Asian Journal of Agriculture and Biology
https://doi.org/10.35495/ajab.2026.04

Original Article

The role of histidine or carnosine in abrogation the neurotoxicity induced by nickel sulfate via modulation of redox status, neurotransmitters, anti-inflammatory and energy level in rats

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Received: 02 January 2026 / Revised: 10 February 2026 / Accepted: 19 February 2026 / Published Online: 08 March 2026

Abstract

Exposure to heavy metals such as nickel can affect many vital organs such as liver, kidney, and nervous system. The current study investigated the neurotoxicity of nickel sulfate in rats and the potential of histidine and its dipeptide derivative (carnosine) in abrogation of this toxicity. The present study was carried out on a total of 48 male Albino rats (100 ±10g). Rats were randomly equally grouped into six (8 rats each). Group I: Control. Group II: Rats received histidine chloride (10 mg/Kg b.w/day) orally for 30 days. Group III: Rats received carnosine (10 mg/Kg b.w/day) orally for 30 days. Group IV: Rats were injected *i.p* with (20 mg/kg b.w) daily of nickel sulfate for 30 days. Group V: Rats were injected *i.p* with 20 mg/kg daily of nickel sulfate and histidine chloride orally (10 mg/Kg b.w) for 30 days. Group VI: Rats were injected *i.p* with (20 mg/kg b.w) of nickel sulfate and carnosine orally (10 mg/Kg b.w) for 30 days. Data showed that nickel administration caused a significant decrease in hemoglobin and GSH levels, elevation of serum MDA, NO, IL-6, TNF-α levels, reduction in the activities of SOD and catalase. In addition, in brain tissue, a significant decrease in the levels of epinephrin, serotonin and ATP levels and acetylcholine esterase activity while increased in glycogen phosphorylase activity. The histidine or carnosine improved and recovered abnormalities induced by nickel significantly compared with untreated. The carnosine showed more effectiveness than histidine. In conclusion, the histidine or its derivative carnosine use is promising in preventing neurotoxicity induced by environmental pollution by nickel via anti-inflammatory, antioxidant and keep energy level of brain tissue.

Keywords: Carnosine, Histidine, Neurotoxicity, Nickel sulfate, Oxidative stress, Rats

How to cite this article:
Kumosani TA, Barbour E, Yaghmoor SS and Moselhy SS. The role of histidine or carnosine in abrogation the neurotoxicity induced by nickel sulfate via modulation of redox status, neurotransmitters, anti-inflammatory and energy level in rats. Asian J. Agric. Biol. 2026: e202604. DOI: https://doi.org/10.35495/ajab.2026.04

Introduction

Environmental pollution caused by chemicals products and heavy metals are accumulated in soil, air and water is considered a risk for many diseases worldwide (Chen et al., 2020). Due to industrial revolution, the ecosystem was affected by release of different pollutants produced from industries Many industrial solvents/lubricants, plastics, plasticizers, pesticides and pharmaceutical agents contain heavy metals and can induce adverse effect (Huang et al., 2013). One of the toxic heavy metals is nickel that causes endocrine dysfunction by interference with synthesis and its mechanism of actions. The nickel is produced from recycling and disposal, battery, plastic and rubber industries (Das and Buchner, 2007). Occupational pollution by nickel can affect many organs such as nervous system and may cause different neurological abnormalities (Wu et al., 2013). Also, the prostate, breast, uterus, and pancreas were affected (Meng et al., 2020). The toxicity of nickel is mediated via production of reactive oxygen species and lipid peroxidation (Hassanen et al., 2025). Long term exposure to nickel can lead to hazardous effects ranging from systemic diseases and development of some types of cancer (Genchi et al., 2020). It was reported that there is an association between carcinogenesis and long-term exposure to nickel (Liu et al., 2016). A new strategy for removal of heavy metals toxicity depends on its chelation high affinity natural compounds and converted to nontoxic (Flora and Pachauri, 2010). The chelating agents in biological system are compounds which can react with the metal ions to form nontoxic complexes which are water soluble and eliminated from the body easily (Flora and Pachauri, 2010). The suitable chelating agent should be hydrophilic able to be available in target tissue, stable at physiological pH and forming neutral complexes that can be removed from body. Histidine is one of semi essential amino acids that plays an important role in protein synthesis and production of histamine, anserine and carnosine (Peters et al., 2015). The imidazole ring of histidine showed to be important for biological roles (Bex et al., 2014). Variations in the structure of histidine dipeptides include anserine or carnosine may have ability to chelate with toxic metals and detoxifying agents. It plays important biological role in maintaining health including antioxidant activity (Babizhayev et al., 2013), and scavenge free radicals (Barski et al., 2013), in addition, inhibition of protein glycation (Alhamdani et al., 2007). The current investigated the possible neuroprotective effect of histidine or carnosine against neurotoxicity induced by nickel sulfate in rats through its antioxidant, anti-inflammatory and modulation of neurotransmitters and energy status.

Material and Methods

Animals

The handling of animals was done according to ethical committee of King Abdulaziz University, Jeddah. Animals were treated in accordance with guide for the care and use of laboratory animals The experiment was carried out on a total 48 male albino rats (100 ±10g), aging 4 weeks. The rats were fed on standard diet and water *ad labium*. Rats were randomly distributed equally into six groups (8 rats each).

Group I: Normal rats as control. **Group II:** Rats received histidine chloride (10 mg/kg b.w) orally for 30 days. **Group III:** Rats received carnosine (10 mg/kg b.w) orally for 30 days, the dose given according to (Fouad and Jresat, 2011). **Group IV:** Rats were injected with nickel sulfate *i.p.* (20 mg/kg b.w) for 30 days. The dose was given according to Pari and Amudha, 2011. **Group V:** Rats were injected 20 mg/kg b.w nickel sulfate *i.p* and histidine chloride orally (10 mg/Kg b.w) for 30 days. **Group VI:** Rats were injected 20 mg/kg b.w nickel sulfate *i.p* and carnosine orally (10 mg/Kg b.w) for 30 days. At the end of experiment, rats were fasted overnight, blood samples were collected and divided into three parts, first part on heparin for hemoglobin assay, second part in plain tube for serum separation and third part on EDTA for plasma separation. Brain was isolated and immersed in ice cold phosphate buffer saline (pH, 6.5) to remove any blood. One gram of brain tissue was homogenized in 10 ml PBS using glass homogenizer, centrifuged at 4000 RPM for 10 minutes (Guan et al., 2007). Supernatant was stored at -80°C till analysis.

Biochemical analysis

Hemoglobin was determined by colorimetric assay kit from ABCAM (ab234046, UK). Serum was subjected to assay of malondialdehyde by Colorimetric method using kit cat # ab11897, nitric oxide by Colorimetric method using kit cat# ab65328, catalase enzymes using colorimetric kit cat # (ab83464), superoxide dismutase activity by Colorimetric method using kit cat# ab65354 and reduced glutathione by fluorometric

method using kit# ab65322. Serum interleukin -6 (IL-6) was determined by ELISA Kit # ab234570. Tumor necrosis factor-α were determined by ELISA cat # ab236712.

Biochemical analysis of brain homogenates

One gram of brain tissue was homogenized in 10 ml ice cold PBS in glass homogenizer and then centrifuged at 4000 RPM for 10 minutes. The supernatant was used for assay of epinephrine, serotonin and acetylcholine and choline esterase activity by ELISA techniques. In addition, glycogen phosphorylase was evaluated by ELISA kit from MyBioSource, Cat # MBS264178, USA and ATP level was determined by colorimetric method using kit from ABCAM, Kit ab83355, UK.

Statistical analysis

Results were statistically analyzed by ANOVA using SPSS version 20. Data was written as mean ± SD. *P* values less than 0.05weres considered significant.

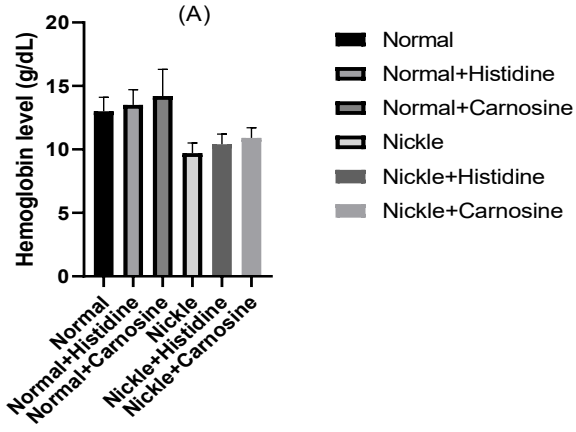
Results

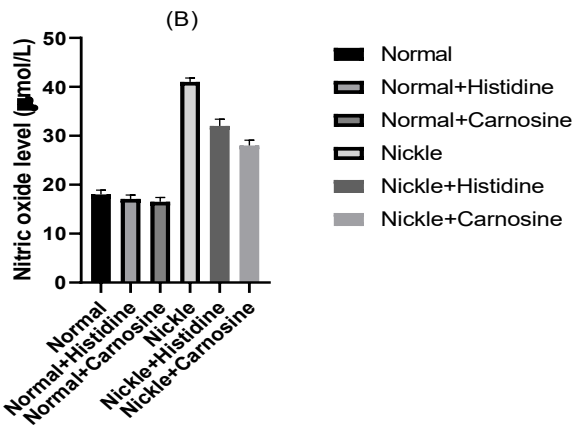
Data obtained in this study showed that, hemoglobin level was significantly decreased in rats exposed to nickel sulfate compared with control group ($p<0.001$). However, treatment with histidine or carnosine improve hemoglobin level but not returned to normal. The effect of carnosine is better than histidine. Normal rats treated with histidine or carnosine are not affected on hemoglobin level or any biochemical markers significantly. Rats injected with Nickel lead to a significant reduction in level of GSH and activities of catalase and SOD compared with normal and a significant elevation in the levels of nitric oxide and MDA ($p< 0.001$) compared with control. However, treatment with histidine and carnosine caused a significant reduction in nitric oxide and MDA and a significant elevation in GSH level ($p<0.01$), SOD and catalase activities compared with untreated group.

Data presented in (figure 2) revealed inflammatory mediators measured in different groups as indicated by a significant elevation in levels of (IL-6 and TNF-α) ($p<0.001$) in rats given nickel sulfate compared with control. Treatment with histidine or carnosine suppress release of these mediators significantly compared with untreated ($p<0.001$). The effect of carnosine is better than histidine.

Results obtained in (figure 3) indicated that, there were a signification reduction in the activity of acetylcholinesterase and levels of epinephrine and serotonin in rats injected with nickel sulfate compared with normal control ($p<0.001$). Treatment with histidine or carnosine stimulated the acetylcholinesterase activity and increased levels of epinephrine and serotine compared with untreated but not reached to normal levels.

The activity of glycogen phosphorylase, a key enzyme in glycogen degradation and level of ATP as shown in (figure 4) were significantly decreased in rats injected with nickel compared with control group ($p<0.001$). Treatment with histidine or carnosine enhances activity of glycogen phosphorylase and increases levels of ATP in brain tissue compared with untreated. The effect was limited to normal levels.





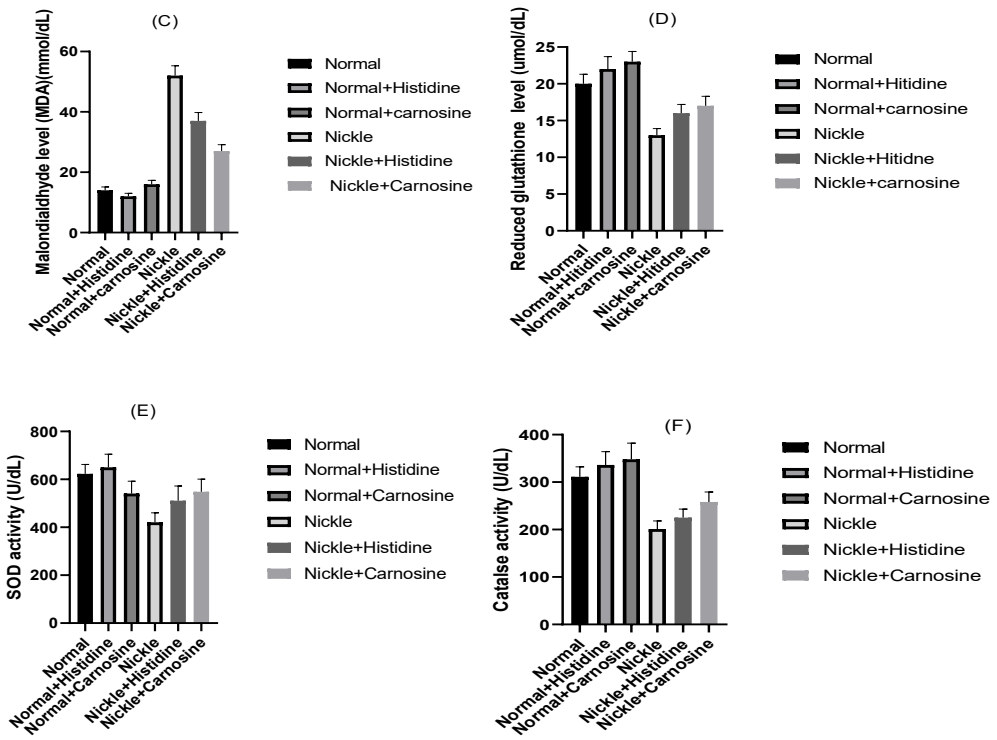


Figure-1. The levels of hemoglobin (A), nitric oxide (B), malondialdehyde (C) and reduced glutathione (D) and the activities of superoxide dismutase (E) and catalase (F) in all studied groups (Mean ±SD).

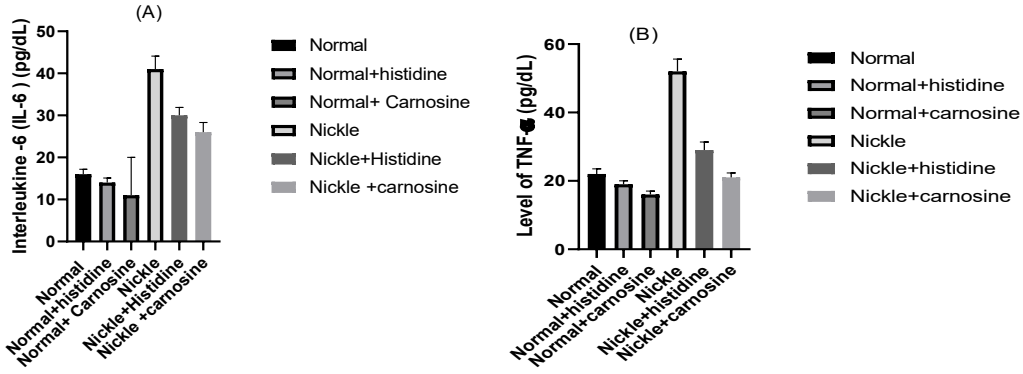


Figure-2. Serum levels of TNF-α (A) and IL-6 (B) in all studied groups (Mean ±SD).

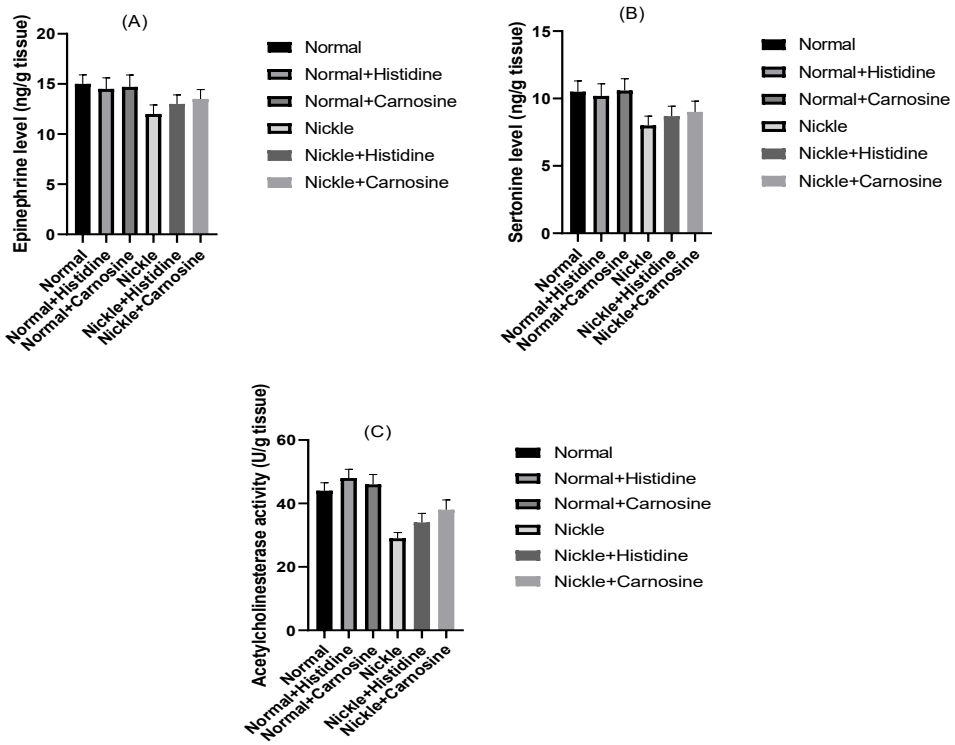


Figure-3. Levels of brain epinephrine (A), serotonin (B) and acetylcholine esterase (C) in all studied groups (Mean ±SD).

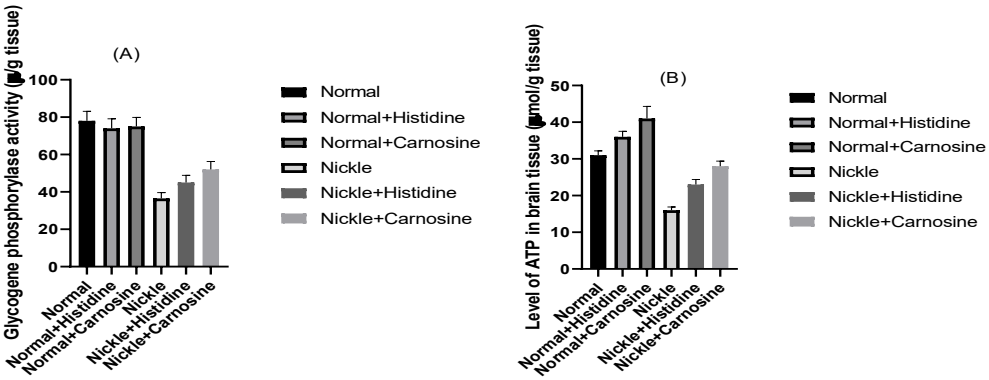


Figure-4. Activity of glycogen phosphorylase (A) and level of ATP (B) in brain tissue of all studied groups (Mean ±SD).

Discussion

Heavy metals present in most products and daily obligatory exposed as medical tools, home containers for water, foods, baby toys and dental biomaterials (Ali et al., 2019). The contamination with toxic heavy metals and waste deposition affects ecosystem in the future for long-life. One of the most probably toxic metal is nickel which is considered harmful in soils and may come from anthropogenic waste, as solid or liquid deposits, agricultural inputs and sludge factories and urban emissions (Su et al., 2014). Excessive accumulation of nickel in soils may contaminate foods products and affect quality and food products safety.

The neuroprotective effect of histidine and carnosine against nickel toxicity was investigated. It was found that nickel caused a significant decrease in hemoglobin level while histidine or carnosine treatment improved its level but not as normal level. This data is in agreement with previous study who reported that nickel administered subcutaneously in rats caused anemia.

This is in agreement with De Luca et al. (2007) and Joshi et al. (2002) who reported that decreased iron absorption from intestine, defect in erythropoiesis, or hemolysis. Also, Arjun et al. (2002) revealed a reduction in blood indices in rats treated with Cr and Ni may be due to injury of hematopoietic stem cells. Tikare et al. (2012) found that low level of hemoglobin may be due to decreased formation from succinate and glycine or interference with iron absorption. In addition, nickel chloride was found to inhibit the activity of glutathione peroxidase in RBCs and increase free radicals' production and lipid peroxidation (De Luca et al., 2007).

In current study, the distribution in antioxidant system in rats injected with nickel is indicated by increased lipid peroxidation and decreased antioxidant potential. This is in agreement with previous work that reported a significant reduction in the activities of SOD and GSRase activities after nickel administration in rats (Adedara et al., 2020). The protective effect of histidine or carnosine against neurotoxicity of nickel was approved by decreased MDA and NO levels and enhancement of catalase, SOD and GSH compared with untreated rats. Histidine or carnosine may chelate with nickel forming nontoxic form to prevent its neurotoxicity. It was stated that carnosine showed a potent free radicals scavenging and anti-inflammatory effect (Wu, 2020). Carnosine was found to exert chelation against transition metals, antiglycation and inhibit protein aggregation (Caruso et al., 2022). The carnosine function inhibits Oxidized LDL-c and protect endothelial cells from damage (Matic et al., 2022; Bingül et al., 2017).

Nickle was found to act as blocker for calcium channel. Also, it can affect the electrophysiological of neurons, so it exerts neurotoxicity (Meng et al., 2024). The heavy metal-induced neurotoxicity is mediated by different mechanisms including oxidative stress and dysregulation of neurotransmission (Goyer, 2001). This toxicity may involve damage of the cell membrane, DNA damage and reduction of antioxidants activity (Singh et al., 2011). Nickle exposure is associated with different neurological abnormalities such as memory, concentration and neuropathy. The neurotoxicity mediated by lipid peroxidation and reduction in superoxide dismutase, and reduced glutathione levels. In addition, alter metabolism of neurotransmitters as acetylcholine as indicated in current study.

The impact of carnosine to reduce inflammatory mediators TNF-α in agreement of the study carried out by Yan et al. (2009) who stated that carnosine pre-treatment suppress hepatic inflammatory cytokines (TNF-α and IL-6) in hepatic injury by acetaminophen. For that, abrogation impact on cytokines release related to anti-inflammatory action of carnosine. Cuzzocrea et al. (2007) stated that carnosine inhibits production of TNF-α in lung injury induced by bleomycin. Also, Andou et al. (2009) found that histidine abrogated intestinal proinflammatory cytokine secretion from macrophages (IL-6 and TNF-α) by lipopolysaccharides injection. Zhang et al. (2015) attenuated brain inflammation by carnosine. Similar data reported by Dkhil et al. (2014) who stated the protective effect of carnosine against toxicity caused by Cd via NO inhibition. It is well recognized that the brain is a very sensitive organ to nickel induced neurotoxicity. It accumulates in and causes neurological dysfunction (He et al., 2013). The neurotoxicity of Ni was associated with abnormalities in metabolism for energy production, redox status, production of inflammatory mediators and apoptosis (Ijomone, 2020).

The data obtained revealed decreased ATP level and glycogen phosphorylase in rats given nickel compared with control. However, histidine or carnosine treatment elevated their levels compared with untreated. The effect of nickel may be due to interference with electron transport chain and cytochrome for energy release while the protective effect may be due to chelation of histidine or carnosine with nickel. The normal rats given histidine or carnosine did not show any significant changes in the parameters studied. This reflects its safety without any side effects.

Conclusion

The basic amino acid histidine or its derivative carnosine is promising in preventing neurotoxicity induced by nickel via anti-inflammatory, antioxidant and keep energy level of brain tissue. Further study needed to track the signals mediated this action on cell line model.

https://doi.org/10.35495/ajab.2026.04

Acknowledgment
This research was funded by Institutional Fund Projects under Grant No. (IFPRC-130-130-2020). Therefore, authors gratefully acknowledge technical and financial support from the Ministry of Education and King Abdulaziz University, Jeddah, Saudi Arabia. The authors, therefore, acknowledge with thanks DSR for technical and financial support.

Disclaimer: None.
Conflict of Interest: None.
Source of Funding: This research work was funded by Institutional Fund Projects under Grant No. (IFPRC-130-130-2020). Therefore, authors gratefully acknowledge technical and financial support from the Ministry of Education and King Abdulaziz University, Jeddah, Saudi Arabia.

Ethical Approval Statement
The study protocol was approved by the Ethics Committee of King Abdulaziz University, Jeddah, Saudi Arabia. The protocol was done according to the ethical guidelines of the 1975 Declaration of Helsinki.

Data Availability Statement
All datasets generated or analyzed during this study are included in the manuscript.

Contribution of Authors
Kumosani TA, Barbour E & Moselhy SS: Conceived idea, designed research protocols, interpreted data and wrote the first draft.
Yaghmoor SS: Conducted experiments and collected data.
Moselhy SS & Kumosani TA: Analyzed and interpreted data and edited the manuscript.

All authors read and revised the manuscript and approved the final draft for submission.

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