes in blood parameters. Nickel toxicity in erythrocytes may occur through the oxidative stress pathway. Also, the FCE can exhibit potent antioxidant potential in red blood cells justified by an increase in glutathione reserves and activities of antioxidant enzymes. The effect produced by *F. carica* extract decreases significantly the haematotoxicity effect

of nickel. Its richness and abundance in bioactive compounds make this fruit very important and can be considered as a way of reducing nickel toxicity in the blood.

Authors' Contributions

All authors read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

The animal experiments were conducted by minimizing the degree of suffering in accordance with the ethical principles and institutional guidelines of the National Institutes of Health Guide for the care and use of laboratory animals (8th edition, 2011). The animal experiments were approved by the local ethical committee for the Care and Use of Laboratory Animals in the Oran 1 University.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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