POSSIBLE PROTECTIVE EFFECT OF CARNOSINE ON CADMIUM-INDUCED RENAL DYSFUNCTION IN OLD RATS

By

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ABSTRACT

Background: L-carnosine can suppress increased renal sympathetic nerve activity (SNA) during the renal ischemia by its action on the central nervous system and that this suppressive effect is probably responsible for the renoprotection against ischemic/reperfusion induced renal injury. In addition, the renoprotective effect of L-carnosine on ischemic acute renal failure seems to be induced by its conversion to L-histidine and L-histamine, and it is mediated through the activation of histamine H3 receptors in the central nervous system.

Objective: Studying the effect of carnosine as a potential antioxidant agent on cadmium–induced lipid peroxidation and renal oxidative stress in aged rats.

Materials and Methods: The present study was performed on 45 aged female Wistar rats, weighing at the start of the study between 280-380 g. Animals were randomly divided into the following equal groups: Control group, Cadmium group, and Carnosine treated group. Blood samples were collected and were subjected to measurement of serum urea, creatinine, albumin, malondialdehyde (MDA), superoxide dismutase (SOD), nitric oxide (NO) levels, tumor necrosis factor-α (TNF-α), interleukin10 (IL-10) levels, renal tissue tumor necrosis factor-α (TNF-α), superoxide dismutase (SOD), nitric oxide (NO) levels and measurement of cadmium (Cd) level in blood and renal tissue. Also, histopathological study of rat kidneys was performed.

Results: Significant increases in serum urea and creatinine, MDA, IL10, serum and renal tissue NO, TNF -α, blood and renal tissue cadmium levels were encountered in cadmium group compared to control group. Carnosine treatment significantly decreased serum urea, creatinine, MDA, IL10, serum and renal tissue NO, TNF -α, blood and renal tissue cadmium levels compared to cadmium group though the levels were still significantly higher than control group. Serum albumin, serum and renal tissue SOD levels significantly decreased in cadmium group compared to control group. By treatment with carnosine, significant increases were observed compared to cadmium group though still significantly less compared to control group.

Conclusion: Increased lipid peroxides induced by cadmium toxicity in aged rats may implicate the renal oxidative stress. Moreover, pretreatment with carnosine successively boosted the antioxidant system through several mechanisms such as scavenging/neutralizing free radicals, regulating enzymatic/non enzymatic antioxidants. However, future work is needed to confirm our results.

Key Words: Cadmium toxicity, L-carnosine, Kidney functions.

INTRODUCTION

Cadmium (Cd) is one of the most toxic non-essential metals, an environmental and occupational pollutant endangering human and animal health (**El-Boshy et al., 2014**). Cigarette smoking is a significant source of environmental Cd exposure (**Gobe and Crane, 2010**). The kidney, skeleton and lungs are the tissues most

affected by chronic Cd toxicity. With chronic exposure to Cd, approximately 50% of the accumulated dose is stored in the kidneys (**Johri et al., 2010**).

Aging in most species associates with impaired adaptive and homeostatic mechanisms that leave an individual susceptible to environmental or internal stress followed by increasing rates of disease and death (**Anderson et al., 2009 and Ning et al., 2013**).

Histidine-containing dipeptides like carnosine and arnesine have protective functions in both health and disease (**Peters et al., 2015**). The best-characterized histidine-containing dipeptide is carnosine (**Boldyrev et al., 2013 and Budzen & Rymaszewska, 2013**), which is stored in several tissues (**Bex et al., 2014**). It plays many roles in maintaining health including antioxidant activity (**Babizhayev et al., 2013**), and the ability to scavenge carbonyls (**Barski et al., 2013**), as well as it inhibits glycation (**Alhamdani et al., 2007**).

MATERIALS AND METHODS

The present study was performed on 45 aged female Wistar rats, weighing at the start of the study 280-380 g. Animals were put in cages (45×30×30 - 5 rats per cage). Animals were randomly divided into the following equal groups:

1. **Control group:** Rats in this group were injected intra-peritoneally (i.p) with normal saline, in volumes equivalent to those in which cadmium chloride (CdCl$_2$) was dissolved, 6 days/week, for 2 weeks.

2. **Cadmium group:** Rats in this group were injected i.p. with cadmium chloride (Nile Company. Egypt) at a

dose of 2 mg /kg daily (**Karabulut-Bulan et al., 2008**), 6 days / week for 2 weeks

3. **Carnosine treated group:** Rats in this group received cadmium chloride at a dose of 2 mg/kg/day i.p. one hour after i.p. injection of carnosine in a dose of 10 mg /kg /day (**Fouad et al., 2009**).

■ **Blood samples were collected, centrifuged, and sera were separated for measurement of:**

1. Serum urea (**Young, 1995**).

2. Serum creatinine (**Bartles et al., 1972**).

3. Serum albumin (**Doumas et al., 1971**).

4. Serum malondialdehyde (MDA), as an indicator of lipid peroxidation products (**Armstrong and Browne, 1994**).

5. Serum and renal superoxide dismutase (SOD) (**Price, 2007**).

6. Serum and renal nitrate concentration level (**Wishnok et al., 1996**).

7. Serum and renal tumor necrosis factor-α (TNF-α) by RayBio® ELISA kit (**Yazihan et al., 2011**).

8. Measurement of serum interleukin 10 (IL-10), by RayBio® ELISA kit (**La Manna et al., 2011**).

■ Cadmium was determined in animal kidney and blood (**Abete et al., 2007**).

■ **Histopathological study of rat kidneys (Semedo et al., 2009**).

Statistical Analysis:

Results were expressed as means ± SEM. One-Way ANOVA was used to test for differences among the studied groups followed by multiple-range test to find inter groupal significance. Statistical significance were performed by using

SPSS (Statistical Program for Social Science) statistical Package (SPSS Inc.) version 20.P value ≤ 0.05 was considered significant.

RESULTS

A significant increase in serum urea and creatinine levels was encountered in cadmium group compared to control group. Carnosine treatment significantly decreased serum urea and creatinine levels compared to cadmium group though the levels were still significantly higher than control group.

Serum albumin level significantly decreased in cadmium group compared to control group but, upon treatment with carnosine, significant increase in albumin level was observed compared to cadmium group though still significantly less compared to control group.

Significant increases in serum malondialdehyde levels were found in cadmium group compared to control group. Upon treatment with carnosine significant decreases were observed compared to cadmium group though still significantly higher compared to the control group.

Superoxide dismutase levels significantly decreased in cadmium group compared to control group. Upon treatment with carnosine significant increase was observed compared to cadmium group though still significantly lower compared to the control group **(Table 1).**

Table (1): Serum urea, creatinine (mg/dl), serum albumin (g/dl), malondialdehyde level (MDA, μM/ml) and superoxide dismutase (SOD, U/ml) in control, cadmium and carnosine treated groups.

Groups / Parameters	Control Group (15)	Cadmium Group (15)	Carnosine Group (15)
Urea (mg/dl) **P** **P***	**24.67 ±0.84**	**77.33 ±3.50** **<0.001**	**42.07 ±1.49** **<0.001** **<0.001**
Creatinine (mg/dl) **P** **P***	**0.48 ±0.02**	**1.83 ±0.05** **<0.001**	**0.99 ±0.04** **<0.001** **<0.001**
Albumin (g/dl) **P** **P***	**3.99 ±0.03**	**2.77 ±0.09** **< 0.001**	**3.43 ±0.03** **< 0.001** **< 0.001**
MDA (μM/ml) **P** **P***	**28.82±1.11**	**139.35 ±5.46** **< 0.001**	**66.98 ±2.95** **< 0.001** **< 0.001**
SOD (U/ml) **P** **P***	**71.16 ±2.97**	**15.45 ±0.65** **< 0.001**	**35.93 ±2.28** **< 0.001** **< 0.001**

Results are expressed as means ±SEM.
P: level of significance from control group.
P*: level of significance from cadmium group.
Between parenthesis: number of rats.

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Significant increases in nitric oxide levels were found in cadmium group compared to control group. Upon treatment with carnosine significant decreases were observed compared to cadmium group though still significantly higher compared to the control group.

The levels of both serum tumor necrosis factor-α and interleukin 10 significantly increased in cadmium group compared to the control group. Treatment with carnosine significantly decreased levels when compared to cadmium group though the level was still significantly higher in the carnosine treated group compared to the control group **(Table 2).**

Table (2): Serum nitric oxide level (NO, µM/L) and tumor necrosis factor -α level (TNF-α, pg/ml) and interleukin 10 level (IL-10, pg/ml) in control, cadmium and carnosine treated groups

Groups / Parameters	Control Group (15)	Cadmium Group (15)	Carnosine Group (15)
NO (µM/l) **P** **P***	20.06 ±0.68	116.17 ±3.48 <0.001	61.02 ±3.60 <0.001 <0.001
TNF- α (pg/ml) **P** **P***	27.19 ±1.08	138.51 ±4.61 < 0.001	64.52 ±3.33 <0.001 < 0.001
IL-10 level (pg/ml) **P** **P***	17.12 ±0.62	77.97 ±2.81 <0.001	44.63 ±1.53 <0.001 <0.001

Results are expressed as means ±SEM.
P: level of significance from control group.
P*: level of significance from cadmium group.
Between parenthesis: number of rats.

Blood and renal tissue cadmium levels showed significant increase in the cadmium group compared to the control group. Treatment with carnosine significantly decreased both blood and renal tissue cadmium levels when compared to the cadmium group though the levels were still significantly higher compared to control group **(Figure 1).**
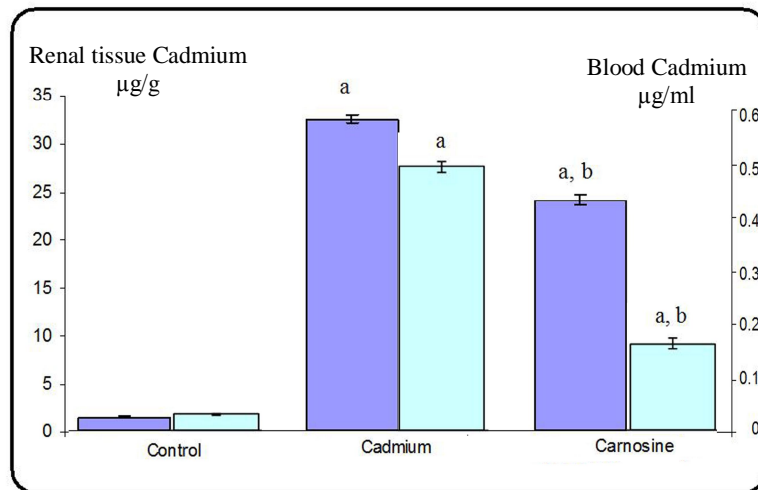
Figure (1): Blood cadmium level (µg/ml) and renal tissue cadmium level (µg/g) in the three studied groups.

Data were presented as mean ±SEM.
a: Level of significance from control group.
b: Level of significance from cadmium group.

Renal tissue superoxide dismutase level significantly decreased in cadmium group compared to control group. Carnosine treatment significantly increased when compared to the cadmium group though the level was still significantly lower in the carnosine treated group compared to the control group.

Renal tissue nitric oxide and tumor necrosis factor- α levels both significantly increased in the cadmium group compared to the control group. Carnosine treatment significantly decreased when compared to cadmium group though the levels were still significantly higher compared to the control group **(Figure 2).**
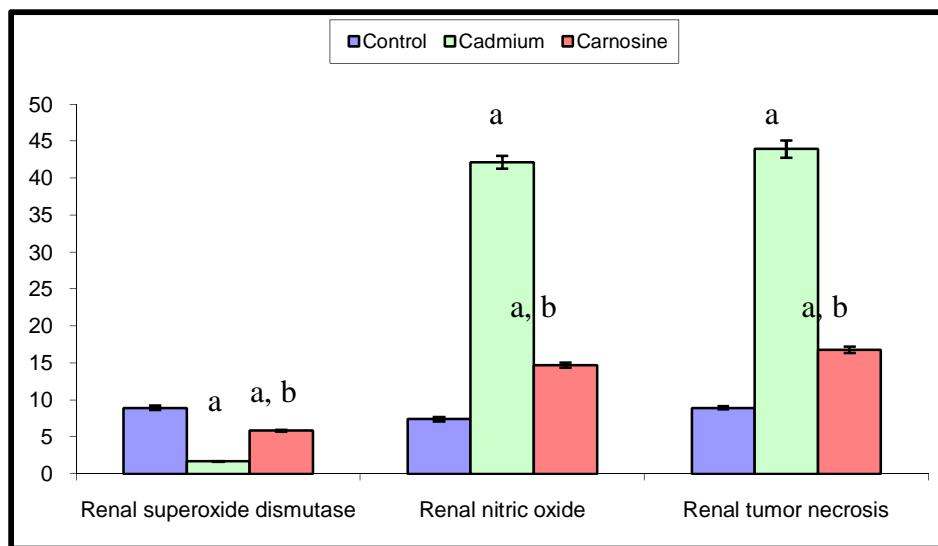

Figure (2): Renal tissue superoxide dismutase level (SOD, U/g), nitric oxide level (NO, µM/g) Renal tissue tumor necrosis factor-α level
(TNF-α, pg/g) in the three studied groups.

Data were presented as mean ±SEM.
a: Level of significance from control group.
b: Level of significance from cadmium group.

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Histopathological Report

Control group showed normal histological structure of the glomeruli and tubules at the cortex **(Figure 3).** Cadmium group showed degeneration and necrosis as noticed in the tubular lining epithelium at the cortex associated with swelling and vacuolization of the lining endothelium of the glomerular tufts **(Figure 4)**, and showed periglomerular inflammatory cells infiltration as well as perivascular focal inflammatory cells aggregation at the cortex **(Figure 5)**. Also, cadmium group showed focal hemorrhage in between the degenerated tubules of the corticomedullary portion **(Figure 6)**. Carnosine group showed degeneration and necrosis in the tubular lining epithelial cells at the cortex **(Figure 7).**
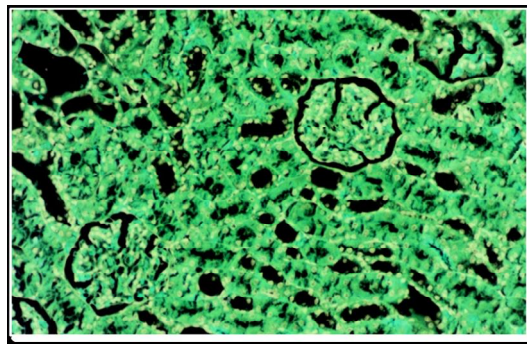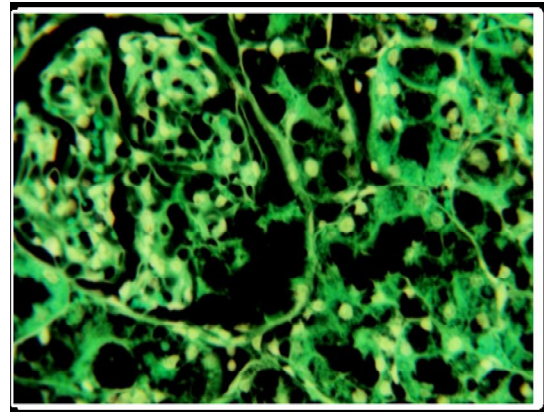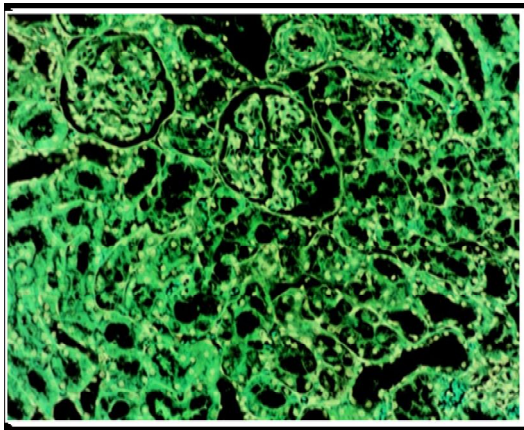

Figure (3): Control group (Hx & E X 40).

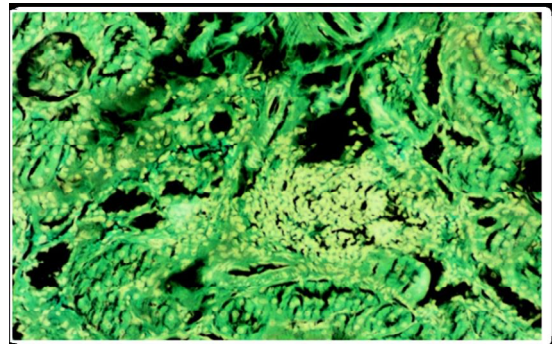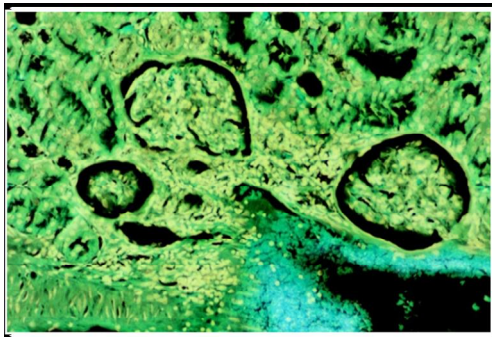
Figure (4): Cadmium group (Hx & E X 40 & 80).

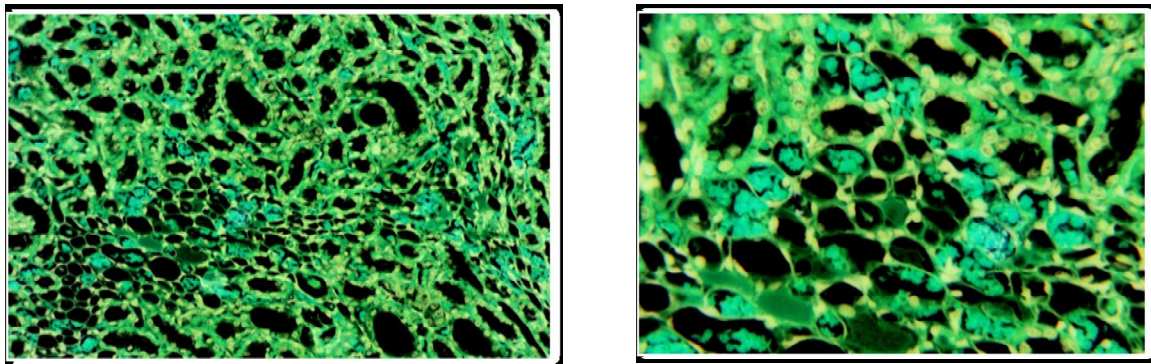**Figure (5):** Cadmium group (Hx & E X 40).

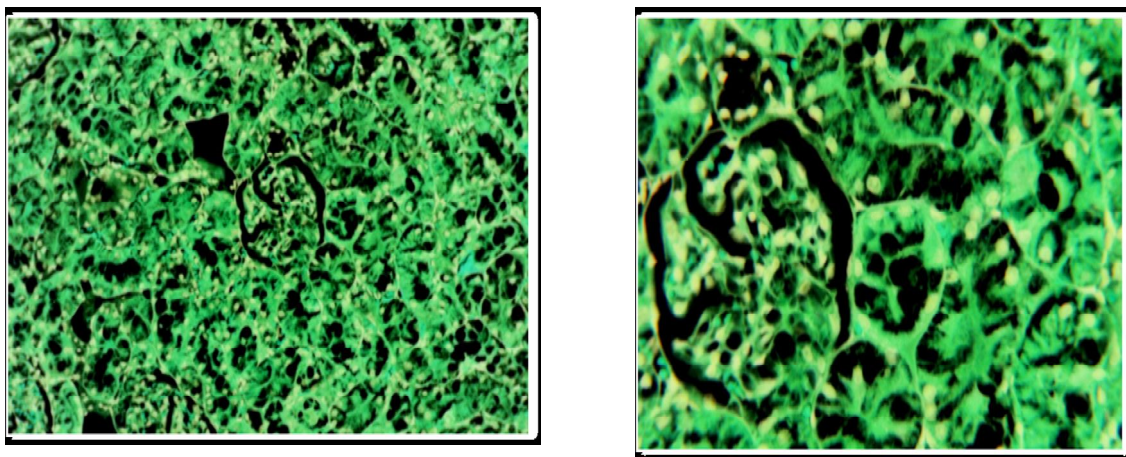**Figure (6):** Cadmium group (Hx & E X 40&80).

Figure (7): Carnosine group (Hx & E X 40 &80).

DISCUSSION

In the present study, we observed that cadmium toxicity caused kidney dysfunction by disturbing antioxidant defense system of the body. Also, the present results suggested that carnosine treatment prevent cadmium -induced alterations of the prooxidant–antioxidant related parameters in the experimental animals. Over time, the proximal tubule began to accumulate cadmium that eventually affect epithelial cell function. These early effects appeared to involve mild oxidative stress, disruption of cellular signaling cascades, and alterations in cell adhesion. These effects, in turn, trigger autophagic responses in the cells. If the level of injury is mild, the autophagic response may be sufficient to repair damage. However, if the injury is more severe, apoptosis and/or autophagic cell death can occur **(Prozialeck and Edwards, 2012).**

Whereas the proximal tubule is the primary target of cadmium-induced kidney injury, there is an evidence that cadmium, particularly at higher levels of exposure can also affect the glomeruli **(Xiao et al., 2009).** Changes in classic markers of glomerular dysfunction such as serum or urinary creatinine are generally not seen during the early or mild stages of cadmium-induced kidney injury **(Prozialeck and Edwards, 2007).** However, there is an associations between cadmium exposure and alterations (either

increased or decreased) creatinine clearance **(Navas-Acien et al., 2009).**

In the current investigation, administration of cadmium elicited kidney injury that was evident by increase in serum urea and creatinine levels. Serum urea and creatinine levels are used as indicators of renal function. Cadmium impedes the incorporation of amino acid into protein causing an increase in level of blood urea. Elevated blood urea is recognized to be related with an increased catabolism of proteins in mammals and/or the conversion of ammonia to urea as a result of increased production of arginase enzyme involved in urea production. Creatinine reflects the diagnosis of renal failure **(Renugadevi and Prabu, 2009).**

The current results agreed with **Borges et al. (2008)** who reported that urea and creatinine elevated in serum of rats intoxicated with cadmium. Creatinine is the most trustable marker which rises when the kidneys suffer any kind of damaging insult. Otherwise, urea is the first renal marker to increase. More recently, the recorded data by **Hussein et al. (2014)** revealed kidney pathological changes including significant elevation of serum urea and creatinine in rats exposed to cadmium.

Cadmium administration causes calcium release from the endoplasmic reticulum, and the overload of intracellular calcium consequently activates ERK and depolarizes the mitochondrial membrane potential which increases the expression of caspases 9 and 3 resulting in autophagy and apoptosis. This mechanism together with ability of cadmium to produce reactive oxygen species in mesangial cells are important mechanisms underlying cadmium induced nephrotoxicity **(Yang et al., 2009).**

These recorded results of deterioration of renal functions were further supported by changes seen in the histopathological pictures of kidney specimen taken from cadmium rats which showed degeneration and necrosis in the tubular lining epithelium at the cortex associated with swelling and vacuolization of the lining endothelium of the glomerular tufts, periglomerular inflammatory cells infiltration as well as focal hemorrhage in between the degenerated tubules. The observed pathological changes came in accordance with **Renugadevi and Prabu (2009)** who revealed that cadmium intoxication caused ultra-structural abnormal changes in renal tissue including marked renal cortical congestion and tubular degeneration, necrosis. Moreover, **Siddiqui (2010)** reported that cadmium caused marked injury to the kidneys and its various cell types particularly cortex of the kidney, proximal and distal renal tubular membranes, cell nuclei and blood vessels in kidneys of cadmium treated rats. **Agency for Toxic Substances and Disease Registry (ATSDR)** declared in **2008** that proteinuria and renal histopathologic damage have been observed in cadmium intoxicated rats. **Lin et al. (2014)** study suggested that low serum zinc concentrations are associated with an increased risk of cadmium nephrotoxicity leading to albuminuria. So, hypoalbuminemia in cadmium intoxicated rats in the present study could be the result of albuminuria resulting from histopatho-logically proved cadmium nephrotoxicity.

The significant decreases in both serum urea and creatinine in carnosine treated

group compared to untreated cadmium group in the present study denoted the protective effect of carnosine on kidneys when it was administered prior to cadmium toxicity. The levels were still significantly higher than the control group which proved that the injury of the kidney was not completely prevented as demonstrated in histopathological pictures taken from carnosine rats which demonstrated marked improvement of degenerative changes, focal hemorrhages as well as focal inflammatory reaction and to lesser extent improvement of glomerular necrobiosis. These pictures were previously demonstrated by **Renugadevi and Prabu (2009)** who found that carnosine treatment of cadmium-induced renal toxicity in rats revealed that the witnessed pathological damages caused by cadmium significantly recovered, indicating that carnosine has the ability of preventing the nephron impairment induced by cadmium. It is thus suggested that carnosine may inhibit Cd-induced renal damage. However, further researches are needed to find out the actual mechanism of action and its doses in the presence of oxidative stress due to Cd toxicity.

The results of the present study showed significant decrease in serum albumin in cadmium group which was ameliorated in carnosine treated group although the albumin level was still significantly lower than the control group.

El Boshy et al. (2014) demonstrated the hepatoxic effect of cadmium by alteration of serum hepatic markers shown through significant increases in ALT and AST serum activities, and a significant decrease in serum protein and albumin.

The authors explained their findings by liver damage which included swelling and rupture parenchymal cell leukocyte infiltration, and focal necrosis. This liver damage may be attributed to cadmium toxicity as most the anti-oxidant enzymes become inactive due to their binding to the active sites of the enzyme containing SH groups, which leads to enhancement of ROS and or direct damage effect of cadmium, where the liver is the primary organ of cadmium toxicity**.**

These present results were supported by the study of **Fouad et al. (2009)** who demonstrated the hepato-protective effect of carnosine against cadmium-induced acute hepatic injury in mice. They found that carnosine significantly suppressed peroxidation of lipid, restored the deficits in the antioxidant defense mechanisms and reduced the cadmium-induced elevations in serum aminotransferases**.**

The results in the present study showed significant elevation in the oxidant markers as demonstrated by significant rise in MDA level in cadmium group which improved upon carnosine pretreatment in treated group although the level recorded is still significantly higher than control group. Also, significant decrease in serum SOD level denoting deterioration in antioxidant capacity in cadmium group was recorded, which further improved by carnosine pretreatment, although the level observed was still significantly lower than control group.

Our outcomes are consistent with those reported by other researchers, who discovered that concentrations of antioxidant markers were declined during Cd intoxication. Cadmium has been shown to decrease the activities of

antioxidant markers such as SOD and to elevate malondialdehyde significantly in rats which received cadmium chloride (**El-Boshy et al., 2014**).

Some of the earliest consistent changes observed, after cd exposure, are increases in ROS and Ca^{2+} (**Thèvenod, 2009**), which are commonly involved as second messengers in the physiological regulation of cell function, but at the same time, cd^{2+} causes cell damage via ROS and Ca^{2+}, which disrupt cell function and trigger cell death. In terms of signaling dynamics, cd^{2+} induces a temporary or persistent imbalance of Ca^{2+} and ROS signals, which lead to reversible or permanent pertubations of the cell's functions i.e. mitochondria, ER, nucleus, cytosol (**Sedelnikova et al., 2010 and Huang et al., 2011**).

Cd has also been documented to influence the body system damage through inhibition of antioxidant markers and inducing oxidative damage with ROS generation which destroy DNA, lipids and proteins by oxidation. Directly, ROS oxidizes proteins, lipids and nucleic acids, leading to damage of basic cell structures. ROS also oxidizes the catalytic cysteine in the enzymes involved in apoptotic and necrotic signaling pathways, i.e. oxidative stress activates the ASK1 (apoptosis signal regulating kinase 1)- JNK (c-Jun N-terminal kinase) pathway implicated in a variety of apoptotic processes (**Pourova et al., 2010**). Lipid peroxidation includes a broad spectrum of cellular alterations and the subsequent cell membranes degeneration. Intermediate products of peroxidation and free radicals are capable of damaging the integrity and changing the bio-membranes functions, which can lead to the origin of many pathological processes (**Milton et al., 2011**).

Accumulating evidence suggests that protein folding and generation of ROS (as a byproduct of protein oxidation in the ER) are closely linked with each other (**Malhotra and Kaufman, 2007**). Some reports indicate that ER stress locates downstream of oxidative stress in some apoptotic processes triggered by TNFα, cigarette smoke and cadmium (**Tagawa et al., 2008**). Previous report suggested that cadmium has the potential to induce ER stress in thymocytes, lung epithelial cells and renal tubular cells (**Liu et al., 2009**).

The degree of cell damage under heavy metal stress depends on the efficiency of detoxification and repair mechanisms and on the rate of reactive oxygen species formation. The defense system of the cell against toxicity from ROS includes superoxide dismutase (**Hagar and Al Malki, 2014**).

The results of the present study showed reduced activities of the antioxidant enzyme SOD in serum and kidney tissues of the Cd-intoxicated rats. Treatment with carnosine, however, prevents the Cd induced changes and keeps the activities of the antioxidant enzymes close to those of the normal animals.

SOD is highly sensitive to hydroxide radical, which causes fragmentation of protein and inhibits its enzymatic activity. Therefore, it was not unexpected that the placement of carnosine into an in vitro system producing reactive oxygen species (ROS) protected the SOD activity (**Boldyrev, 2012**). It is quite definite that the antioxidant potential of carnosine plays a significant role in mediating its reno-protective effect.

In the present study, the MDA which is a lipid peroxidation end product. It significantly elevated in serum and renal tissues of rats treated with cadmium compared to control rats. This result was previously explained by **Noori and Mahboob (2010)** who reported that increased MDA in kidney tissue was accompanied by impaired kidney functions.

Carnosine (CAR; β-alanyl-L-histidine) is an endogenous dipeptide that possesses various functions such as membrane stabilizing, pH buffering, metal ion chelating, antioxidant hydroxyl radical and carbonyl scavenging, and antiglycating **(Kumral et al., 2015).** Carnosine and related derivatives of histidine are found in high concentrations in kidney tissue. CAR is considered a multifunctional molecule with antioxidant action and operates as a selective inhibitor of protein glycation and protein-protein cross linking. CAR has a powerful antioxidant activity and can serve as an efficient electron donor, which prevents lipid peroxidation. It also quenches singlet oxygen and interacts with superoxide. CAR can also chelates copper and iron, and this chelation prevents these ions from catalyzing Fenton chemistry, thus blocking production of hydroxyl radicals **(Hipkiss, 2009 and Boldyrev et al., 2013).** Moreover, CAR-Cu complexes possess SOD activity and bind covalently to reactive degradation products of lipid peroxides, which prevent them from reacting with other cellular targets **(Hipkiss, 2009 and Boldyrev et al., 2013).**

Previous researchers showed that carnosine significantly increased GSH content, decreased MDA level, enhanced glutathione peroxidase and catalase, and diminished the release of interleukin-6, C-reactive protein and tumor necrosis factor-α in hepatic tissue of mice with chronic liver injury induced with ethanol **(Liu et al., 2008). Zhang et al. (2014)** observed clearly the increased expression of oxidative marker of lipid in cortical brain tissue homogenate which is MDA. On the other hand, carnosine administration attenuated elevated MDA concentration in post subarachnoid hemorrhage.

Moreover, **Noori and Mahboob (2010)** noticed that pretreatment with carnosine counteracted the deleterious effects of cisplatin effects on the kidney and reduced the pathological changes as reflected by decreases in plasma urea, creatinine, nitrate, serum and kidney tissue malondialdehyde, and increases in superoxide dismutase, 4-hydroxynonenal and catalase activities.

Also, in accordance with histopathological pictures of the present study**, Renugadevi and Prabu (2009)** histopathological observations in Cd-intoxicated rats showed tubular degeneration, inflammatory cell infiltration, tubular necrosis, swelling, vacuolization and hemorrhage of tubules in cd intoxicated rats. This could be due to increased lipid peroxidation as a consequence of the accumulation of free radicals by free Cd ions in the kidney tissues of Cd-intoxicated rats as explained by authors.

In the current investigations, Cd administration elicited significant increases in both serum TNF-α and IL-10 compared to control group. Amelioration of these parameters was observed upon carnosine pretreatment, although their levels did not match those of the control group.

These results came in accordance with **Abbès et al. (2007)** who reported a significant increase in TNF-α, resulted from treatment of albino rats with CdCl$_2$ for 2 weeks. **Marit et al. (2010)** showed elevation in pro inflammatory cytokines (TNF-α) induced by cadmium. **El-Boshy et al. (2014)** noticed elevation in the serum cytokines including TNF- α in the cadmium administrated group compared with those of the control group.

Tumor necrosis factor (TNF) plays a pivotal role in various inflammatory and immune processes, including cellular activation, proliferation and survival, as well as cell death by apoptosis and necrosis **(Keystone and Ware, 2010)**. Elevation of TNF-α from monocytes exposed cells occur through signal transduction induced by cadmium toxicity **(Freitas and Fernandes 2011 and Djokic et al. 2014).**

El-Boshy et al. (2014) noticed that cadmium exposure led to absolute neutrophilia with lymphopenia. The authors explained their findings that lymphopenia and neutropenia could be as a result of elevation of both IL6 and TNFα induce bone marrow neutrophils release and mobilization as well as redistribution from tissues (marginal pool) into circulating neutrophils under base and inflammatory condition.

There is a strong evidence representing that stimulation of the renin-angiotensin system is involved in the pathophysiology of cadmium -induced tissue injury **(Varoni et al., 2010).** The most active factor in this system, angiotensin II, is a well-known inducer of oxidative stress which increases the production of hydrogen peroxide, hydroxyl radicals and superoxide anion by activating the NADPH oxidase enzyme which is the main source of cadmium-induced reactive oxygen species **(Souza et al., 2009 and Banakou & Dailianis., 2010).** Also, angiotensin II activates cascades inflammation with increased generation of the proinflammatory cytokine TNF-α which is responsible for further renal tissue damage **(Cau et al., 2009 and Hayashi et al., 2010).**

The amelioration of TNF-α in carnosine treated group in the present study may be explained by **Yan et al. (2009)** who reported that pre-treatment with carnosine reduced hepatic levels of inflammatory cytokines (TNF-α and IL-6) in acteminophen induced hepatic injury. Thus, inhibitory effect on the production of these cytokines is the cause of anti-inflammatory protective effect of carnosine. Also, carnosine reduced the release of pro-inflammatory cytokines as tumor necrosis factor-α in bleomycin-induced lung injury **(Cuzzocrea et al., 2007).** In addition**, Andou et al. (2009**) demonstrated that histidine amino acid component of carnosine ameliorated intestinal inflammation in a model with IL-10 cell transfer colitis because it has the potentiality as a scavenger of the nonradical toxic oxygen species and the hydroxyl radical and inhibits proinflammatory cytokine secretion from macrophages (including IL-6 and TNF- α) that are induced by lipopolysaccharides.

Zhang et al. (2014) found that experimental subarachnoid hemorrhage caused elevation in pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) expression in cortical brain tissue homogenate, which was significantly

attenuated by administration of carnosine. Microglia activated by injured neuron led to the elevation of the pro-inflammatory cytokines. The authors concluded that the mechanisms of carnosine-against inflammatory response after subarachnoid hemorrhage are needed to be explored by further studies.

The results of the present study showed significant elevation in serum and tissue NO in cadmium groups. Upon carnosine pretreatment, serum and tissue NO showed significant decrease although the levels were still significantly higher than the control group.

These concurrent results came in accordance with the studies of **Al-Azemi et al. (2010) and Othman et al. (2014)** who showed that exposure to cadmium caused overexpression of NO in several tissues as a result of intense inflammatory reaction tissues. Cd-induced toxicity was found to be mediated through the production of NOS and ROS in the early stage of Cd-induced kidney damage (**Zhong et al., 2015**).

In agreement with this study, **Ansari et al. (2017)** reported that Cd-intoxicated rats exhibits elevated level of NO, whereas synaptic acid (10 and 20 mg/kg) treatment inhibits the elevation of renal NO in rats. The authors concluded that synaptic acid possesses an effective ability to curb nitrosative stress induced by Cd. NO is an inflammation biomarker; thus has ability to curb the inflammatory response induced by Cd .

Cd is known to increase hydrogen peroxide, hydroxyl radicals, superoxide, and nitric oxide production, disrupt anti-oxidant enzymes, increase lipid peroxidation, cause changes in thiol proteins, inhibit energy metabolism, and cause changes in membrane function and DNA structure. The cellular toxicity of Cd is known to be mediated by oxidative stress (**Cannino et al., 2009**).

Redox disturbances are known to negatively influence the body systems through ROS production, which destroy lipids, proteins, and DNA, by oxidation. Although cadmium itself does not directly produce free radicals, it indirectly generates numerous radicals such as nitric oxide, nitrogen species such as peroxy-nitrite, hydroxyl radical, and superoxide radical, thus causing harm consistent with oxidative stress (**Renugadevi and Prabu, 2009**). Meanwhile, it has been established that increased NO generation is involved in cadmium-mediated oxidative damage and cytotoxicity (**Fouad et al., 2009**).

NO elevation can be explained by the ability of TNF-α to up-regulate the induced nitric oxide synthase enzyme. Superoxide anion reacts with excess NO to generate peroxynitrite radical that causes further cell injury by nitrating and oxidizing macromolecules of the cells. Also, intracellular GSH is depleted by excess NO increasing the cellular vulnerability to oxidative stress (**Fouad & Jresat, 2011 and El-Habit &Abdel Moneim, 2014**). Moreover, **Demenesku et al. (2014)** study showed increases in inducible nitric oxide synthase (iNOS) production and expression of NO by splenic cells in cadmium treated rats.

These results revealed that administration of carnosine minimized the deleterious effects of Cd on renal tissues

such as the rise in nitric oxide and lipid peroxidation. These findings were in agreement with the previous study of **Dkhil et al. (2014**) who explained their results through the protective effect of carnosine against Cd toxicity at the kidney which may be attributed to its inhibitory effect in NO generation, where NO plays crucial roles in inflammation, oxidative stress and apoptosis. However, further studies are needed to elucidate its exact mechanism.

This study showed significant decrease in serum and tissue cadmium levels in carnosine pretreated group which came in agreement with **Belcastro et al. (2009)** who demonstrated that carnosine decreased hepatic cadmium ion overload indirectly by increasing the level of antioxidants which are powerful cadmium ion chelators and are considered very important for detoxification of intracellular cadmium.

CONCLUSION

Increased lipid peroxides induced by cd toxicity may implicate the renal oxidative stress. Moreover, pretreatment with carnosine successively attenuated the antioxidant system through several mechanisms such as scavenging/ neutralizing free radicals, regulating enzymatic/ non enzymatic antioxidants. However, future work will be needed to confirm our results.

ACKNOWLEDGMENTS

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التأثير الوقائي المحتمل للكارنوسين على اختلال وظائف الكلى الناتجة عن الكادميوم في جرذان التجارب المسنة

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خلفية البحث: وجدت بعض الدراسات السابقة أن الكارنوسين يمكنه قمع زيادة نشاط العصب الودي الكلوي خلال نقص التروية الكلوية عن طريق عمله على الجهاز العصبي المركزي، وهذا التأثير القمعي هو المسئول على الأرجح عن حماية الكلى ضد الإصابة الناجمة عن نقص التروية. وبالإضافة إلى ذلك، فإن تأثير الكارنوسين الوقائي على الفشل الكلوي الحاديبدو كأنه ناتج عن تحوله الى هستيدين وهستامين وذلك من خلال تنشيط مستقبلات الهستامين (H3)في الجهاز العصبي المركزي.

هدف البحث : دراسة تأثير الكارنوسين كعامل مضاد للأكسدة ضد تاكسد الدهون المستحث بالكادميوم ومضاد للإجهاد التأكسدي الكلوي في الجرذان المسنة.

مواد و طرق البحث :أجريت الدراسة الحالية على ٤٥ أنثى من جرذان ويستار، وزن كل جرذ بين ٢٨٠-٣٨٠ جراما عند بداية الدراسة ،قسمت عشوائيا إلى المجموعات المتساوية التالية : المجموعة الضابطة ومجموعة الكادميوم ومجموعة الكارنوسين وبعد جمع عينات الدم خضعت لقياس اليوريا، الكرياتينين ، والزلال، MDA ،NO ، SOD ، IL_{10} ، TNF-α ، في المصل وقياس TNF-α ، NO،SOD في نسيج الكلية و قياس مستوى الكادميوم في الدم وفي نسيج الكلية. أيضا أجريت دراسة نسيجية لكلى الجرذان.

النتائج : وجدت زيادة في اليوريا والكرياتينين ، IL_{10} , MDA وإرتفاع NO, TNF-αفي المصل والأنسجة الكلوية ومستويات الكادميوم في الدم والأنسجة الكلوية في الجرذان التي حقنت بالكادميوم مقارنة مع المجموعة الضابطة.

وقد قللت المعالجة بالكارنوسين اليوريا ، الكرياتينين ، MDA ، IL_{10} في المصل NO & ، TNF-αفي المصل ونسيج الكلية، ومستويات الكادميوم في الدم و نسيج الكلية مقارنة بمجموعة الكادميوم إلا أن مستوياتها أعلى من المجموعة الضابطة.

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كما أظهر أن الألبومين و(SOD) في المصل ونسيج الكلية إنخفضا بشكل ملحوظ في مجموعة الكادميوم مقارنة مع المجموعة الضابطة، ولكن عند العلاج بالكارنوسين لوحظت زيادة مقارنة مع مجموعة الكادميوم وإن كانت لا تزال أقل بالمقارنة مع المجموعة الضابطة.

الإستنتاج: من الدراسة الحالية، يمكننا أن نخلص إلى أن زيادة بيروكسيدات الدهون الناجمة عن سمية الكادميوم قد تنطوي على الإجهاد التأكسدي الكلوي. وعلاوة على ذلك، المعالجة المسبقة بالكارنوسين يضعف على التوالي نظام الأكسدة داخل الجسم من خلال عدة آليات مثل تحييد الجذور الحرة، وتنظيم مضادات الأكسدة الإنزيمية / غير الإنزيمية فى الفئران المسنة.