World Journal of Pharmaceutical research

Volume 3, Issue 2, 3093-3130. Review Article ISSN 2277 – 7105

CARNOSINE: A POTENT MODULATOR FOR DIFFERENT DISEASES

Maha Z. Rizk, Hanan F. Aly* and Afaf K. El-Ansary

Therapeutic Chemisty Department, National Research Center, Cairo, Egypt.

Article Received on
05 January 2014,

Revised on 25 January 2014,
Accepted on 27 February 2014

***Correspondence for Author**
Prof. Dr. Hanan Farouk Aly
Therapeutic Chemisty Department, National Research Center, Cairo, Egypt.

CONTENTS

ABSTRACT
L-Carnosine ((3-alanyl-L-histidine) is an active physiological dipeptide that is distributed naturally in several human tissues, especially, the skeletal muscle, cardiac muscle, nervous tissue and brain. The dipeptide is a potent hydrophilic antioxidant, preventing oxidative damage of membrane lipids and proteins under oxidative stress. Carnosine is also an antiglycating antinflammatory agent, pH buffer and heavy metal chelator. Further, it can prevent aldehyde adducts and nucleic acid oxidation. In addition, carnosine is reported to be involved in natural system of body immune response **.**One of the most important developments regarding carnosine is its ability to prevent and cure cataract, glucoma and other age related eye. Carnosine also, has a role in regulation of blood glucose and neuro-protective function. Moreover, carnosine was exploited for its antiparasitic activity against schistosomiasis and fascioliasis.

Key words: Carnosine , antioxidant , oxidative stress , biological activities.

1. Carnosine overview

L-Carnosine ((3-alanyl-L-histidine) is an active physiological dipeptide that is distributed naturally in several human tissues, especially, the skeletal muscle, cardiac muscle, nervous tissue and brain **(Gariballa and Sinclaur, 2000).** The dipeptide is a potent hydrophilic antioxidant, preventing oxidative damage of membrane lipids and proteins under oxidative stress; for example, after using monosodium glutamate as a flavour ingredient in food after alcohol intoxication **(Zieba and Wagrowaska, 2003),** or by using gentamicin (GM) which is an antibiotic clinically limited by its nephrotoxicity **(Soliman and Abdel Monem, 2001; Sorokina et al., 2003)**. Carnosine is also an antiglycating antinflammatory agent, pH buffer and heavy metal chelator **(Boldyrev etal., 1999).** Further, it can prevent aldehyde adducts **(Hipkiss et al., 2002)** and nucleic acid oxidation **(Boldyrev et al., 1999)** and. In addition, carnosine is reported to be involved in natural system of body immune response **(Suzuki et al., 2001).**

One of the most important developments regarding carnosine is its ability to prevent and cure cataract, glucoma and other age related eye **(Babizhayev et al., 2000).** Furthermore, **Nagai et al. (2003)** and **Yamano et al. (2008)** reported the possible role of L-carnosine in regulation of blood glucose while **Cheng et al. (2002)** indicated the neuro-protective function of carnosine. In addition, carnosine was exploited for its antiparasitic activity against schistosomiasis **(Soliman et al., 2000)** and *Trichinella spiralis* and fasciolisis **(Soliman et al., 2002).**In a related study, **Soliman et al. (2007)** revealed the promoting effect of canosine on partially hepatectomized mice.

2. Physiological aspects of carnosine

2. 1. Biosafety of carnosine administration

The biosafety of L-carnosine (LD50) was recorded to be 18.5g/kg body weight **(Soliman et al., 2002).**

2. 2. Carnosine during physiological stress

Early studies have demonstrated a link between carnosine, free histidine and histamine synthesis following several types of physiological stresses **(Flancbaum et al., 1999).** It is proposed that carnosine serves as a non-mast cell reservoir for histidine which becomes available for histamine synthe **(Fitzpatrick et al., 1980).**

Conditions that cause endoplasmic reticulum mal function (ER stress) play a key role in the development of various human diseases including neurodegenerative diseases. Carnosine is an endogenous peptide, present in excitable tissues such as brain and skeletal muscle. Although there are reports suggesting that carnosine has a biological role independent of its antioxidant activity, there have been no reports of the effects of carnosine on the ER stress responses is during periods of stress. It was found that, carnosine almost completely inhibits 6-OHDA-induced ER stress responses and cytotoxicity, and that slight antioxidant activity of carnosine against 6-hydroxydopamine(6-OHDA) is observed **(yavarj and subramoniam, 2009).**

Although the physiological role of carnosine has not been completely understood yet, many beneficial actions have been attributed to carnosine, such as being an antioxidant, antiglycating and ion-chelating agent, a wound healing promoter and a free-radical scavenger. The role of carnosine in the neuroprotection of oxidative stress-driven disorders has been reviewed. The effects of carnosine have been extensively studied both *in vivo* and *in vitro* models of cerebral damages, such as neurodegenerative disorders, hypoxia–ischemia injuries and hypoxia-reoxygenation damage. Beside the classical sacrificial agent, carnosine has been reevaluated as a molecular chaperon and an inducer of antioxidant systems in oxidative stress conditions. Thus, beneficial effects on most of the common biochemical events that characterize neurological disorders make carnosine a very promising molecule among all the endogenous compounds in the treatment and/or prevention of oxidative driven diseases **(Fouad et al ., 2007 and Bellia et al ., 2011) .** Urgent need exists for new therapeutic options in ischemic stroke. It was demonstrated that carnosine, an endogenous dipeptide consisting of alanine and histidine, is robustly neuroprotective in ischemic brain injury and has a wide clinically relevant therapeutic time window. The precise mechanistic pathways that mediate this neuroprotective effect are not known. Following *in vivo* administration, carnosine is hydrolyzed into histidine, a precursor of histamine. It has been hypothesized that carnosine may exert its neuroprotective activities through the histidine/histamine pathway **(Bellia et al., 2011).**

Carnosine's possible biological activities include scavenger of reactive oxygen species (ROS) and reactive nitrogen species (RNS), chelator of zinc and copper ions, and antiglycating and anticross-linking activities. Carnosine's ability to react with deleterious aldehydes such as malondialdehyde, methylglyoxal, hydroxynonenal, and acetaldehyde may also contribute to its protective functions. Physiologically carnosine may help to suppress some secondary complications of diabetes, and the deleterious consequences of ischemic–reperfusion injury, most likely due to antioxidation and carbonyl-scavenging functions. Other, and much more speculative, possible functions of carnosine considered include transglutaminase inhibition, stimulation of proteolysis mediated via effects on proteasome activity or induction of protease and stress-protein gene expression, upregulation of corticosteroid synthesis, simulation of protein repair, and effects on ADP-ribose metabolism associated with sirtuin and poly-ADP-ribose polymerase (PARP) activities. Evidence for carnosine's possible protective action against secondary diabetic complications, neurodegeneration, cancer, and other age-related pathologies is ascertained **(Hipkiss, 2009).** Pretreatment with carnosine significantly reduced the infarct volume and the number of terminal-deoxynucleotidyl

transferase-mediated dUTP nick end labeling (TUNEL)-positive cells in the hypoxia–ischemia brain. Carnosine also inhibited mRNA expression of apoptosis-inducing factor (AIF) and caspase-3, which was accompanied by an increase in superoxide dismutase (SOD) activity and a decrease in the malondialdehyde(MDA)level in carnosine-treated rats. Furthermore, carnosine also improved the spatial learning and memory abilities of rats declined due to hypoxia–ischemia. These results demonstrate that carnosine can protect rats against hypoxia–ischemia-induced brain damage by antioxidation **(Zhang et al., 2011).**

In addition, carnosine can be considered as a potential candidate to protect the liver against the deleterious effect of acute cadmium intoxication **(Fouad et al ., 2009).** Ageing is characterized by a wide variety of physiological changes and, as a consequence, an anti-ageing compound must fulfill a wide variety of roles to be effective. Carnosine is an antioxidant, antiglycating and neuroprotective compound with well-studied clinical benefits. It is becoming a clinically accepted nutritional supplement with uses across a considerable spectrum of chronic diseases, from senile cataract to dementia **(Kyriazis, 2010).**

3. Carnosine and pathological stresses

3.1 . Carnosine and toxicity

3.1.1 . Carnosine and compound 48/80 lethal toxicity

Several studies showed that administration of compound 48/80 to rats induces lethal stress which was associated with mobilization of mycardial carnosine to histamine **(Flancbaum et al., 1990).** The histamine release causing death was attributed to production of an anaphylactoid reaction characterized by hypotension, bronchospasm, decreased intravascular volume, diminished venous return and reduced cardiac output which resembles surgical or traumatic shock **(Douglas, 1995). Soliman et al. (2002)** showed that carnosine produced dose-related protective effect against compound 48/80-induced lethal stress. The authors reported that carnosine might have produced its effect by an action at the level of histamine action on cardiovascular response induced by the compound. Thus, carnosine might have inhibited 48/80-induced histamine release from mast cells either directly or by forming histamine to act on H_2-receptors. They concluded that carnosine attenuating the deleterious effect of compound 48/80 protecting rats against its lethal shock that contributed to the same role of the dipeptide in the physiological response to stresses.

Furthermore, carnosine treatment significantly reduced blood urea nitrogen and serum creatinine levels elevated by cisplatin administration. Also, carnosine significantly attenuated cisplatin-induced increase in malondialdehyde and decrease in reduced glutathione, and catalase and superoxide dismutase activities in renal cortical homogenates. Additionally, histopathological examination and scoring showed that carnosine markedly ameliorated cisplatin-induced renal tubular necrosis. In conclusion, carnosine can be considered a feasible candidate to protect against nephrotoxicity commonly encountered with cisplatin treatment **(Fouad et al., 2009)**

The accumulation of malondialdehyde (MDA), a lipid peroxidation by-product that has been used as an indicator of cellular oxidation status, is significantly increased in many neurological diseases such as brain ischemia/reperfusion, Alzheimer's disease and Parkinson's disease *in vivo*. It was found that MDA treatment *in vitro* reduced cortical neuronal viability in a time- and dose-dependent manner and induced cellular apoptosis as well as necrosis simultaneously. Furthermore, exposure to MDA led to accumulation of intracellular reactive oxygen species, dysfunction of mitochondria (denoted by the loss of mitochondrial transmembrane potential ($\Delta\psi m$)) and activation of JNK and ERK. Carnosine exhibited better

protection against MDA-induced cell injury than antioxidant N-acetyl-cysteine (NAC) with its multi-potency, which alleviated MDA-induced protein cross-linking, $\Delta\psi m$ decrease, reactive oxygen species burst, and JNK and ERK activation. Thus, it was suggested that MDA induced cell injury *in vitro* via protein cross-linking and successive mitochondrial dysfunction, and the activation of reactive oxygen species-dependent MAPK signaling pathway. Carnosine alleviated all these alterations induced by MDA, but NAC merely inhibited Bcl-2 family-related activation of JNK and ERK. These results prompt the possibility that carnosine, but not other conventional antioxidants, can protect neurons against MDA-induced injury through decomposition of protein cross-linking toxicity and may serve as a novel agent in the treatment of neurodegenerative diseases **(Cheng et al ., 2011).**

3. 1. 2. Carnosine and alcohol intoxication

Chronic alcoholism produces a wide spectrum of stomach, liver and other organ diseases depending on the amount and duration of alcohol intake. Protein deficiency and enzyme activity depression were proved to be associated with chronic alcoholic liver disease **(Ozaras et al., 2003).** The toxicity of ethanol was mainly attributed to disturbed biochemical interactions of the two ethanol oxidizing enzymes, ADH and cytochrome $_{P450}$ isoenzymes specially CYP_2E_1 , both involved in ethanol oxidation producing acetaldehyde and ROS **(Lieber, 2000 and Roy Chengappa et al., 2012).** These products were further proved, in addition to lipid peroxidation, to lead to deleterious modifications of both structural and functional protein molecules by non-specific effect **(Niemela, 2001 and Addolorato et al., 2006).** Functional protein modifications were reflected as disturbances of many enzyme systems. Depression of both glycolytic and CAC. Pathways were reported by **Addolorato et al. (2006)**. Lowered MDH activity aggravating shift of the oxidoreductive equilibrium of malate/ oxaloacetate causing inhibition of CAC was also presented **(Volpi et al., 2002).** Further, alteration of the hepatocytes redox state, depression of the respiratory chain and limitation of ATP availability were stated in alcoholic intoxication **(Soliman et al., 2003).** Protein deficiency in alcoholism has been considered for decades to be associated with chronic liver disease characterized by a fall in serum albumin & loss of muscle mass. Studies in this concern have shown that alcoholism caused significant increase in serum ALP, AST and ALT and bilirubin **(Soliman et al., 2003).**

The effect of carnosine on individual enzymes of different organs in alcohol intoxication was studied by many researchers. Carnosine antioxidant protective effect on the parenchymatous gastric glands in chronic alcoholism was proved **(Choi et al., 2009). Fontana et at. (2002)** added that carnosine protected pancreatic α-antitrypsin against injurious fate. Similar effects of carnosine on different liver enzymes were reported **(Soliman et al., 2004).** Carnosine activating transcription could be a further potentiation of carnosine promoting effects on serum proteins **(Chen et al., 2002)**.

Soliman and Mohamed (2004) studied the effect of combination of carnosine before, with or after alcohol administration on certain hepatic biochemical factors. ADH, hexokinase (HK) phosphofructokinase (PFK), MDH, and creatine phosphokinase (CPK) activities were investigated in animal liver tissue **(Soliman et at., 2003).** The authors deduced that, apart from ADH, for which ethanol is the substrate, all enzymatic activity insults were ameliorated by carnosine treatment with the best results in animal groups receiving the dipeptide at the same time with ethanol. **Soliman and Mohamed (2004)** further studied the action of carnosine on the glycolytic enzyme LDH & its isoenzymes, CAC enzymes, glycogen content, the glycogenolytic metabolic machineries; glycogen phosphorylase, G-6-Pase, the hydrolytic enzymes; acid & alkaline phosphatase, the amino acid metabolic enzymes; AST & ALT and the nucleic acids

catabolic enzyme 5'-nucleotidase. The authors confirmed the toxic effect of ethanol inducing an oxidative stress on liver tissue and revealed the corrective action of carnosine on these studied parameters. In a related study, **Soliman and Mohamed (2004)** deduced the effect of L-carnosine on hepatic tissue lipid peroxides (LPO) and both intrinsic and extrinsic antioxidant factors namely, catalase activity, glutathione as well as vitamins C and E after ethanol intoxication. They found that LPO and vitamin C were increased while GSH, vitamin E & catalase were reduced by administration of alcohol. Carnosine relieved enzyme activities from the toxic action of ethanol, improved the levels of antioxidants and decreased LPO. This found support in its membrane protecting activity **(Nagasue et al., 1987 and Huang et al., 2005)** due to carnosine potent biological antioxidant effect **(Chen et al., 2002).**

This corrective action of carnosine could be attributed to its reported multibeneficial effects under different stressful conditions similar to its ability to protect glycolytic enzymes in anoxia and hyperthermia **(Deev et al., 1997).** This was explained by carnosine stimulating glycolysis, protecting protein modification mediated by peroxyl radicals generated by ethanol toxicity **(King and Mahmoud, 1999). Le Blanc and Soucy (1994)** previously recorded significant increase in serum albumin after carnosine administration. Carnosine activating transcription could be a further potentiation of carnosine promoting effects on serum proteins **(Chen et al., 2002). Silaeva et al. (1992)** showed that carnosine also increased mitotic activity in hepatocytes and accelerated liver recovery from toxic methanol hepatitis in rats.
In addition carnosine could play a role in delaying apoptosis by decreasing protein denaturation as well as in participating in the disposal of glycated protein in the affected tissue **(Yeargans and Seidler, 2003).**

The dipeptide could also combine with harmful active acetaldehyde thus preventing its combination with protein carbonyl groups **(Hipkiss, 2009). Silaeva et al. (1992)** showed that carnosine also increased mitotic activity in hepatocytes and had accelerated liver recovery from toxic methanol hepatitis in rats.

It was found that, polaprezinc (PZ), which consists of l-carnosine and zinc, is widely used to treat gastric ulcers. In a rat model of ethanol-induced gastric mucosal damage, polaprezinc administration ameliorated ethanol-induced mucosal injury and showed protective effects on the mucosa by reducing the levels of inflammatory cytokines and increasing the expression of antioxidant enzymes and growth factors. Furthermore, PZ showed cytoprotective effects by increasing the heat shock proteins (HSP) levels (**Choi et al., 2001).**

3. 1. 3. Carnosine and Monosodium glutamate (MSG) toxicity

Monosodium glutamate (MSG) is one of the main flavour enhancers used as an ingredient of various food products. Recently MSG toxicity has gained a lot of interest because of its association with Chinese restaurant syndrome in human. It was further reported to induce oxidative stress **(Ahluwalia et al., 1996).**

Soliman et al. (2003) studied the protective effect of carnosine against MSG toxicity in rats by evaluating the effect of the drug on some biochemical and ultrastructural parameters. Their study revealed that MSG caused increased LPO and superoxide dismutasee (SOD) enzyme activity, lowered activities of glutathione peroxidase (GPX) and glutathione reductase (GRX) and decreased glutathione (GSH) concentration. The activities of both GRX & GPX were significantly increased with increase in GSH content. These deteriorations resulted from MSG inducing excess liberation of reactive oxygen species (ROS) emphasizing its toxic action and inhibition of the antioxidant defense system **(Shaheen et al., 2000).** The increased SOD

activity after MSG could be a compensatory response to oxidative stress causing accumulation of its reaction product H_20_2. The latter would thus be involved in exhaustion of GPX and GRX **(Shaheen et al., 2000).** Furthermore, histochemically, MSG causes increased collagen deposition, numerous big vacuoles, and dilatation of endoplasmic reticulum. In support, frequent association of the pathogenesis of tissue fibrosis with enhanced lipid peroxidation and damaged antioxidant defense system was reported **(Poli and Parola, 1997).**

Carnosine given with MSG was effective in protecting all biochemical machineries. There was a sharp decrease in LPO and SOD activity. The increased GSH content and its redox-cycling enzymes (GPX and GRX) might provide the liver with greater protection from excess ROS liberation and actions. The micrographic picture of the liver showing that carnosine administrated with MSG efficiently minimizes the number & size of vacuoles, disappearance of collagen fibrils, and prevention of increased fibrinogenesis. This could reflect both normal structure and metabolic reactions of hepatic cells.

Its beneficial antioxidant potency against MSG toxicity indicated that the rate of free radical production was decreased in carnosine protected rats than in those receiving MSG alone.

3. 1. 4. Carnosine and gentamicin nephrotoxicity

Gentamycin (GM) is an antibiotic whose clinical use is limited by its nephrotoxicity. GM produced functional failure in rats shown as increased blood creatinine and urea. Histopathological, ultrastructure and enzyme histochemical studies proved this failure. Specifically, the excessive insult of the proximal tubules could result from being the primary site of drug accumulation **(Maldonado et al., 2003).** It was found that O_2', H_2O_2 and hydroxyl radicals were increased with GM treatment **(Martinez-Salgado et al., 2002,2007).** Experimentally induced oxidative stress was shown to produce tubular damage **(Cuzzocrea et al., 1998).** GM, structurally disturbing cellular mitochondrial membranes could lead to alteration in most enzymes of oxidative phosphorylation thay caused suppression of metabolic activity and reduction of ATP production **(Cohn et al., 2004). Madden et al. (2000)** also reported that GM induced apoptosis in the renal proximal tubular cells. **Soliman et al. (2007)** showed by histopathological and ultrastructural examinations that GM- nephrotoxicity presented apoptotic reaction. Their histochemical results showed that sections of GM injected animals, reflected activation of LDH **(Morel and Friday, 1994 and Soliman et al., 2005)** and inhibition of SDH, ATPase, ACP and ALP **(Soliman et al., 2005)**, that GM decreased ATP and SDH was also previously recorded in chronic liver insult **(Soliman et al., 2002). Varalakshmi et al. (2008)** attributed ACP decrease to cellular degeneration & necrosis of renal tubules. The authors added that, GM inhibition of ALP was explained by binding to anionic phospholipids present on the brush-border membrane.

However, **Soliman et al. (2007)** showed that carnosine presented great modulating actions, massively correcting the damaged renal histological elements, the three enzymes LDH, SDH and ATPase. The of carnosine on the three energy machinery related enzymes reflected equal hypercorrections that could help more energy production for utilization in defending GM damage. In support, carnosine proved to cause increased liberation of ATP in cardiac and skeletal muscle **(Millar and Rice-Evan, 1997)** and in the liver **(Churchill et al., 1995). Soliman et al. (2003 and 2004)** also reported the correctively stimulatory action of carnosine on CAC enzymes. The variabilities of protective actions of carnosine that lead to the favourable normalization of both renal function and structure could be related to selectivity of carnosine actions **(Soliman et al., 2005).**

4. Carnosine and infections diseases

4. 1. Carnosine and bacterial infection

4. 1. 1. Carnosine and nonspecific bacterial infection

For both types of bacterial non-specific infection, **Fitzpatrick et al. (1980)** recorded that in acute infection reduction in leg muscle carnosine much lagged behind that in chronic infection amounting to 25 and 95 % respectively. This exhaustion of carnosine in the chronic type clearly pointed to a more role of the dipeptide in chronic infections than in acute ones. **Stadnikov et al. (2000),** demonstrated the suppressive effect of carnosine with respect to the pathogen and its positive influence on the processes of the regeneration of eukaryotic tissues. In this concerns, **Kashimura et al. (1999)** and **Suzuki et al. (2001)** found that, polaprezinc inhibited *Helicobter pylori*-associated gastric mucosal oxidative inflammation, including initial micro-vascular leucocyte activation, in Mongolian gerbils.

Babizhayev and Deyev (2012) and **Babizhayev et al. (2013),** reported that histidine-containing compounds can modulate the Influenza virus release from neutrophills and reduce virus dissemination through the body of the organism. This review points the ability of therapeutic control of Influenza viral infections associated with modulation by oral non-hydrolized forms of carnosineand related histidine-containg compounds of Polymorphonuclear neutrophils (PMN) apoptosis which may be involved at least in part in the pathophysiology of the disease in animals and humans. Thus, these findings may have implications for global influenza surveillance and planning for pandemic influenza therapeutic prevention with oral forms of non-hydrolized natural L-carnosine as a suitable alternative to the conventional vaccination for various flu ailments.

4. 1. 2. Carnosine and specific bacterial infection

The above mentioned effect of carnosine on chronic non specific infection research matched the series of work investigating one type of specific bacterial infection, namely tuberculosis. Carnosine *in-vivo* action proved effective for both liver and lung affection in guinea pigs, even more than the traditional streptomycine-isoniazid (INH) combination therapy. Although streptomycine-INH treated animals showed normal spleen and liver, yet the exacerbation of tuberculous lesions in the lung tissue was a major drawback **(Atabai and Matthay , 2002).** The authors recorded that carnosine treatment caused microscopic abatement of tuberculousis in 6 out of 8 animals. These two animals still presented mild occational hepatic regressive tuberculous granulomata. The regression was accompanied by signs of increased immunity; presence of epitheleioid cells, few binucleated cells and also infilteration with macrophages.

However, a favourable non tuberculous manifestation in all the eight-carnosine treated animals was the smooth liver enlargement. The increase of liver weight mounted to 80to 100%. Microscopically, this enlargement proved to be due to ubiquitous intracellular increased glycogen storage. The excess glycogen however, was shown to be hydrolysable as the liver regained the normal size and weight after a night fast and microscopic examination showed abatement of cellular glycogen engorgement **(Atabai and Matthay , 2002).**

Comparing this carnosine *in-vivo* antituberculous effect with similar researches on other imidazole compounds; histidine **(Abdel Kader et al., 1977),** histamine **(Abdel Kader et al., 1979)** and the mother imidazole ring itself **(Abdel Kader et al., 1993).** Although all showed marked antituberculous action yet, carnosine proved to be the most effective. The drawback of imidazole treated group was the presence of some remnants of tuberculous lymphocytic follicles **(Abdel Kader et al., 1993).** The drawback of histidine treatment were areas of hepatic central atrophy (++) and few scattered pulmonary tubercles limited by thick fibrous

tissue and immature new alveoli **(Abdel Kader et al., 1977).** The drawback of histamine treatment was the presence of moderate tuberculous insults in spleen, liver and lung **(Abdel Kader et al., 1977).** Further no increased hepatic glycogen was observed with any of the other tested compound other than carnosine

4. 2. Carnosine and parasitic infection

Although, the above mentioned carnosine effects on chronic bacterial infections (both non-specific and specific) were earlier studied yet, researches on other chronic infections (parasitic) were delayed to 2001.

4. 2. 1. Carnosine and schistosomiasis

The effect of carnosine administration on *Schistosoma mansoni (S. mansoni)* infected hamsters, was studied by **Soliman and Abdel Monem (2001).** Liver examination showed that the dipeptide effectively reduced worm burden and egg count. The authors observed that the earlier the treatment by carnosine, the more diminished the ability of both male and female worms to couple (as extracted by liver perfusion). This explained the relative diminished number of fertilized eggs. The authors concluded that this uncoupling effect could be one of the carnosine mechanisms combating infection. They also recorded that carnosine normalized the liver tissue antioxidant status indicated by correction of MDA concentration, adenylate energy charges (AEC) and glycogen content.

Further, the ability of carnosine to improve the disturbed serum liver parameters also induced by S. *mansoni* parasite in hamsters was tested by **Soliman et al. *(*2002).** The authors indicated that infestation induced depletion of liver glycogen and lowered blood glucose concentration**.** This low glucose in Schistosoma infested hamsters and the diminished glycogen content of hepatocytes were also previously found by **Skelly et al. (1998).** The decrease of both carbohydrate parameters was attributed to two different mechanisms by the host as wellas by the parasite; the host inflammatory response exhausting blood glucose & hapatocyte glycogen **(Soliman and Abdel Monem, 2001)** and the adult schistosomes depending on host blood glucose absorbed across their outer body tegument **(Skelly and Shoemaker, 2000). Soliman et al. (2002)** also reported disturbed levels of liver function tests. There were increased activities of serum AST, ALP and gamma-glutamyl transferases. Infestation also increased serum procollagen III peptide (PIMP). PIMP was stated as a marker of liver fibrosis, induced in schistosoma parasitized subjects **(Modha et al., 1998).** PIMP was further recorded as as the most relevant factor in assessing severity of liver injury in chronic hepatic inflammations **(Mahmoud et al., 2001).**

Administration of carnosine either concurrent with, 2 and 4 weeks post infection was effective in reducing differential worm burden **(Soliman et al., 2001),** in improving blood glucose level (only when administered 2 and 4 weeks after infestation), reducing serum PIMP level and correcting all tested enzyme activities except gamma-glutamyl transferase **(Soliman et al., 2002).** Histopathological sections showed abatement of schistosomal infection; diminution in number and size of granulomata, destruction of schistosoma ova in the granuloma, with, diminution of its fibrotic a collagen content, accompanied by evidence of enhancement of the host immune response evidenced by increased histocytic and lymphocytic content and a lymphocytic cuff surrounding the granulomta. However, slight degree of increased portal fibrosis was noticed in the late-treated group. These actions support supplementation of schistosomiasis therapy by carnosine, being a chronic inflammatory disease **(Soliman et al., 2002).**

The enhancement of immune response was further proved by studying the effect of carnosine on individual Schistosoma mansoni antigens; SEA (soluble egg antigen), CAP (cercarial antigen preparation) and SWAP (soluble worm antigen) was studied in rabbit **(Soliman et al., 2003).** Carnosine treatment caused variable individual modifications of serum immunoelectrophoretic pattern in response to each of the three tested Ags. The patterns of SWAP, CAP and SEA presented disappearance of two, one and no band respectively in comparison to untreated group. This variable action of carnosine treatment could be explained by the dipeptide reported function as a universal buffer. Carnosine involved in body defense machineries logically reacts according to two biological evolutionary factors governing body response. Here, they are exposure to the stress agent and time. Concerning direct exposure, it is obvious that mammals, on natural infection, are in direct contact with the body of both cercaria, then the worm. The egg contents, on the other hand, being covered by its shell does not directly come in contact with the host tissues. Thus, the body and consequently its general defense molecule, carnosine, .do not elicid any immunological response to SEA. The time of exposure to the cercaria is shorter than that of the adult worm; being the final stage chronic inhabitant in the liver. Hence, the immunological response to SWAP is double that of CAP i.e. disappearance of two bands in comparison to one respectively.

The reduction in number of detectable antigens as recognized with anti-sera of rabbits treated with carnosine could confirm the role of carnosine in modulating immune response to the antigenicity of the two stages of *S. mansoni* antigens, CAP and SWAP. The modulating action of carnosine on the natural immune resistance was previously studied **(Nagi and Suda, 1988 and Silaeva et al., 1992)**. Carnosine was proved to have the ability to bind to macrophage and lymphocyte receptors stimulating their synthetic and secretory abilities and liberating immune modulator intermediates; cytokines and interlukins **(Suzuki et al., 2001).** Antigen were tested as vaccines against the invading larvae to prevent or reduce infection, but only little protection has been achieved **(Attalah et at., 1999, Qui-Lishue et al., 1999 and Bethony et at., 2006).**

Histopathological examination showed that increased response in the SEA animals could be indicated by the marked increased lymphoid follicle number and size in both the spleen and lymph nodes that could be supported by the persistence of all Ag-Ab bands. On the other hand, the marked decrease of lymphoid follicle number and size as well as the disappearance of one Ag-Ab band in CAP groups presented a decreased immunological reaction by carnosine. In SWAP animals, the increased sinus histocytosis and the disappearance of the two protein bands might be due to the phagocytic action of histiocytes **(Golasby et al., 2001)** engulfing the Ag-Ab complex molecules. These findings could be interpreted as being proportionate to the importance of the host-pathological reaction and clinical benefit.

The short period of the cercarial stage in the final host presenting the primary insult might explain the action of carnosine **(Muller, 2001).** These changes in the three I-C groups could be a reasonable involvement of carnosine in the actual natural sequence of biological events. The possible mechanisms by which carnosine regulates these action was previously supported by several authors demonstrating the ability of carnosine to improve both liver histopathological and some biochemical disorders induced by *S. mansoni* **(Soliman et al., 2002 and Diazgroundosca et al., 2003)**. In addition carnosine has the ability to bind to macrophage and lymphocyte receptors stimulating their synthetic and secretory abilities, which may eventually lead to the activation of the natural systems of body immune resistance **(Silaeva et al., 1992).** It induces liberation of immune modulator intermediates, cytokine and interleukin **(Shimida et at., 1999, Suzuki et al., 2001 and Hsien et al., 2002).** Carnosine

demonstrates a protective effect on T-cell that is attributed to diminished oxidative DNA damage **(Hyland et al., 2000).** It is also effective in diminishing apoptotic cell death **(Boldyrcv et al., 1999).** Carnosine modulation of immune response and decreasing apoptosis could, in part, be due to its antioxidant property.

The effect of carnosine in relation to the three Schistosoma antigens (SEA, CAP and SWAP) was further extended by **Soliman etal. (2005)** studying some biochemical parameter changes induced in rabbits by immunization and the influence of carnosine co-administration on these parameters. Namely total protein, glycogen and glycogen phosphorylase b in liver & also some serum protein fractions with varying molecular weights the authors deduced that CAP and SWAP have energy suppressive abilities while the passive effect of SEA might reflect the difference of native biological activities between the three parasite stages, cercariae & worms on one side and egg on the other towards energy metabolism of the animal host. This might be explained by the eggs being metabolically quit, while the cercariae & adult worms do actively complete their hepatic reside **(Mullar, 2001).**

However, those groups which were co-administered carnosine showed more pronounced changes in the serum protein fractions compared to those immunized with the different antigen only. Although, the dipeptide regained the normal levels of depleted glycogen in *S. mansoni* infected hamsters **(Soliman et al., 2003a).** This repletion in glycogen was more remarkable in CAP than in SWAP which might indicate that carnosine was more capable to nullify the strong action of CAP that could possibly be attributed to short life duration of the cercariae in the animal host.

In case of the studied serum protein, SEA and CAP showed induced reduction in most electrophoretic protein fractions while SWAP induced only lowered level of one protein. The decrease of almost all parameters in SEA and CAP opposite to the small number in SAWP might be attributed to the biological interrelations between both parasite & host tissues. The duration of the two developmental stages, eggs & cercariae, being transient inhabitant of host tissues is very short **(Mullar, 2001).** On the host side, the animal body constituents had evolutionary, long been exposed to worm Ag. Thus carnosine, a natural body component, became unable to compete with such high dosages of egg or cercarial antigens that the dipeptide might have not ever experienced during evolution. Carnosine, then, faced with these unnatural experimental high amounts of either antigen, which it had never acquired the proper ability to manage, was perplexed and unable to normalize the decreased protein parameters. It even caused further numerous decreases **(Leinonen et al., 2004).**

A special perculiarity in results of **Soliman et al. (2005)** was the record of the presence of both favourable increase in glycogen content (antioxidant action) as well as decrease in serum protein concentrations (moderate proxidant effect). However, this difference could be explained by the previously reported selectivity of carnosine in regulating animal body biochemical machinerics in pathological insults **(Quinn et al., 1992, Soliman et al., 2003a and soliman and Aly, 2003c).**

The mechanisms by which carnosine could cause selective changes are multiple the dipeptide facilitates the removal of deleterious proteins inactivated by forming protein carbonyl carnosine adducts (Hipkiss et al., 2002). Carnosine prevents oxidation and glycation, both of which could contribute to protein cross-linking promoting beta-amyloid plaque formation **(Hobart et al., 2004).**

4. 2. 2. Carnosine and fascioliasis

Comparing the antibody (Ab) response to *Fasciola gigantica* in experimentally infected rabbits treated 14 weeks with mirazid or carnosine by using ELISA. Results showed highly significant difference between the numbers of *Fasciola* worms in liver of treated and control rabbits. A reduction of 54.5% in worm burden was detected in the carnosine treated group. However, mirazid treated group showed complete worm eradication in the liver. It is concluded that the natural compound carnosine potentiates the immune response against infection and presented more increased antibody level than mirazid. However, mirazid has anthelmintic effect against *F. gigantica* infestation and carnosine was effective in declining the number of worms. Thus, a combination of both carnosine and mirazid might only be recommended in patients presenting other causes of diminished immunity in addition to *Fasciola* infection **(Soliman et al., 2004).**

4. 2. **3. Carnosine and trichinellosis**

The ability of carnosine to affect the infectivity as well as certain metabolic disturbances induced by *Trichinella spiralis (T. sp.)* infection in rats as compared to the antitrichinellosis drug, abbendazole was studied by **Soliman et al. (2007).** The search involved investigation of worm and encysted larvae burdens of both intestinal and muscular parasitic phases (after 1 and 6 weeks respectively) as well as serum metabolic parameters. These parameters included; peroxidation/ antioxidant parameters; MDA as an index of lipid peroxidation, tissue damage, and the antioxidant factors; vitamin C, GSH and G6PDH activity has an important role in generation of NADPH needed for the maintenance of GSH in its reduced form **(Ristof et al., 2001).** Activities of other four enzymes CPK (a marker of muscle function), LDH (a marker of both liver and muscle functions) and ALT and AST (markers of liver function) were also estimated in addition to, glucose and total proteins.

Both intestinal worms and muscular encysted larvae phases of *T. sp* invasion showed oxidative damage represented by different degrees of increased MDA levels positively correlated with the intensity of the helminthic infection This finding matched the report stating increased MDA in parasitic invasion **(Grudunski et al., 2003)** that was accompained by proportionate decreases of G6PDH activity, concentrations of GSH and vitamin C. These decreased antioxidant levels were stated to be due to intensification of infestation inducing host phagocytes to generate large amounts of ROS that might exceed the capability of host antoxidants to catabolize them **(Sharma and Agarwal, 1996).** The deficient antioxidant levels during trichinillosis were stated by other authors as an initial non-specific defense reaction of the host toward parasitic invasion **(Derda et al., 2004).** An increase in ALT, AST as well as LDH activities were observed during the two phases of trichinellosis. This found support in similar increases in serum of infected patients **(Sohn et at., 2000).**The increased serum enzymes were attributed to two successive insults affecting the liver. The presence of the parasite within the intestine was stated to primarily elicit an immune response that subsequently affects the liver. Afterwards, newborn larvae merging to circulation, release substances that are hepatotoxic **(Wang et al., 2000).** The development of large areas of multifocal coagultive necrosis in the liver further documented both statements **(Bliss et al., 2003).**

That CPK activity (marker of muscle function) increased only later, in the muscular phase of invasion, indicated the arrival of larvae to muscles and coinciding with the muscular disorder **(Garacia et al., 2003 and Guillermo et al., 2008).** CPK activity insult chronologically lagged 6 weeks beyond that of LDH to increase only in muscular phase. This found a previous support stating that the increment of serum CPK was attributed to oxidative stress causing inflammatory reactions in muscles **(Daoud et al., 2000).** This could indicate the more

tolerance and defense ability of musclar system to strongly withstand stresses in other organs (liver and intestine). The high increases of serum LDH activity in both infection phases matched deteriorated liver (in both phases) and muscle (in muscular phase) functions.

Both phases of *T sp.* infection reflected low serum glucose concentration, indicating that infection with this parasite is hypoglyceamia inducer **(Nishina and Suzukim, 2002)**. The lowered blood glucose by parasitic infection could be attribued to three factors: 1-the reduced glucose intestinal absorptive capacity of the insulted intestine **(Maden et at 2004)** 2- high glucose consumption by the parasite 3- liver glycogen depletion **(Reina et al., 1989 and Bliss et al., 2003).** Both disturbances in two tested energy substrate & the energy building enzyme in muscle (CPK) might be a factor explaining the presentation of general easy fatigability of patients infected with helminthic parasites **(King and Mahmoud, 1999 and Guillermo et al., 2008).**

In general, the deterioration of all tested biochemical parameters, except total protein that presented normal levels in all rat groups, showed more advanced defect in the muscular phase. This could be attributed to longer period of infection, the insult of the huge mammalian muscle bulk as well as to the possible 95% depletion of body carnosine by the chronic infection **(Fatzpatric et at., 1980).** The great diminution of body carnosine, could deplete the body from an important protective ability.

The pathochemical atiology of *Trichinella spiralis* invasion of both intestine and muscles was studied. **Daoud et at. (2000)** and **María et al .(2011)** stated that infection primarily caused inflammatory responses in both tissues. Both intestinal and muscular stages of *T. spiralis* and different host cell types of all host tissues, established complex interaction that lead to general immunological, pathological and metabolic disturbances **(Mitreva et at., 2004 and Zhao et al., 2013).** An additional weakening factor might be due to muscle tissue losing its store of carnosine. The majority of muscle carnosine content (95%) was previously found to be lost in chronic infection **(Fatzpatric et al., 1980).** This absence of carnosine could be a participating factor in the generalized stress phenomenon of *T. spiralis* infection.

Results showed that administration of albendazole effectively resulted in 100% cure rate against intestinal worms and muscle larvae. This agrees with the report of several authors that benzimidazoles, including albendazole, effectively eradicated both worms and larvae in early and late stages of *T spiralis* infection **(Chung et al., 2001, Maherani et al., 2012and Siriyastien et al., 2003)**. However, concerning derangement of metabolic parameters, the peroxidation (MDA) in both invasion stages after treatment with albendazole, remained equal to that of infection-untreated group. The antioxidant status evaluated by vitamin C, GSH and G6PDH proved to remain deteriorated in the intestinal phase similar to infected group. Even GSH activity became more deteriorated. Vitamin C, sill lagging, below normal showed mild increase. In the muscular phase the improvement of the antioxidant status was better than in the intestinal one as indicated by acquiring significant increased differences, in vitamin C and GSH, to that of infected group. CPK, only affected in the muscular phase was mildly improved by the drug. ALT, AST as well as LDH and G6PDH remained deteriorated although milder than the infected animals. However, the activities of these four enzymes were much increased by albendazole treatment than those of infected control, indicating specific hepatic toxic action of the drug, a fact which was further emphasized by other reports stating more deterioration of liver function after treatment with the benzimidazoles drugs **(Davis et al., 1989, Reuter et al., 2003 and Mido et al ., 2012).**

CPK being normal when albendazole was given early in the intestinal phase denoted that muscles are not yet insulted by the parasite larvae. However, when the treatment was given given after beginning of muscular phase the improvement was only moderate in spite of complete eradiction by elbendazole **(Bruschi, and Murrell, 2011).**

Serum glucose level showing midway improvement in aldendazol animals could be attributed to nullification of glucose utilization by parasite. This action was stated to result through 2 mechanisms; impairment of the intestinal uptake of glucose thereby increasing the parasite glycogen depletion & hampering its ability to form ATP which is used as the energy source by the worms **(Bolas-Fernandez et al., 2004).**This impairment of worm glucose absorption and utilization by albendazole was further completed by the drug eradicating the parasite. Eradication of the parasite was explained by selective binding of the drug to nematode tubulin, inhibiting the tubulin polymerase, thus impending cell division. Serum host glucose level was still not normalized and remained in a hypoglyceamic level, could feasibly be due to hepatotoxic action of albendazole **(Lacy, 1990, Bolas-Fernandez et al., 2004 and Mido et al., 2012).**

Oral administration of carnosine either before, concurrent with or after T. spiralis infection effectively reduced the intestinal adult worm burden & completely eradicated muscle larvae, indicating its feasible biocidal activity against trichinellosis. Metabolically the carnosine group showed great amelioration of the damage indicated by a subnormal level of MDA pointing to high antioxidant protective effect of the dipeptide. Carnosine, as well, correctively increased the concentrations of both vitamin C and GSH and G6PDH activity. Carnosine presented more protection of GSH than that of vitamin C and even increased above normal in both the Co-and post infection treatment groups. In addition carnosine normalized G6PDH activity being in line with the corrected GSH concentrations. That carnosine preferably protected GSH than the other vitamin C. Although both acting as antoxidant agents, GSH is the most abundant non protein thiol in cells and the first line against oxidative stress. This ensured the selective action of the dipeptide previously stated by **Soliman and mohamed (2004).**

Carnosine administration restored glucose level to normal was in full agreement with the previous results of **Soliman et al.*(* 2002)** reporting the involvement of carnosine in the repletion of liver glycogen level in hamsters under the effect of *S. mansoni* infection. The mechanism might be explained by the finding of **Ikada et al. (1980)** that carnosine could inhibit phosphorylase b at pH 7 through changing its conformation. Carnosine through its buffering action against changes in muscular pH safety prevented tissue acidification, thus slowing the rate of action of phosphorylase b and hence helping glycogen repletion **(Parkbouse et al., 1985 and Jia et al ., 2009).**

Carnosine improved ALT, AST and LDH activities, presenting a regular change pattern for the three animal groups of each phase. The correction of both Co and post infection groups showed complete recovery of enzyme activities opposite to their more deterioration result by albendazole.

This could give a clue that carnosine has the ability to ameliorate pathological disorders as emphasized by previous studies **(Soliman et al., 2002 and Iovine et al., 2012).** All these present biochemical serum parameters improvement could indicate equal abilities of carnosine to alleviate both toxic effects of adult worm inhabiting the gut as well as those of larvae inhabiting muscles.

That carnosine correction of parameters was more presented in the muscular phase, starting 6

weeks after infection, matched the old reports that the dipeptide presented more abatement of chronic infection than acute one **(Fatzpatric et al., 1980 and Seo et al., 2012).**

Having a back-comparing notice to the pathological reactivity of either organs; muscle and liver, in the untreated group, could very feasibly indicate that muscles, not as much affected by liver insults, could be attributed to it being the store house of carnosine, the marvelous general defensive buffer against variable body stresses. Many researches proved the variable abilities of exogenous carnosine administration to selectively combating insults of all body organs **(Soliman et al., 2007).** Here one might state that carnosine imparting reasonable defense power to different body organs, logically present more protection towards its host tissue!, the muscle! Often, carnosine had proved to be a wise agent (Presenting selective actions) and now additionally, proved to be just and generous for its main host, the muscle.

The possible additional mechanisms by which carnosione regulates these actions are numerous. It binds with macrophage and lymphocyte receptors, stimulating their synthetic and secretory abilities, leading to the activation of body immune resistance against the parasite **(Silaeva et al., 1992, Soliman et al., 2003and Williams et al., 2012).** It induces liberation of immune modulator intermediate, cytokine and interleukin (Suzuki et al., 2001). It is capable to combat non specific **(Fitzpatrick et al., 1980 and Seo et al., 2012)** as well as specific chronic infection **(Soliman et al., 2002).**

5. Possible role of L-carnosine in regulation of blood glucose

5. 1. control of hyperglycemia

L-Carnosine (0.01-0.001%) proved to be implicated in the control of hyperglycemia produced by lateral cerebral ventricular (LCV) injection of 2-deoxy-D-glucose (2DG). This hyperglycemia was attributed to disturbance of autonomic nerves control, to excitation of sympathetic nerves and inhibition of parasympathetic nerves leading to suppression of insulin secretion and enhancement of adrenalin and glycogen secretion **(Chum, 1998).**

The mechanism of carnosine action was stated to be through lowering activities of sympathetic nerves and facilitating those of parasympathetic nerves **(Yamano, 2001 and Niijima, 2002).** The suppressive action of the dipeptide might also be due to its transformation to L-histidine, then histamine, both of which cause inhibition of 2DG-hyperglycemia when injected into LCV through the stimulation of the histaminergic H_3 receptor **(Nagai et al., 2003).**

In patients with type I diabetes mellitus, **Gayova et al. (1999)** showed that carnosine levels in red blood cells decreased, which suggests that the dipeptide is less available for metabolic processes, therefore it should be supplemented. Moreover, in streptozotocin-induced diabetic rats, carnosine (50 mg/ kg/ day) orally for 7 days was shown to prevent the decrease in the hemolytic stability of red blood cells. The authors also showed that the dipeptide normalized the acid erythrogram parameters in these diabetic models **(Korobov, 2000).**

In addition, carnosine as well as GABA and taurine levels in serum of diabetic mothers and their off springs were significantly below normal **(Aerts and Van-Assche, 2001).** This deficiency in carnosine, previously entitled as neuroprotector **(Quinn et al., 1992)** and both neurotransmitters involved in the hypothalamo-hypophyseal regulation of insulin secretion, might contribute to development of impaired glucose tolerance and gestational diabetes, thereby, transmitting the effect to the next generation.

The advanced glycation end-product (AGE) hypothesis proposes that accelerated chemical modification of protein molecules by glucose during hyperglycemia contributes to the pathogenesis of diabetic complications. The two most commonly measured AGE are N (espition)-carbonxy-methyl lysine and pentosidine. L-Carnosine showed inhibition of AGE formation that result from chelating or antioxidant activity than from nucleophilic trapping for reactive carbonyl intermediates in the formation of AGE_S **(Price et al., 2001)**. **Hipkiss et al. (2001) and Yamano et al. (2001),** showed that carnosine combining with small carbonyl compounds (or groups) on glycated/ oxidized proteins and other molecules inhibited cross-linking of glycoxidized polypeptides. The authors termed this process carnosinylation. They also found that carnosine suppressed diabetes-associated increase in blood pressure in fructose-fed rats. On the other hand, **Sztanke and Pasternak (2003)** stated that carnosine is a natural substance that inhibits the AGE cross-links as a result of Maillard reaction but do not seem to break AGE-derived protein cross-links already formed. Therefore, they reported that the dipeptide might not be effective in patients with a long history of the disease.

5.2. Carnosine and its effect on appetite

Nagai et al (2003) reported that IP-injection of 100mg (0.44mmol) of the dipeptide inhibited the food intake for one hr after injection. On the contrary, other researches proved that L-histamine suppressed appetite in rats and mice **(Yoshimatsu, 1999 and 2000).** In support **Tagboto and Townson (2001)** reported the inhibition of food intake in a dose dependent manner. Therefore, these contradictory results could possibly be explained that smaller doses of L-carnosine might enhance appetite *via* 11_3 receptors in rats.

6. Role of carnosine in cholesterol abnormalities

6. 1. Role of carnosine in hypercholesterolemia

Diniz et al. (2004) supported the concept that the susceptibility of body tissues to oxidative stress might depend on dietary factors. The authors' emphathized that the surplus oxidative metabolism of fuels results in excess ROS production. Hypercholesterolemia, a common metabolic error of common occurrence, causes oxidative stress, resulting in functional and pathological disturbances in most organs. This elicits wide spread cytotoxic damage to cell constituents such as membrane lipids, structural proteins as well as enzymes. The disturbance of many biochemical parameters in chronic HC was reported by several authors in different body organs as well as in blood of chronic hypercholesterolemic (HC) subjects **(Lee et al., 2003, Lim et al., 2003 and Yanni et al., 2003).** The oxidative stress is not only associated with increased unsaturated fatty acid peroxidation (MDA production) but also, dependeds on metabolic pathways shifting energy production **(Yeda et al., 2004).**

Soliman and mohamed (2004) proved increased MDA and NO production as well as decreased activities of some energy machineries enzymes in the liver and kidney tissues namely, hexokinase (HK), aldolase (ALD) phosphoglucoisomerase (PGI), and creatine phosphokinase (CPK). Disturbances of other serum functional and metabolic parameters of both organs were proved in HC rabbits. Serum analysis documented impaired functions of both organs. AST and ALT amounted to 80 and 59.5 IU/Lrespectively and bilirubin was much increased (12mg/dl). Uric acid and creatinine were highly increased (25 and 4.5 mg/ dl respectively). These disturbances were supported by histological examination revealing deleterious pictures in both liver and kidney of HC rabbits. The hepatic architecture was disturbed. The hepatocytes were swollen, some cells showed darkened cytoplasm and others presented cytoplasmic vacuolations. The central veins were congested. Microscopic sections of the kidney showed distended hypercellular glomerioli, swollen elongated edematous tubules with obliterated lumina. Their epithelial lining was degenerated with karyolysis of

most nuclei.

Previous researches on protein metabolic parameters in HC showed the decrease of serum total proteins and amino acids **(Farmer and Gotto, 1995). Dadimarz et al. (1998)** stated that under stressful HC conditions, these amino acid concentrations changes in either blood or liver indicated stress-induced organ pathology. Decreased serum total proteins concentration and disturbed levels of most serum amino acids were also recently stated by **Soliman et al. (2005)** The authors found 11 disturbed amino acid levels out of the 17 tested. Nine amino acids, including arginine, were decreased while, only 2 were increased.

In correlation with the decreased total proteins and most amino acid levels, there was increased serum transaminases and urea cycle enzymes **(Fan et al., 2003 and Soliman et al., 2005).** Increased serum ALT and AST, in HC-animals would possibly indicate liver dysfunction or degeneration of muscle, either of which could result in disturbed amino acid metabolism **(Pearce, 2003).** In addition, the reported increased urea cycle enzymes participated in increased catabolism of most amino acids and hence, their decreased serum levels **(Fouad et al., 1983)**.This was supported by **Soliman et al. (2005)** proving increased activities of three urea cycle enzymes (OAT, ASS and arginase). These increased activities of serum metabolic protein enzymes in both these two HC-groups could be explained by three mechanisms. 1- Metabolic disturbances of the liver **(Crespo etal.,1999, Soliman and Mohamed, 2004 and Soliman etal., 2005).** 2- ROS liberation leading to accumulation of calcium in mitochondria causing the discharge of enzymes in circulation **(Alabovskii etal., 1999).** 3- Hyperactivation of arginase causing more production of urea and liver dysfunction leading to discharge of enzymes. Arginine. presenting low serum level, could be documented by the associated increased arginase activity **(Soliman et at., 2005).** Decreased arginine could disturb endothelial NO production, a potent inhibitor of platelet aggregation **(Ueda et at., 2001and Reid Sutton et at., 2003)**, leading to endothelial dysfunction and atherosclerosis **(Spieker et at., 2002).** Some researches indicated that increased urea cycle activity could anticipate in HC being a risk factor for atherosclerosis **(Novelli et al., 2002 and Ogita and Liao, 2004).**

The effect of treatment of by an authorized hypocholesterolimic drug, fluvastatin, in reducing the above mentioned disturbances in both liver and kidney tissue; was studied comparing its efficacy to that of the natural dipeptide carnosine **(Soliman and Mohamed, 2004 and Herculano et al., 2011).** The study involved MDA level, NO production and the three tissue energy enzymes GPI, ALD, CPK as well as serum functional tests of both organs. Serum transaminases activity, albumin and bilirubin evaluated liver function. Serum creatinine and uric acid evaluated kidney function. **Soliman et al. (2005),** further compared serum total proteins, 17 individual amino acids levels, transaminases and urea cycle enzymes.

HC-carnosine results reflected marked improvement of the cellular oxidative stress in vital organs **(Soliman and Mohamed, 2004 and Mong et al ., 2011)**. This was shown by normalization of liver MDA concentration and variable degrees of corrective action on the three enzymes of energy metabolism, PGI, ALD and CPK in both liver and kidney tissues. In the liver, the decrease of energy enzyme activities mounted to normalization of CPK. There was also favorable improvement of the other two tested enzyme activities (PGI and ALD). These improvements, however, denoted that recovery of the liver was incomplete inspite of much amelioration by carnosine. These results were documented by microscopic examination. The liver showed normal architecture. The hepatocytes were only slightly swollen with scanty vacuolations. The sinusoidal spaces were narrowed. Previous studies had also supported the partial improving effects of carnosine on the liver **(Soliman et al., 2003 andSorokina et al., 2003)**.

The corrective action of carnosine on the same parameters in kidney tissue was extremely evident. Normalization of all three enzyme activities indicating complete correction of the kidney faculties. Normalization of renal function by carnosine was explained by several functional mechanisms **(Soliman et at., 2004).** 1- Increase in GFR caused by carnosine arteriolar dilation **(Ririe. et at., 2000)** and hence increased capillary pressure **(Kaplan et al., 1990 and Rahman et at., 2001)**. 2- Improvement in endothelial vasodilator functions by carnosine inhibitory effect on lipid peroxidation and preventing further formation of free radicals. On the other hand, renal microscopic examination showing normal histological structure of renal glomeroli, tubules and interstitial spaces documented complete renal recovery.

HC-carnosine animals presented much amelioration of the other disturbed parameters. Examining serum protein metabolic parameters, plasma cholesterol concentration was decreased although, it was still higher than control **(Steiner et at., 2001). Soliman et al. (2005)** recorded normalization of total serum proteins and most amino acids (13 amino acids out of 17). AST and ALT showed significant improvements, although they were not normalized. The corrective ability of carnosine on urea cycle enzymes reflected lowering of OAT and ASS enzyme to their normal activities. This normalization of both activities could denote much amelioration of the cycle action. Arginase activity, not completely decreased to control levels might be attributed to plasma cholesterol not completely normalized. Thus marked correction of both urea cycle machinery and serum transaminases activity could point to normalization of protein catabolism by carnosine reflected as normalization of serum total proteins and most a. a. levels.

For HC-fluvastatin animals, **Soliman et al. (2004)** stated that although, all fluvastatin data reflected improvement yet, they still presented lagging deviations from control and HC-carnosine results. The authors reported marked amelioration of MDA and NO concentrations and the 3 energy metabolic enzyme activities; PGI, ALD and CPK of both liver and kidney tissues,. In support, several reports proved that statins, like many drugs, carry the risk for adverse effects on the liver being the target organ for drug detoxication. Previous reports of untoward effects of statin therapy included; increased liver cholesterol and triglycerides **(Farmer and Gotto,. 1995)**, alteration of hepatic key enzymes of carbohydrate metabolism (Crespo et al., 1999), increased serum liver function tests **(Steiner et at., 2001). Soliman et al. (2005)** proved increased both bilirubin (11mg/dl) and the two transaminases (ALT andAST; 62: 76 IU/L respectively) by fluvastatin. Histopathological reports of liver necrosis and gall blader inflammation with mucosal hyperplasia **(Zagoyaet at., 1999)** and vacuolated heptocytes with pyknotic or karyolitic nucleoli as well as engorged central veins **(Soliman et al., 2005)** indicated hepatotxicity.

Other biochemical blood examinations proved an incomplete down-regulating role of cholesterol concentration. by statin **(Steiner et at., 2001).** This down-regulatation of blood cholesterol concentration lagged behind that of carnosine although; both were higher than control animals. A harmful increase in cholesterol content of the liver by fluvastatin was previously recorded **(Zagoya et al., 1999).** This increased cholesterol liver tissue content was then explained by the statin hypocholesterolemic mechanism. Statin action was through inhibiting HMGCOA reductase leading to down regulation of cholesterol synthesis and re-regulation of hepatic high affinity receptors for low density lipoproteins followed by increased catabolism of LDL cholesterol **(Ness and Chambers, 2000).** This increased liver tissue cholesterol could indicate diminished fluidity of plasma membranes revealing impaired hepatocyte metabolic abilities (R++) thus, explaining the still marked lowering of serum total

proteins and nine amino acids after fluvastatin treatment. This statin, on the other hand showed correction of 6 amino acids only; a score similar to the insulted HC group. The numerical ratio between the numbers of normal amino acids was 6: 13: 6. for HC: HC-carnosine: HC-statin. In document, **Yilimaz et al. (2004)** stated that fluvastatin treatment was accompanied by few a. a. improved levels.

Of the five catabolic protein enzymes tested (AST, ALT, OAT, ASS and arginase), only one namely, ASS was down-regulated **(Soliman and Mohamed, 2004).** This might impart a minor beneficial effect to fluvastatin as it did not save serum protein nor a. a. concentrations. Both these results much lagged behind that of carnosine. In support, records about drawback effects of statin were increased serum liver enzymes, increased cholesterol content in liver and disturbances of key enzymes of liver carbohydrate metabolism **(Gespo et al., 1999 and Zagoya et al., 1999).**

In another research **(Soliman et al., 2005)** on seven serum parameters; amino acids, total protein concentration, the two transaminases (AST and ALT) and three enzymes of urea cycle (OAT, ASS and arginase), also selective improvements were noticed. Only three parameters; total protein, OAT and ASS were normalized. However, the majority of amino acids were also normalized. The dipeptide improved both transaminases and arginase.

Thus, HC-carnosine groups presented the best ameliorated results of both tested agents.

6. 2. Carnosine and hypercholesterolemic cataract

Morel (1994) and **Vendemil et al. (1996)** reported that HC rabbits showed increased LPO and reduced glutathione levels respectively in the fluids and tissues of the eye due to exhaustion of the natural antioxidant mechanisms. In hyperlipidemia, the lense was more susceptible to oxidative stress that caused development of cataract **(Atef et al., 1998).** The authors attributed it to enrichment of the lens with lipid constituents particularly cholesterol Serum HDL-cholesterol level was also associated with posterior subcapsular cataract in men **(Hiller et al., 2003).** Another explanation was previously stated by **Putilina et al. (1999)** that epithelial cells degeneration could cause more severe disruption of Na/ K ATPase pump causing efflux of Na and water. This leads to vacuoliation and separation of lens fibers which could be indicative of edema. High lens cholesterol content presented self-associated forming immusible domains in the plasma membrane, a phenomenon that contributed to the pathologic cellular processes participating in cataractogenesis **(Pertson et al., 2003).**

The effect of prophylactic carnosine administration on cataract induced by hypercholesterolemia was tested in comparison to fluvastatin **(Soliman and Mohamed, 2004).** In HC-carnosine rabbits, the lenses remained transparent. Light and SEM examination revealed intact capsule and epithelial cells as well as regular arrangement of lens fibers. These findings are a good evidence that carnosine could help in maintaining the transparency of the lens. These data could be confirmed by those of **Quinn et al. (1992)** that rabbits fed a high cholesterol diet were well protected against atherosclerosis and cataract if given carnosine supplements.

The ability of carnosine was also reported to eliminate existing cataracts by actually restoring the the lens proteins **(Babizhayev et al., 2002). Wang et al.(2000)** reported 100% effect of carnosine eye drops on primary senile cataract and 80% on mature senile in different cataract types with no side effects. This potential carnosine role to its ability to penetrate to the lens and increases Na-K-ATPase activity and thus had a potential role in treatment & prevention

of cataract. However, an essential factor in this carnosine cataract preventing effect could be reffered to its potency in lowering blood cholesterol level in HC rabbits **(Soliman and Mahmoud, 2004).** The authors advised the conjoined systemic carnosine administration in addition to topical NAC (N-acetyl carnosine) eye drops for cataract treatment.

Fluvastatin showed mild changes in the form of thickened lens capsule, vacuolation and deformation of epithelial cell nuclei as well as swollen cortical lens fiber **(Soliman and mohamed, 2004)** that was previously reffered to inhibition of cholesterol biosynthetic pathway **(Cendella, 1996 andChang et al., 2003)**. **Novelli et al. (2002)** recorded that alteration in fuel food constituents leading to inhibition of cholesterol biosynthetic pathway. The mechanism of action of carnosine being corrective of lens cataract might be mainly attributed to its antioxidant effect, having a di-potent antioxidant action **(Salganik et al., 2001and Hipkiss, 2011)**. Oxidation of proteins initiates the process of cross-linking forming inactive carbonylated and glycosylated protein end products which can further adduct to other native protein molecules causing more tissue damage **(Yeargans and Seidler, 2003 and Maherani et al., 2012).** Carnosine protects the tissues from these "second-wave" chemicals. It activities disposal of the damaged proteins by forming protein-carbonylcarnosine adducts **(Hipkiss et al., 2001, Hipkiss et al., 2002 and Hipkiss ,2011).**

7. Carnosine and Cardiovascular diseases

7. 1. Carnosine and blood pressure (BP)

Carnosine proved a dose dependent effect on the BP. Smaller doses presented hypotensive effect **(Nishina and suzuki 2002, Soliman et al., 2003). Bae and Majid (2013)** correlated this hypotensive effect of carnosine to its vasodilatory action. The authors observed that carnosine (0.625-20mM) produced a dose-dependent vascular relaxation of rat aorta that was independent of endothelium, and was in part mediated via cyclic GMP. **Ririe et al. (2000)** showed that low IV dose (16.7mg/kg) of carnosine produced insignificant change in blood pressure in rats whereas reduction in blood pressure was observed with higher IV dose (33.3mg/kg). This hypotensive action was proved to be through vascular muscles and not through endothelium. However, they demonstrated that carnosine produced concentration-dependent relaxation of the isolated rat aortic rings pre-constricted with phenylalanine, an effect which was endothelial independent, and decreased by soluble guanylate cyclase. The authors' proveded that the effect of carnosine was at least in part mediated via cyclic GMP production in vascular smooth muscle. **Niijima et al. (2002)** found that a diet containing 0.0001% or 0.001% L-carnosine decreases blood pressure elevation in DOCA-salt hypertensive rats. They postulated that L-carnosine may be an endogenous factor controlling blood pressure in a manner possibly antagonistic to the obesity-associated hypertensive effect of leptin.

In intact anaesthetized animals, the results of **Soliman et al. (2003)** were in accordance with these data where dose-dependent short-term hypotensive effect of carnosine (250 µg-128mg/kg) was observed in intact anaesthetized cats. Matching with this hypotensive effect of small doses of carnosine in producing hypotension, the authors reported an insignificant increase was observed in heart rate with IV carnosine doses up to 16 mg/kg while a mild significant increase was produced using 32, 64 and 128 mg/kg doses (idicating hypotensive action). **Tanida et al. (2004),** stated that carnosine in doses ranging from 250-128 µg/kg produced a significant dose dependent short-term reduction in the carotid blood pressure of chloralized anethesized cats.

In the spinal cat carnosine IV injection still produces hypotensive effect although, less than that observed in intact anaesthetized cats **(Soliman et al., 2003)**. Previously **Quinn et al. (1992)** reported that neither transection of both trunks of vagus nerve nor high transection of spinal cord affected the hypotensive carnosine effect.

The hypotensive effect however, was completely antagonized by I V injection of mepyramin suggested the involvement of H_I-agonistic activity of carnosine. This pointed that the hypotensive effect of carnosine could be mediated centrally and peripherally. Although H_I receptor mediated hypotensive effect was suggested, the possibility then remained that carnosine could be acting at a novel receptor with coincidental sensitivity to mepyramine. The possible mechanism involved in this observed hypotensive effect of carnosine was also investigated by **Tanida et al. (2004).** The authors found that intralateral cerebral ventricular injection of low doses of L-carnosine (1µg I. V; 0.01µg) significantly suppressed renal sympathetic nerve activity (RSNA) and reduced the blood pressure. The authors further studing the effects of antagonists of histaminergic receptors (H_1 and H_3) on L-carnosine-induced effects. They observed that an H_3 receptor antagonist (thioperamide) given peripherally and centrally, blocked RSNA and any lowering of blood pressure induced by smaller doses of peripheral L-carnosine. On the contrary, higher doses (1001.tg I. V; 101.tg LCV) elevated the RSNA and blood pressure **(Tanida et al., 2004).** Diphenylhydramine (an H_1 receptor antagonist) inhibited increases induced by higher doses of L-carnosine. However, it could be concluded that the equilibrium between carnosine and its constituent amino acids in vascular tissues may represent a new and novel mechanism for modulation of vascular tone and treatment of hypertension.

Soliman and Abdel Monem (2001) revealed that *in-vitro,* large doses of carnosine induced concentration-dependant contractions of isolated rabbit aortic spiral strips which was not affected by the addition of both a-adrenergic and angiotensin receptor blockers. On the other hand, methyl sergid (5 HT_1-a_2 antagonist) and mepyremain (H_1-anagonist) produce a rightward shift of the contractile response curves of carnosine reflecting the involvement of serotonegic-like a (or and) H_1-receptors.

Moreover, **Tanida et al. (2004)** recorded that bilateral lesions of hypothalamic suprachiasmatic nucleus eliminated both effects on RSNA and blood pressure induced by.low and high doses of peripheral carnosine they suggested the involvement of hypothalamic suprachiasmatic and histaminergic nerves in the activity of L-carnosine and that it acts in the brain and possibly other organs. Furthermore, the authors found that H_3 and H_1 histaminergic receptor antagonists (thioperamide and diphenylhydramine respectively), inhibited any decreases or increases in BP induced by carnosine, which proved the involvement of histaminergic nerve in the activities and that carnosine acts in the brain hypothalmic suprachiasmatic nucleus. They also found that carnosine suppressed diabetes-associated increase in blood pressure in fructose-fed rats. On the other hand, **Sztanke and Pasternak (2003) Lee et al . (2005),** stated that carnosine is a natural substance that inhibits the AGE cross-links as a result of Maillard reaction but do not seem to break AGE-derived protein cross-links already formed. Therefore, they reported that the dipeptide might not be effective in patients with a long history of the disease.

7. 2. **Cardiac effect of carnosine**

The dipeptide also proved a cardioprotective effect during stressful conditions. A decreased incidence of ischemia-induced cardiac arrhythmia was reported with carnosine perfused hearts compared to those perfused with either control buffer of beta antagonist **(Zaloga et al.,**

1997). In the same beneficial direction, carnosine proved a protective effect during cardioplegia **(Alabovakki et al., 1999).** It was also reported that in stressed hearts, carnosine significantly improved the functional recovery of perfused isolated rat hearts after 40 min global ischemia **(Lee et al., 2009).** During reoxygenation, after experimental hypoxia in intact animal, the addition of carnosine on top of the perfusing solution increased the coronary blood flow and decreased contractile activity .This may be due to the replenishing of the blood supply in order to wash accumulated hypoxia-metabolites for the benefit of cardiac muscle recovery.

In addition, **Zeiba and Wagrowska (2003)** and **Kalaz et al. (2012)** studied the influence of carnosine on the cardiotoxicity of doxorcebicin (DOX), which induces congestive heart failure. They found that Co-administration of carnosine with DOX normalized the values of the mean arterial pressure in rabbits and increased the cardiac index and stroke index while its effect on total peripheral resistance was non-significant. The histopathological examination of cardiac muscle cells revealed smaller damage of cardiac muscle in rabbits which received DOX with carnosine compared to those receiving DOX alone **(Zieba and Wagrowska-Danilewicz, 2003).**

These cardio-protective actions of carnosine could be related to a previously proved carnosine regulatory action on intracellular calcium. It had a direct action on the major calcium release channel in the sacroplasmic reticulum since it increases the intracellular cytoplasmic calcium level which causes increased cardiac muscle contractility **(O'Dowd and Miller, 1998, Robert and Zaloga, 2000 and Kalaz et al., 2012).**

7. 3. Carnosine and renal vascularal stress

Fujioka et al. (2003) studied the preventive effect of L-carnosine on ischemia/ reperfusion induced acute renal failure in rats (by occlusion of the left renal artery and vein for 45 minutes followed by reperfusion-2 weeks after contraleteral nephrectomy. Pre-ischemic treatment with L-carnosine (1-10µg/ kg IV) attenuated the induced renal dysfunction. Histopathological examination of the kidney of untreated acute renal failure rats revealed severe renal damage which was significantly suppressed by pre-treatment with L-carnosine at each dose given. Moreover, the authors recorded that the effect of the dipeptide is accompanied by suppression of the enhanced norepinephrine release in the kidney immediately after perfusion. Thus, the preventing effect of L-carnosine in ischemic acute renal failure is probably through suppression of enhanced renal sympathetic nerve activity induced by ischemia reperfusion.

The effect of carnosine in complete kidney recovery (function & structure) in HC-animals was also reported by **Soliman and mohamed (2004)** and **Harini et al. (2011).**

7. 4. Effects of carnosine on brain ischemia

Carnosine had a protective effect on rat brain **(Stadnikov et al., 2000, Zhang et al ., 2011 and Nam- Bae and Majid ,2013).** The authors investigated the effect of carnosine on rat brain subjected to 45min. global ischemia. They found that this type of ischemia characterized by decreased Kp-nitrophenyl-phosphate monamine oxidase B & A, disordering of membrane bilayer by reactive oxygen species attack and lead to 67% mortality in animals. Pretreatment with carnosine offered a protection of the brain against these oxidative injuries and increased the % survival.

8. Carnosine and teratogenesis

The effect of maternal treatment with phenytoin on the neonatal rats varied from small sized completely distorted non viable one (about 10% of animals) to others with manifest gross congenital malformation which appeared in clubbing of foot. Microscopic examination neonatal rat's liver and kidney showed marked degenerative changes. The liver's capsule became disturbed and the hepatic cords became disorganized most of hepatocytes showed marked cytoplasmic vacuolations. Their nuclei appeared small and faint but some cells lost their nuclei. The blood sinusoids could not be detected but, the haemopoietic cells appeared normal. In addition, the central veins were dilated and congested and their endothelial lining was disturbed. The portal area was surrounded with infiltrated cells. The portal vein was markedly dilated and congested. The collagen fibers deposition around the portal tract and in the capsule was moderately increased while hepatocyte glycogen was markedly reduced. Administration of phentoin (PHT) induced a highly significant decrease in the perimeter nucleus of hepatocytes in the liver and the nucleus of the tubules of the kidney. Carnosine given to the mothers with PHT caused improvement of body weight and length of neonates. No dead offspring or congenital anomalies were detected. Microscopic examination of neonatal rat's liver showed marked improvement. The hepatic architecture, blood sinusoids and hepatocytes were normal. Polyhedral in shape, they had easinophilic granular cytoplasm and had large vesicular basophilic nuclei with one or more nucleoli. The blood sinusoids were decreased in size by hepatocytes distended with cytoplasmic glycogen. The sinusoids were lined with flat endothelial cells and large Von kupffer cells. The central vein was slightly congested and mildly dilated. The portal tract was normal and the cells of bile duct have a large vesicular nucleus. The portal vein presented normal size with slight congestion. The distribution of the collagen fibers in the capsule and around the portal tract remained moderately increased. The effect of carnosine was dose dependant. The lower dose caused more vascular congestion as well as markedly increased collagen fibers and glycogen engorgement **(Soliman et al ., 2003b)** .

Microanatomy of the neonatal rat's kidney of treated mothers with PHT showed severe degenerative changes which could be manifested by areas of cells with ill-defined boundaries formed a syncytium of eosinophilic cytoplasm containing faint nuclei were seen within the cortex and medulla. Some distal convoluted and collecting tubules appeared. Both thick and thin loops of Henle within the outer medulla appeared small in size and the identification of them was difficult in the inner medulla. The cells of these loops had deeply eosinophilic stain and their nuclei had eosinophilic stain. The vasa recta could not be recognized while the interstitial cells appeared clearly. The majority of collecting ducts within the inner medulla presented partially interrupted lumina and their cells boundaries were lost. Some collecting ducts had obliterated lumina with irregular arrangement of cells in their wall. The collagen fibers were not seen in the glomerular tuft of capillaries, in between the renal parenchyma nor within the capsule. The PAS positive reaction appeared less than the control in the basement membrane of renal tubules, in the luminal borders of proximal convoluted tubules and in the renal corpuscle **(Lee et al ., 2009).**

Carnosine "10mg or 5 mg" and PHT showed mild improvement in the renal parenchyma. The glomeruli appeared normal in both groups. An apparent improvement of renal tubular structure was noticed in these groups. Many tubules acquired an improved epithelial lining but the epithelium was not completely normalized. The proximal convoluted tubules lost their brush luminal borders. Few cells of the distal convoluted tubules had vacuolated cytoplasm. Few of collecting tubules appeared with obliterated lumena and disrupted cells.Few cells had vacuolated cytoplasm. The thick loops of Henle appeared differentiated but most of cells had

vacuolated cytoplasm. The thin loops of Henle appeared in the outer and inner medulla with large oval nuclei. The majority of collecting ducts within the inner medulla were differentiated but their cells became cubical with less basophilic nucleus, some of them had disturbed cell. The vasa recta appeared congested. The interstitial cells appeared increased with large nucleus. There were an increase in the amount of the collagen fibers in the renal capsule which became thick and in between the renal improvement findings were dose dependent except for collagen fiber formation and cytoplasmic glycogen were more hown with the small carnosine dose. The small carnosine dose group less improvement parenchyma. The PAS positive reaction was seen in the basement membrane of all renal tubules, in the glomerular tuft of capillaries, in the parietal layer of Bowman's capsule and in the lumens of proximal convoluted tubules **(Soliman et al ., 2003b and 2009).**

Morphometric showed that administration of PHT induced a highly significant decrease in the erimeter nucleus of hepatocytes in the liver and the nucleus of the tubules of the kidney. On the other hand, the administration of either carnosine dose 5mg or 10mg with PHT induced a marked improvement in the mean perimeter nucleus of hepatocytes in the liver and the nuclei of the tubular cells of the kidney. The mean gray of PAS positive material in the hepatocytes was depressed, basal laminae of kidney tubules and its brush borders convoluted **(Soliman et al ., 2003b).**

PHT induced significant decrease of the mean gray of PAS positive material in the hepatocytes of liver, basal laminae of kidney proximal convoluted tubules and its brush borders when compared with the control group. On the other hand, the administration of carnosine 5mg orl0mg with PHT induced a marked improvement where the mean gray of PAS positive material in the hepatocytes of liver spatially in group treated with 5mg carnosine. The basal laminae of kidney proximal convoluted tubules and its brush borders showed a highly significant increase the mean gray of PAS positive material when compared to the control group**(Soliman et al ., 2003b).**

9- Effect of carnosine on partial hepatectomy (PH)

Soliman and mohamed(2004), due to the above wide range of biological effects of carnosine on various metabolic and biochemical aspects, the ability of carnosine to prevent biliary sludge in liver transplantation **(Barton et al., 1995)** and its wound healing effect **(Roberts et al., 1998)** investigated the role of the histidine dipeptide on mice liver regeneration after partial hepatectomy (PH). Liver regeneration in insults, including surgical trauma, was governed by acute phase response **(Fujioka et al., 2001)** being for regeneration and limitation of inflammation. It is usually orchestered cytokines and hepatocyte stimulating factors associated with characteristic metabolic changes in liver protein synthesis. Individual acute phase reactant proteins have different biochemical functions. Some are protease inhibitors; al-macroglobulin, al-acid glycoprotein, al- antitrypsin. Others are transporters α and β -lipoproteins ceruloplasmin, hemopexin, haptoblobulin, transferrin **(Ganong, 1999).** They have different regulatory mechanisms that are differentially expressed within hours or days after PH **(Campbell et al., 2001).** Hence, they are good indicators of liver condition as they are affected by its regeneration rate.

PH operation was recorded to elicit the specific acute phase response of serum proteins associated with characteristic metabolic changes in liver protein synthesis **(Fujioka et al., 2001). Soliman and Ali (2004)** studied the effect of carnosine administration to both normal mice and those 70% partially hepatectomized. Biochemical investigations of 16 liver tissue and serum parameters were tested after 15 and 30 days after operation: liver weight, DNA ,

RNA as well as serum total protein, albumin and protein profile were examined . Serum protein profile using two dimensional immuno-electrophoresis **(Fouad et al., 1983)** so, quantitate separation of 11 protein fractions was investigated ; prealbumin, α and β-lipoproteins α-macroglobulin, acid glycoprotein, α-antitrypsin,, cholinesterase, ceruoloplasmin, hemopexin, haptoblobulin and transferrin.

Healthy mice treated with carnosine for 15 days (Hlth-15 C) showed the increase of 4 paramters, while those treated with carnosine for 30 days (Hlth-30 C) showed the increase of 13 parameters. This was attributed to the selective protein promoting action of carnosine on liver tissue proteins. Some proteins were increased while the catabolic enzymes were suppressed **(Soliman and mohamed, 2004).**

This was assured by the increased concentration of DNA in PH-C (15 days) to that ofPH-C (30 days). However, in the later group it was only promoted to normal level. Thus, the more actively regenerating liver cells in the operated (PH-C-15 days) mice were more labile to stimulation by carnosine treatment. This indicated that embryonic cells are more responsive to carnosine action.

10. Carnosine and diabetes

It was found that, carnosine (50mg\kg\day orally for 7 days) prevent the decrease in the hemolytic stability of red blood cells in streptozotocin-induced diabetic rats **(Korobov, 2000).** It normalizes the acid erythrogram parameters in this diabetic model in rats. This finding suggested usefulness of carnosine as a possible treatment for diabetic patients **(Korobov et al. 2000),**In patient with type I diabetes mellitus, **Gayova et al.,(1999)** and **Kamei et al .(2008)** showed that the plasma carnosine levels were not significantly increased compared to the levels in healthy population, while the levels in red blood cells decreased. Lowered levels of carnosine in red blood cells could point out similar deficit in other cells. Due to its lower levels in cells, the authors suggested that carnosine is less available for metabolic processes, like antioxidant reactions. Its participation in antioxidant defense reactions is limited, non-enzymatic glycosylation of proteins. Therefore, it should be supplemented.

Carnosine as well as GABA and taurine levels in serum of diabetic mothers and their offspring were found significantly below normal **(Aerts and Van-Assche (2001).** The investigators concluded the low serum levels of the endogenous neuroprotector and both neurotransmitters taurine , GABA and the endogenous neuroprotector.

Carnosine in diabetic mothers and their fetuses might compromise the normal structural and functional development of the fetal brain. The effect of gestational diabetes on fetal development and induction of diabetogenic effect in the offspring are not limited to glucose and insulin metabolism. It appears to be modulated by alterations at the hypothalamo-hypophyseal axis. Therefore, the deficiency of the circulating levels of these neurotransmitters involved in the hypothalamohypophyseal regulation of insulin secretion, might contribute to development of impaired glucose to tolerance and gestational diabetes, thereby, transmitting the effect to the next generation **(Aerts and Van-Assche, 2001).**

The advanced glycation end-product (AGE) hypothesis proposes that accelerated chemical modification of proteins by glucose during hyperglycemia contributes the pathogenesis of diabetic complications. The two most commonly measured AGE; N(epsition)-Carboxymeth l lysine and pentosidine are glycoxidation reaction products **(Price etal.,2001 and Rashid et al**

., 2007). L-carnosine showed inhibition of AGE formation. That results from chelating or antioxidant activity than nucleeophylic trapping for reactive carbonyl intermediates in the formation of AGE **(Price et al., 2001).** Another study by **Hipkiss et al. (2001 and 2002)** showed that carnosine react with small carbonyl compounds (aldhyde and ketones) and protects macromolecules againest their cross- linking action. These authors found that carnosine can react non-enzymatically with carbonyl groups on glycated / oxidized proteins and other molecules inhibit cross- linking of glycoxidized polypeptides. This reaction was termed "carnosinylation". Those authors reported that carnosine suppressed diabetes-associated increase in blood pressure in fructose- fed rats, an observation consistent with carnosine's antiglycating actions.

On the other hand, **Sztanke and Pasternak, (2003)** found that carnosine is one of the substances of natural origin that inhibit the AGE cross-links as a result of Maillard reaction but do not seen to break AGE-derived protein cross- links that already formed. Therefore, it might not be effective in patients with a long history of the disease.

A study by **Babizhyev et al. (2000)** showed that naturally occurring compound N-alpha-acetyle carnosine is proposed as a pro drug of L-carnosine that is resistant to enzymatic hydrolysis by carnosinase. Topical ocular administration of this compound in rabbit eyes by different treatment techniques, instillation, sub-conjunctiva injection .In aqueous humor, L-carnosine might act as an antioxidant and enter the lens tissue when present at effective concentration (5-15 mm). The advantage of the ophthalmic prodrug N-alpha- acetlycarnosin and its bio-activated principle L- carnosine as universal antioxidant related to their ability to give efficient protection against oxidative stress both in the lipid- phase of biological membranes and in aqueous environment. Therefore, these agents are proposed for treatment of ocular disorders that have a component of oxidative stress in their genesis as complications of diabetes mellitus, cataract, glaucoma, retinal degeneration and ocular inflammation.

Thus, **Nagai et al. (2003)** examining this possibility, they tested the effects of dephenhydramine (HI-blocker) and FMH (a specific inhibitor of histidine decarboxylase) on the 2DG-hyperglycemia. Consequently, both treatments significantly inhibited the hyperglycemia. This suggests that the histaminergic H1-receptor is involved in the mechanism of the 2DG-hyperglycemia by elevating the blood glucose level. It was previously stated that lipolysis in rat white adipose tissue was stimulated by facilitating the sympathetic nervous system functions through HI-receptors of histaminergic neurons **(Tsuda etal., 2002).** The authors also proved that LCV-injection of a higher amount of histamine enhanced the 2DG-hyperglycemia**.**

In contrast, previously **Arrang (1988)** reported that the histaminergic H3 receptor has a higher affinity for lrisiaInine Arun H1 and H2 receptors and that it was implicated in inhibition of histaminergic nerves as an inhibitory presynaptic receptor for the endogenous histamine release in the central and peripheral nerves. Therefore, it is possible that LCV-injections of smaller amount of L-carnosine or L-histidine suppressed the 2DG-hyperglycemia through the stimulation of the histaminergic H3 receptor **(Nagai et al., 2003).** In accordance with this possibility, it was found that thioperamide, an antagonist for histaminergic H3 receptor, could inhibit both suppressive action of L-carnosine and L-histamine on the 2DG-hyperglycemia**(Yamano, 2001).**

11. Carnosine and Alzheimer's disease

The dipeptide carnosine (β-alanyl-L-histidine) has contrasting but beneficial effects on cellular activity. It delays cellular senescence and rejuvenates cultured senescent mammalian cells. However, it also inhibits the growth of cultured tumour cells. Based on studies in several organisms, we speculate that carnosine exerts these apparently opposing actions by affecting energy metabolism and/or protein homeostasis (proteostasis). Specific effects on energy metabolism include the dipeptide's influence on cellular ATP concentrations. Carnosine's ability to reduce the formation of altered proteins (typically adducts of methylglyoxal) and enhance proteolysis of aberrant polypeptides is indicative of its influence on proteostasis. Furthermore these dual actions might provide a rationale for the use of carnosine in the treatment or prevention of diverse age-related conditions where energy metabolism or proteostasis are compromised. These include cancer, Alzheimer's disease, Parkinson's disease and the complications of type-2 diabetes (nephropathy, cataracts, stroke and pain), which might all benefit from knowledge of carnosine's mode of action on human cells (**Hipkiss** et al., 2013).

12. Carnosine ameliorates stress-induced glucose metabolism disorders

Carnosine could ameliorate stress-induced glucose metabolism disturbance. It is presumable that carnosine exerts its anti-stress effects by indirectly affecting the histaminergic neuron system, modulating the stress-activated hypothalamic–pituitary–adrenal axis and improving glucose metabolism through regulation of the enzymes in the glucose metabolic pathways **(Tosi et al ., 2011).**

13. L-Carnosine and Autism

Oral supplementation with L-Carnosine resulted in demonstrable improvements in autistic behaviors as well as increases in language comprehension that reached statistical significance. Although the mechanism of action of the amino acid is not well understood, it is believed that it acts to modulate neurotransmission and affect metal ion transfer of zinc and copper in the entorhinal cortex. This may enhance neurological function or act in a neuroprotective fashion **(Chez et al ., 2013).**

14. Carnosine the best antiaging

Carnosine is considered as the most important anti-aging supplements available to us today. The therapeutic potential of carnosine supplementation has been tested in numerous diseases in which ischemic or oxidative stress are involved. For several pathologies, such as diabetes and its complications, ocular disease, aging, and neurological disorders, promising preclinical and clinical results have been obtained. The carnosine system has evolved as a pluripotent solution to a number of homeostatic challenges. L-Histidine, and more specifically its imidazole moiety, appears to be the prime bioactive component, whereas β-alanine is mainly regulating the synthesis of the dipeptide **(Boldyrev et al., 2014).**

CONCLUSION

It could be concluded that carnosine is a potent antiglycating antinflammatory agent, pH buffer and heavy metal chelator. It can prevent aldehyde adducts, nucleic acid oxidation and enhanced immune response **.**Also, it prevent and cure cataract, glucoma and other age related eye. Carnosine also, has a role in regulation of blood glucose and has neuro-protective function as well as antiparasitic and antiaging activities .Thus, Supplementation with carnosine and food rich

(Poultry, beef and pork and fish) protects against several diseases *via* reducing oxidative stress through its effects as free radical scavengers. Also, the antioxidant can activate neurons and preserve cellular viability. Eating fish once a week is recommended for reducing the risk of Alzheimer's disease due to carnosine rich and its polyunsaturated fatty acids contents. These types of fatty acids may suppress brain inflammation and have a role in brain development and protecting nerve cells degeneration.

REFERENCES

Abdel-Kader FH, Jackson ML and Lee G B (1977). Soil kaolinite, vermiculite and chlorite identification by an improved lithium DMSO X-ray diffraction test: Agron. Abstr. p. 194; J. Soil Sci. Soc. Am.

Abdel-Kader MHK, Peach ME, Stiles DA (1979). Determination of ethylene dibromide in fortified soils by molecular emission cavity analysis using a modified extraction process. J Assoc Off Anal Chem 62:114-118.

Abdel-Kader MS, Omar AA, Abdel-Salam NAand Stermitz FR (1993). Totoxic hydroazulene diterpenes from the brown alga, Erythroxan diterpenes and Dictyota dichotoma. Z. Naturforsch. 58c, 17D22. flavonoids from Fagonia bruguiri. Phytochemistry 33.

Addolorato G, Di-Campli C, Simoncini M, Pasini P and Nardo B *(* 2001). Oxygen free radicals production in rat liver: Dose related effect of ethanol on reperfusion injury. Dig Dis Sci, 46, 1057-1066.

Aerts L and Van Assche FA (2001). Law taurine, gamma-amiobutyric acid and carnosine levels in plasma of diabetic pregnant rats. J.Perinat-Med, 29(1), 81-4.

Ahluwalia P, Tewari K, Choudhary P (1996). Studies on the effect of monosodium glutamate (MSG) on oxidative stress in erythrocytes of adult male mice. Toxicol Lett, 84: 161-165.

Alabovskii VV, Boldyrev AA, Vinokurov AA, Gallant S and Chesnokov DN (1999). Comparison of protective effects of carnosine & aceltylcarnosine during cardioplegia. Biull Eksp Biol. Med. 127:290-4.

Arrang JM, Devaux B, Chodkiewicz JP, Schwartz JC (1988). H3- receptors control histamine release in human brain. J Neurochem 51:105-108.

Atabai K, Matthay MA (2002). The pulmonary physician in critical care. 5: Acute lung injury and the acute respiratory distress syndrome: definitions and epidemiology. Thorax. May;57(5):452-8.

Atef MM, Ebrahim N, El-Taher F, El- Shobaki and Liala R, Abd Elkhalek (1998). Study on the relation between abnormalities in lipid metabolism and pathogenesis occuring in the eye. Ph.D.Thesis in physiology Faculty of cience. Cairo university.

Attalla AM, Attia H, El-Nashar EM, Nawar A, Abdel Kader K, Ismail H and El-Ebeidy G (1999). Vaccination against Schistosoma mansoni infection using 74 kDa Schistosoma protein antigen. Vacine, 17: 2786-2791.

Babizhayev MA, Deyev A and Yarkakova V (2002). Efficacy of N - acetyle carnosine in the treatment of cataract. g RD, 3 (2): 87- 103.

Babizhayev MA, Deyev AI (2012). Management of the virulent influenza virus infection by oral formulation of nonhydrolized carnosineand isopeptide of carnosine attenuating proinflammatory cytokine-induced nitric oxide production.Am J Ther. 19(1):e25-47.

Babizhayev MA, Yermakova UN, Semiletor YA and Deyen AI (2000). The natural histidine-containign dipeptide Naalpha-acetyl carnosine as an antioxidant for ophthalmic use. Biochemistry (Mosc), 65(5): 588-98.

Babizhayev MA, Deyev AI, Yegorov YE. (2013).L-Carnosine Modulates Respiratory Burst and Reactive Oxygen Species Production in Neutrophil Biochemistry and Function: May Oral Dosage Form of Non-Hydrolized Dipeptide L-Carnosine Complement Anti-Infective Anti-Influenza Flu Treatment, Prevention and Self-Care as an Alternative to the Conventional Vaccination ? Curr Clin Pharmacol. 2013 ,20,1,234-239.

Bae O and Majid A (2013). Role of histidine/histamine in carnosine-induced neuroprotection during ischemic brain damage Brain Research, 1527, 21 , 246-254

Barton P, Steininger R, Maier A, Muhlbacher F and Lechner P (1995). Biliary sludge after liver transplantation. Treatment with interventional technique versus surgery and/or oral chemolysis. Am. J. Radiol. 4, 865.

Bellia F, VecchioG, Cuzzocrea S, Calabrese V, Rizzarelli E. (2011). Neuroprotective features of carnosine in oxidative driven diseases Molecular Aspects of Medicine, 32,4–6, 258-266.

Bethony J, Brooker S, Albanico M, Geiger SM, Loukas A, Diemert D & Hotez PJ (2006). Soil-transmitted helminth infections; Ascaris, Trichuriasis and hookworm. Lancet 367, 1521.

Bliss SK, Alcaraz A, Appleton JA (2003). IL-10-prevents liver necrosis during murine infection with Trichinella spiralis. J. Immunol., 171, 31421-3147.

Bolas-Fernandez F, Rama-Iniquez S and Torrado JJ (2004). Ex-vivo anthelmintic activity of albendzole-sulphoxide enantiomers. J. Parasitol., 90: 407-409.

Boldyrev A, Song R, Lawrence D, Carpenter DO (1999). Carnosine protects against excitotoxic cell death independently of effects on reactive oxygen species. Neuroscience 94, 571–577.

BoldyrevA A, Aldini G, Derave W. (2014). Muscle carnosine loading by beta-alanine supplementation is more pronounced in trained vs. untrained muscles J. Appl. Physiol. 116 (2): 204-209.

Bruschi F and Murrell KD (2011). CHAPTER 110 - Trichinellosis Tropical Infectious Diseases: Principles, Pathogens and Practice (Third Edition), 768-773

Campbell JS, Prichard L, Schaper F, Schmitz J, Stephenson FA, Rosenfeld ME, Argast GM, Heindrich PC and Fausto N (2001). Expression of suppressors of cytokines signaling during liver regeneration J.Clin Invest 107 1285.

Cenedella RJ (1996). Cholesterol and cataracts. Surv ophthalmol, 40(4): 320-3.

Chen YC, Shen SC, Lee WR, Lin HY, Ko CH, Shih CM, Yang LL (2002). Wogonin and fisetin induction of apoptosis through activation of caspase 3 cascade and alternative expression of p21 protein in hepatocellular carcinoma cells SK-HEP-1. Arch. Toxicol. 76, 351–359.

Cheng J, Wang F, Yu D, Wu P, Chen J (2011). The cytotoxic mechanism of malondialdehyde and protective effect of carnosine via protein cross-linking/mitochondrial dysfunction/reactive oxygen species/MAPK pathway in neurons .European Journal of Pharmacology, 650, 1, 184-194

Cheng Q, Gerald Robison W and Samuel Zigler J (2002). Geranylgeranyl pyrophosphate counteracts the cataractoge effect of lovastatin on cultured rat lenses. Exp Eye REs., 75(5): 603-9.

Chez M G, Buchanan C P, KomenJ L, Marina M.A, Becker RN.(2013). L-Carnosine and Autism. Nutrition Review Archive,45:34-48.

Choi HS, Lim JY, Chun HJ, Lee M, Kim ES, Keum B, Seo YS, Jeen YT, Um SH, Lee HS, Kim CD, Ryu HS, Sul D (2009). The effect of polaprezinc on gastric mucosal protection in rats with ethanol induced gastric mucosal damage: comparison study with rebamipide. Life Sci. 93(2-3):69-77.

Choi MS, Do KM, Park YB, Jeon SM, Jeong TS, Lee YK, Lee MK, Bok SH (2001). Effect of naringin supplementation on cholesterol metabolism and antioxidant status in rats fed high cholesterol with different levels of vitamin E. Ann. Nutr. Metab. 45, 193–201.

Chun S, Niijima A, Nagai K (1998). Effect of bilateral lesions of the suprachiasmatic nucleus of the hyperglycemia caused by 2-deoxy-D glucose and vasoactive intestinal peptide in rats. Brain Res(809):165-174.

Chung MS, Jook H, Quan FS, Kwon HS and Cho SW (2001). Efficacy of flubendazole and albendazole against T. spiralis in mice, Parasite., 8: 195-198.

Churchill TA, Green CJ and Fullar BJ (1995). Stimulation of glycolysis by histidine buffer in mammalian liver during cold anoxia. Arch. Biochem. Biophys., 320: 43-50.

Cohn T, Prud'homme D, Streiner D, Kameh H, Remington G (2004). Characterizing coronary heart disease risk in chronic schizophrenia: high prevalence of the metabolic syndrome. Can. J. Psychiatry 49 (11), 753-760.

Crespo N, Illnait J, Mas R, Fernandez L, Fernandez J, Castano G (1999). Comparative study of the efficacy and tolerability of policosanol and lovastatin in patients with hypercholesterolemia and Noninsulin dependent diabetes mellitus. Int. J. Clin Pharmacol Res., 19(4), 117-127.

Cuzzocrea, S;Zingaelli,B;Villari,D;Caputi,AP and longo,G. (1998). Evidance for in vivo peoxynitrite production in human chonic hepatitis. Life sci.,63(2),L25.

Dadmaz M.,Burg C.,Milakofskyl.,HoffordJ.M. and Vogel W.H.(1998). Effect of stress on aminoacids and related compounds in various tissues of fasted rats.life.,63,1485-1491.

Daoud AA, Abdel-Ghaffar AE, Dayab FA and Essa TM (2000). The effect of antioxidant preparation (Antox) on the course and efficacy of treatment of trichinosis. J. Egypt. Soc. Parasit., 30: 305-314.

Davis,A,Dixon H;Pawlowski,Z.S.(1989). Multicenter clinical trials of benzimidazole carbamates in human cystic echinococoosis(phasez). Bull.WHO,67,503-508.

Deev L, Geronsharenko E.N, Baizhumanov AA, Akhayala MY, Antonova SV and. Shestakova SV (1997). Protective effect of carnosine in hyperthermia. Bull. Exp. Biol. Med., 7: 665-667.

Derda M, Wandurska-Nowak E, Hada E (2004). Changes in the level of antioxidants in the blood from mice infected with Trichinella spiralis. Parasitol. Res. 93(3), 207-210.

Diazgrandosca DWA, Albrcht H, Zakim D and Boyer TD (2003). Parasitic diseases of the liver. In Hepatology: A Textbook of Liver Diseases. Saunders, Philadilphia, London.

Diniz YS, Cicogna AC, Padovani CR, Santana LS, Faine LA, Novelli LB (2004). Diet rich in saturated and polyunsaturated fatty acids; metabolic shifting and cardiac health. Nurition, 20, 230-243.

Douglas W.W. (1995). Histamine and 5-hydroxytryptamine(serotonin)and their antagonists.In:Gilman A.G.,Goodman L.S.,Gilman A.(eds.):The pharmacological basis of Therapeutics.Newyork,Maxwill-Macmillan publishing Co.,pp605-38.

Fagherazzi EV, Garcia VA, Maurmann N, Bervanger T, Halmenschlager LH, Busato SB, Hallak JE, Zuardi AW, Crippa JA, Schröder N.(2012). Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders. Psychopharmacology (Berl). 219(4):1133-40.

Fanchauml H. ,Fitzpatrick.J.C.,Fischer,H.(1990).: Effect of histamine receptor antagonists on mortality in compound 48/80-induced shock.32,133-40.

Farmer JA, Gotto AM (1995). Currently available hypolipidemic drugs and future therapeutic developments. Baillieres Clin Endocrinol. Metab., 9(4), 825-47.

Fitzpatrick D, Amend JF, Squibb RL and Fisher M (1980). Effects of chronic and acute infections on tissue levels of carnosine, anserine and free histidine in rats and chicken. Proc. Soc. Exp. Biol. Med. 165, 404.

Fontana M, Pinnen F, Lucente G, Pecci L (2002). Prevention of peroxynitrate-dependent damage by carnosine and related sulphona- mide pseudopeptides. Cell Mol. Life Sci. 59, 546 – 551.

Fouad AA, El-Rehany MA, Maghraby HK (2007). The hepatoprotective effect of carnosine against ischemia/reperfusion liver injury in rats European Journal of Pharmacology, 572, 1, 61-68.

Fouad AA, Qureshi HA, Yacoubi MT, Alid. Melhim WN (2009).Protective role of carnosine in mice with cadmium-induced acute hepatotoxicity. Food and Chemical Toxicology, 47, 11, 2863-2870.

Fouad FM,Goldberg M and Ruhenstroth BG (1983). Plasma protein determination as a clinic probe for liver injury in rats induced by thioacetamide, alloxan or ixoten. J. Clin. Chem. Clin. Biochem. 21, 203.

Fujioka T, Murakami M, Niiya T, Murai N, Enami Y and Kusano M (2001). Effect of methylpridnisolone on the kinetics of cytokines and liver function of regenerating liver in rats. Hepatol. Res. 19, 60.

Ganong WF (1999). Review of Medical physiology, 19th ed., pp. 516-617, Appelton and Lange Norwalk, Connecticut, California.

García-González V, Govantes F, Shaw LJ, Burns RG, Santero E (2003). Nitrogen control of atrazine utilization in Pseudomonas sp. strain ADP. Appl Environ Microbiol. Dec;69(12):6987-93.

Gariballa A and Sinclaur A (2000). Carnosine; physiological ptoparties and therapeutic potential. Age Ating, 29: 207-210.

Gayova E, Kron I, Suchozora K, Pavlisak V, Fedurco M and Novakova B (1999). Carnosine in patients with type I diabetes mellitus. Bratisl. Lek. Listy, 1009): 500-2.

Goldsby RN, Kindt TJ and Osborne BA (2001). Kusby Immunology. W.H. Freeman Company, USA.

Grudzinski IP, Frankiewicz-Jozko A, Bany J (2001). Diallyl sulfide-a flavour component from garlic (Allium sativum) attenuates lipid peroxidation in mice infected with Trichinella spiralis. Phytomedicine, 8(3), 174-177.

Guillermo G, Nuñez Susana N. Costantino, Teresa Gentile, Stella M. Venturiello. (2008). Immunoparasitological evaluation of Trichinella spiralis infection during human pregnancy: a small case series .Transactions of the Royal Society of Tropical Medicine and Hygiene, 102, 7, 662-668.

Harini A, Chakkera RL, Hanson and Johanna KD (2011). Association of variants in the carnosine peptidase 1 gene (CNDP1) with diabetic nephropathy in American Indians. Mol gene Metabol. 103(2), 185-190.

Herculano B, Shimatan MI, TaniguchiK, Hisatsune T (2011). Carnosine (beta-alanyl-L-histidine) treatment ameliorates memory deficits caused by high-fat diet in APPswe/PSEN1dE9 miceAlzheimer's & Dementia, 7, 4, S520-S521

Hiller R, Sperduto RD, Reed GF, D Agostino RB and Wilson PW (2003). Serum lipids and age - related Zens opacities: a longitudinal investegation : the Framingham studies. Ophthalmology, 110 (3): 578 - 83 .

Hipkiss AR (2002). Could carnosine be a naturally-occurring scavenger of acrolein and other reactive aldehydes in the brain? Neurobiol. Aging 23, 645–646.

Hipkiss AR (2011). Energy metabolism, proteotoxic stress and age-related dysfunction – Protection by carnosine Molecular Aspects of Medicine, 32, s 4–6,267-278.

Hipkiss AR, Brownson C, Mariana F, Ruiz E and Ferro A (2002). Reaction of carnosine **with aged protein: another protective process? Ann. N.Y. Acad., 959:285-294.**

Hipkiss AR, Browson C and Carrier MJ (2001). Carnosine the antiaging, anti-oxidant dipeptide may react with protein carbonyl groups. MechAgeing-Dev., 122(13): 1431-45.

HipkissA R (2009). Chapter 3 Carnosine and Its Possible Roles in Nutrition and Health .Advances in Food and Nutrition Research, 57, 87-154.

Hipkiss A R, Cartwright S P, BromleyC, GrossS R and Bill M R.(2013). Carnosine: can understanding its actions on energy metabolism and protein homeostasis inform its therapeutic potential? Chemistry and Aging, 17, 1-7.

Hobart LJ, Seibel I, Yeargans GS, Seidler NW (2004). Anti-crosslinking properties of carnosine: significance of histidine. Life Sci. 75, 1379–1389.

Hsieh CL, Ho YC, Lai HH, Yen GC (2002). The inhibitory effect of carnosine and anserine on DNA oxidative damage . Food Drug Anal. 10: 47-54.

Huang CC, Chen JR, Liu CC, Chen KT, Shien MJ and Yang SC(2005). Effect of long term ethanol consumption on jejunal lipase and disaccharidase activities in male and female rate. World J Gastroenterol, 11, 2603-2608.

Hyland BI, Reynolds JN, Hay J, Perk CG, Miller R (2002). Firing modes of midbrain dopamine cells in the freely moving rat. Neuroscience. 114:475–492.

Ikdada T, Kimura C and Tamaki N (1980). Activation of rabbit muscle fructose-1 ,o-biphosphatase by histidine and carnosine. J. Biochem., 87: 179-185.

Iovine B, Iannella ML, Ocella FN, Pricolo MR, Bevilacqua MA (2012). Carnosine inhibits KRAS-mediated HCT116 proliferation by affecting ATP and ROS production Cancer Letters, V315, , 28 , 122-128.

Jia H, Qi X, Fang S, Jin Y, Han X, Wang Y, Wang A, Zhou H (2009). Carnosine inhibits high glucose-induced mesangial cell proliferation through mediating cell cycle progression Regulatory Peptides, Volume 154, Issues 1–3, 10 , 69-76.

Kalaz EB, Evran B, Develi S, Erata GÖ, Uysal M, Koçak-Toker N (2012). Effect of binge ethanol treatment on prooxidant–antioxidant balance in rat heart tissue Pathophysiology, Volume 19, Issue 1, February, Pages 49-53

Kamei J, Ohsawa M, Miyata S, Tanaka S (2008). Preventive effect of l-carnosine on changes in the thermal nociceptive threshold in streptozotocin-induced diabetic mice European Journal of Pharmacology, 600, 1–3, 14 2008, 83-86.

Kaplan K, Aynedjian HS, Schlondorff D, Bank N (1990). Renal vasoconstriction caused by short-term cholesterol feeding is corrected by thromboxane antagonist or probucol. J Clin Invest, 86, 1707-1714.

Kashimura H, Suzuki K, Hassan M, Ikezawa K, Sawahata T, Watanabe T, Nakahara A, Mutoh H, Tanaka N (1999). Polaprezinc, a mucosal protective agent, in combination with lansoprazole, amoxycillin and clarithromycin increases the cure rate of Helicobacter pylori infection. Aliment Pharmacol Ther.;13(4):483-7.

King CH and Mahmoud AA (1999). Schistosomiasis. In "Tropical Infectious Diseases. Principal, Pathogens and Practice", Guerrant, RI.; Walker, DH and Wellar, PF.(Eds.).. New York, Churchill Livingstone. pp: 1031-1038.

Korobov VM (2000). Effects of carnosine on the erythrocyte membrane in normal states and in diabetes. MKR- Biokhim — Zh., 72(2) : 94-6.

Kyriazis M. (2010). Anti-ageing potential of carnosine: approaches toward successful ageingmore. Drug Discovery Today , 2,3-4.

Le Blanc J and Soucy J (1994). Effects of carnosine on insulin and glucagons secretion in the dog. Nutr. Res., 14: 1655-1660.

Lee JS, Joon SM\, Park EM, Huh TL, Kwon OS, Lee MK, Choi MS (2003). Cinnamatic supplementation enhances hepatic lipid metabolism and antioxidant defense systems in high cholesterol-fed rats. J. Med. Food, 6(3), 183-191.

Lee S, Kim M, Yon J, Baek I, Park CG, Lee BJ, Yun YW, Nam S (2009). Black ginseng inhibits ethanol-induced teratogenesis in cultured mouse embryos through its effects on antioxidant activity Toxicology in Vitro, 23, 1, 47-52

Lee Y, Hsu C, Lin M, Liu K, Yin M (2005). Histidine and carnosine delay diabetic deterioration in mice and protect human low density lipoprotein against oxidation and glycation European Journal of Pharmacology, 513, 1–2, 145-150.

Leinonen E, Santala M, Hyotyla T, Santala H, et al. (2004). Elderly patients with major depressive disorder and delusional disorder are at increased risk of subsequent dementia. Nordic Journal of Psychiatry 58(2):161-4.

Lieber CS (2000). Hepatic metabolic and nutritional disorders of alcoholism: From pathogenesis to therapy. Critisism Rev Clin Lab Sci, 37, 551-584.

Lim BO, Seong NS, Chou RW, Kim JD, Lee HY, Kim SY, Yu BP, Jeon TI, Park DK (2003). Efficacy of dietary aloe vera supplementation on hepatic cholesterol and oxidative status in aged rats. J. Nutr. Sci Vitaminol., 49(2), 292-6.

LoPachin RM (2004). The changing view of acrylamide neurotoxicity. Neurotoxicology 2004;25:617–30.

Madden KB, Yeung KA, Zhao A, Gause WC, Finkelman FD, Katona IM, Urban JF, Donohue TS (2004). Enteric nematodes induce stereotypic STAT6- dependent alteration in intestinal epithelial cell function. J. Immun., 172, 5616-5621.

Maherani B, Arab-Tehrany E, Kheirolomoom A, Cleymand F, Linder M (2012). Influence of lipid composition on physicochemical properties of nanoliposomes encapsulating natural dipeptide antioxidant l-carnosine Food Chemistry, 134, 2, 632-640.

Mahmoud GM, Mohamed AA and Aly SA (2001). Strange attractors and chaos control in periodically forced complex Duffing,s oscillators, physica A 292, 193-206..

Maldonado JL, Fridlyand J, Patel H (2003). Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst 95:1878–1890,

María V, Gentilini, Guillermo G, Nuñez María E, Roux SM, Venturiello (2011). Trichinella spiralis infection rapidly induces lung inflammatory response: The lung as the site of helminthocytotoxic activity mmunobiology, 216, 9,1054-1063

Martínez-Salgado C, Eleno N, Tavares P, Rodríguez-Barbero A, García-Criado J, Bolaños JP, López-Novoa JM (2002). Involvement of reactive oxygen species on gentamicin-induced mesangial cell activation. Kidney Int. 62:1682-1692.

Martínez-Salgado C, López-Hernández FJ, López-Novoa JM (2007). Glomerular nephrotoxicity of aminoglycosides. Toxicol. Appl. Pharmacol. 223:86-98.

Mido S, Fath EM, Farid AS, Nonaka N, Oku Y, Horii Y (2012). T richinella spiralis: Infection changes serum paraoxonase-1 levels, lipid profile, and oxidative status in rats Experimental Parasitology, 131, 2, 190-192

Miller NJ, Rice-Evans CA (1997). The relative contributions of ascorbic acid and phenolic antioxidants to the total antioxidant activity of orange and apple fruit juices and blackcurrant drink. Food. Chem. 60, 331–337.

Mitreva M, Jasmer DP, Appleton J, Martin D, Wylic T, Clifton SW, Waterston RH and McCarter JP (2004). Gene discovery in the adenophorean nematode Trichinella spiralis an analysis of transcription from three life cycle stages. Mol. Biochem. Parasitol., 137: 277-291.

Modha et al (1999). "Concept Decompositions for Large Sparse Text Data Using Clustering", pp. 1-32.

Mong M, Chao C, Yin M (2011). Histidine and carnosine alleviated hepatic steatosis in mice consumed high saturated fat diet European Journal of Pharmacology, Volume 653, Issues 1–3, 25 February, Pages 82-88

Morel DW de ia Liera-Moya M and Friday KE (1994). Treatment of cholesterol-fed rabbits with dietary vitamins E and C inhibitis, lipoprotein oxidation but not development of atherosclerosis, J. Not., 124, 2123.

Müller P (2001). Hasselmann's stochastic climate model viewed from a statistical mechanics perspective, in Stochastic Climate Models, eds. P. Imkeller and J.-S. von Storch, Birkhäuser, 285-295.

Nagai K and Suda T (1988). Acceleration of metabolism of stress-related substances by L-carnosine. Nippon-Seirigaku-Zasshi, 52: 221-228.

Nagai K, Niijima A, Yamano T, Otan H, Okumra N, Tsuruoka N, Nakai M and Kiso Y (2003). Possible role of L. carnosine in regulation of blood glucose through controlling autonomic nerves. Exp. Biol. Med 288(10): 1138-45.

Nagasue,N;Yukaga,H.;Ogawa,Y.;Kohno,H.andNakamura,T.(1987). Human liver regeneration after major hepatic resection: Astudy of normal liver and livers with chronic hepatitis and cirrhosis.Ann.Surg.206,30.

Ness GC and Chambers CM (2000). Feedback and hormonal regulation of hepatic 3-hydroxy-3 methylglutaryl coenzyme A reductase; the concept of cholesterol buffering capacity. Proc. Soc Exp. Biol Med. 224, 8- 12.

Niemela O (2001). Distribution of ethanol-induced proteinadducts *in vivo*: Relationship to issue injuiry. Free Radic Biol Med, 15, 1533-1538.

Niijima A, Okui T, Matsumura Y, Yamano T, Tsuruoka N, Kiso Y, Nagai K (2002). Effects of L-carnosine on renal sympathetic nerve activity and DOCA- salt hypertension in rats. Auton Neurosci: Basic Clinical 97:99-102.

Nishina M, Suzuki M (2002). Biophasic hypothermia in mice infected with a parasitic nematode, Trichinella spiralis. Exp. Anim., 51(2), 207-211.

Novelli ELB, Fernandes AAH, Diniz YS, Alemida JA, Faine LA and Ribas BO. (2002). The adverse effect of a high energy dense diet on cardiac tissue. J. Nutr. Environ. Med., 12, 287-290.

O'Dowd AA and Miller DJ (1998). Analysis of an H1-rceptor-mediated, Zn potentiated vasoconstrictor action of the histidyl/dipeptide carnosine in rabbit saphenous vein. Br. J. Pharmacol. 125(6):1272-1280.

Ogita H and Liao J (2004). Endothelial function and oxidative stress. Endothelium, 11. 123-132.

Ozaras, R., V. Tahan, S. Aydin, H. Uzun, S. Kaya and H. Senturk (2003). N-acelylcysteine attenuates alcohol-induced oxidative stress in rats. World J. Gastroenetrol., 9: 125-128.

Parkhouse WS, Mckenzie DG, Hochachka PW and Ovalle WK (1985). Buffering capacity of deproteinized human rastus lateralis muscle. J. Appl. Physiol., 58:14-17.

Pearce DA (2003). Altered amino acid levels in sera of a mouse model for juvenile neuronal ceroid lipofuscinoses. Clinica Chemica Acta, 332, 145-148.

Pertson MR, Tulenko TN and Jacob RF (2003). Direct evidence for cholesterol crystaline domines in biological membranes: Role in human patho biology, Biochem . Biophys Act., 10 (2): 198 - 207.

Poli G, Parola M. (1997). Oxidative damage and fibrogenesis Free Radic Biol Med.;22(1-2),287-305.

Price DL, Rhett PM, Thorpe SR and Baynes JW(2001). Chelating activity of advanced glycation end- product inhibitors. J.Biol-Chem,276(52):48967-72.

Putilina T, Zhang ZW and Augustyen RC (1999). The effects of sonification on alpha - crystaline . Curr-Eye Res., 10, 113 - 117.

Qui L, Liu S, Xue H, Zhang Y, Li H and Hu Y (1999). SDS-PAGE and EITP analysis of the protein components of different isolates of Schistosoma japonicum in China and Japan. Chinese J. Parasitol. Parasit. Dis., 17: 367-369.

Quinn PJ, Boldyrev AA and Formazuyk VE (1992). Carnosine its properties, function and potential therapeutic application. Mol. Aspects Med. 13, 379.

Rahman M, Varghese Z, Moorhead F (2001). Paradoxical increase in nitric oxide synthase activity in hypercholesterolaemic rats with impaired renal function and decreased activity of nitric oxide. Nephrol. Dial. Transplant, 16, 262-268.

Rashid I, van Reyk DM, Davies MJ (2007). Carnosine and its constituents inhibit glycation of low-density lipoproteins that promotes foam cell formation in vitro FEBS Letters, Volume 581, I5, 2007, 1067-1070

Reid Sutton V, Pan Y, Davis EC and Craigen WJ (2003). A mouse model of argininosuccinic aciduria: biochemical characterization. Mol. Genet. Metab., 78: 11-16.

Reina D, Habela M, Navarrete I and Gomez FM (1989). Hypoglycemia in experimental canine trichinellosis. Vet. Parasitol., 33: 289-296.

Reina D, Habela M, Navarrete I, Gomez FM (1989). Hypoglycemia in experimental canine trichinellosis. Vet. Parasitol., 33(3-4), 289-296.

Reuter S, Merkle M, Brehm K, Kern P and Manfras B (2003). Effect of Amphotericin B on larvae growth of Echinococcus multilocularis. Antimicrobiol Agents and Chemotherapy, 47: 620-625.

Ririe DG, Roberts PR, Shouse MN and Zaloga GP (2000). Vasodilatory action of the dietary peptide carnosine. Nutrition, 16, 168-172.

Robert PR and Zaloga GP (2000). Cardiovascular effects of carnosine. Biiochemistry (Mosc.), 65(7): 856-861.

Roberts PR, Blac KW, Santamouro JT and Zaloga GP (1988). Dietary peptides improve wound healing following surgery.Nutr. 1, 266.

Roy Chengappa KN, Scott R, Turkin S, De S, Christopher R, Bowie JS, Brar PJ, Schlicht, SL, Murphy, ML, Hetrick RB, David F (2012). A preliminary, randomized, double-blind, placebo-controlled trial of L-carnosine to improve cognition in schizophrenia Schizophrenia Research, 142 ,145-152.

Salganik RI, Dikalova A, Dikalova S, La D, Bulygina E, Stvolinsky S and Bolderyv A (2001). Antixodiants selectively protecting neurochemical functions in rat overproducting reactive oxygen species. J. Anti=Ageing Med., 4: 49-54.

Seo H, Ogata-Ikeda I, Ishida S, Okano Y, Oyama Y (2012). A comparison of the cellular actions of polaprezinc (zinc-l-carnosine) and ZnCl2 Life Sciences, 90, 25–26, 27, 1015-101

Shaheen SO, Sterne JAC, Songhurst CE, Burney PGJ (2000). Frequent paracetamol use and asthma in adults. Thorax 2000;55:266-270.

Sharma RK, Agarwal A (1996). Role of reactive oxygen species in male infertility. Urology. Dec;48(6):835-50.

Shimada T, Kawai T, Takeda K, Matsumoto M, Inoue J, Tatsumi Y, Kanamaru A, Akira S (1999). IKK-i, a novel lipopolysaccharide-inducible kinase that is

Silaeva SA, Golenchenko VA, Gavril'chak AV, Onufriev MV, Khatsernova BYA, Gulyaeva NV and Shekhter AB (1992). Effects of carnosine and 4-methyluracil on the course of experimental hepatitis in rats. Biokhimiya, 57: 1366-1372.

Siriyasatien P, Yingyourd P. and Nuchprayoon S (2003). Efficacy of albendazole against early and late stages of T. spiralis infection in mice. J. Med. Assoc. Thai., 86: 257-262.

Skelly PJ and Shoe Maker CB (2000). Induction cues for tegument formation during the transformation *mansoni cercariae.* International journal for parasitology 30, 625-631.

Skelly PJ Tielens AGM and Shoe maker CB (1998). Glucose tranport and metabolism in mammalian stage schistosomes. Parasitology Today 14, 402-406.

Sohn HY, Keller M, Gloe T, Morawietz H, Rueckschloss U, Pohl U (2000). The small G-protein Rac mediates depolarization induced superoxide formation in human endothelial cells. J. Biol. Chem. 2000;275:18745–18750.

Soliman K, Abou-El Dobal S, Marei N (2003). Effect of carnosine administration on the immune response of rabbit to Schistosoma mansoni antigens. J Egypt Soc Parasitol. 2003;33(3):663–78.

Soliman K, Aly HF and Aly SA (2003). Stimulatory effect of carnosine on serum proteins in ethanol intoxicated rats. Egypt. J. Pharm. Sci., 44 (2), 267-291.

Soliman K, Aly HF, Hamed MA and Aly SA (2005). Corrective action of l- carnosine in hypercholesterolemic rabbit The Egyptian J. Medicalo of The National Research Center, 1687-1278.

Soliman KM and Aly HF (2003c). Promoting action of carnosine on serum proteins in normal andpartially hepatectomzed mice. Egypt. J. Physiol. 25, (in press).

Soliman KM and Mohomed AH (2004). Effect of carnosine and Fluvastatin on serum lipids in dietary hypercholesterolemic (in press).

Soliman KM, Abdel AzizM, Nassar YH, Abdel-Sattar S, El-Ansary A (2002). Effects of carnosine on bilharzial infestation in hamsters: biochemical and histochemical studies Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology, 131, 3, 535-542

Soliman KM, Abdel-Monem E (2001). Acute toxicity study and some pharmacological effects of carnosine on smooth muscles. Kasr El-Eini Med. J. 7, 225-252.

Soliman KM, Abdul-Hamid M, Othman AI (2007). Effect carnosine on gentamicin-induced nephrotoxicity. Med Sci Monit. 13(3):BR73-83.

Soliman KM, Aly HF and Ay SA (2003b). Stimulatory action of carnosine on serum proteins in ethanol intoxication. Egypt J Pharmst. Sci. 44, 1012-1024.

Soliman KM, El-Ansary A, AlyH F and MahmoudS (2004). Effects of carnosine on liver enzymes of bilharizia infection. Endem. Dis., 26, 1-18.

Soliman KM, Mohamed AM and Metwaly NS (2003a). Corrective action of carnosine on liver enzymes in ethanol iontoxication. Med. J. Cairo Univ. 71, 135-143.

Sorokina EV, Bastrikova NA, Stvolinsky SL and Fedorova TN (2003). Effects of carnosine and selegiline under MPTP— induced parkinsouism in senescence accelerated mice. Neurochem. Moscow, 20, 133-138 in Russian.

Spieker LE, Sudano I, Harlimann D, Lerch PG, Lang MG, Ibnggeli C, Corti R, Ruschitzka F, Luscher TF and Noll G (2002). High-density lipoprotein restores endothelial function in hypercholesterolemic men. Circulation, 105, 1399- 1402.

Stadnikov AA, Chernova OL, Kovbyk LV, Shevliuk NN (2000). Effect of carnosine on the morphofunctional state of mucosal cells of the soft palate of rats in staphylococcal infection. Zh Mikrobiol Epidemiol Immunobiol. 2000 ,59-62.

Steiner S, Gatlin CL, Lennon JJ, McGrath AM, Seonarain MD, Makusky AJ, Aponte AM, Blasco RE, Anderson NL (2001). Cholesterol biosynthesis regulation and protein changes in rat liver following treatment with fluvastatin. Toxciol. Lett. 120(1-3), 3690377.

Suzuki H, Mori M, Seto K, Miyazawa M, Kai A, Suemalsu M, Yoneta T, Miura S. and Ishii H (2001). Polaprezine attenuates the Helcobater pylori-include gastric mucosal leucocyte activation in Mongolian gerbis: A study intra vital videomicroscopy. Alime. Pharmacol. Thi., 15: 715-725.

Sztanke K and Pasternak K (2003). The Maillard reaction inhibitors and their biological and therapeutic significance. Ann. Univ. Mariae-Curie-Sklodowska (Med),58(2):156-8.

Tagboto,S. and Townson,S.(2001). Antiparasitic properties of medicinal plants and other naturally occurring products.Adv.parasitol.,50:199-295.

Tanida M, Niijima A, Fukuda Y, Sawai H, Tsuruoka N, Shen, J, Yamada S, Kiso Y and Nagai K (2004). Dose dependent effects of L-carnosine on the renal sympathetic nerve and blood pressure in urethane-anesthetized rats. Am. J. Physiol. Regul. Integr. Comp. Physiol.288, R447–R455.

Tsoi B; Rong He R; Yang D; Li Y; Li X; Li W; Abe K; Kurihara H.(2011). Carnosine Ameliorates Stress-Induced Glucose Metabolism Disorder in Restrained Mice. Journal of Pharmacological Sciences; 117(4):223-229.

Tsuda K, Yoshimatsu H, Niijima A, Chiba S, Okeda T, Sakata T (2002). Hypothaamic histamine neurons activate lipolysis rat adipose tissue. Exp Biol Med 227:208-213.

Ueda S, Katagiri M, Matsumoto Y, Nishimura T, Matsushita S, Mori M, Ozawa T and Orimo H (2001). Nitric oxide dependent inhibition of platelet aggregation in elderly patients with hypercholesterolemia. Nippon Ronen Igakkai Zasshi, 38, 177-184.

Varalakshmi CH, Ali AM, Pardhasaradhi BV, Srivastava RM, Singh S, Khar A (2008). Immunomodulatory effects of curcumin: In vivo. Intern Immunopharmacology 8: 688–700.

Vendemil G; Micelli-Ferrari T, Cardio L and Altomare E (1996). Abnormal protein redox status in the lens and vitreous of diabetic subjects. Diabetologia 39,130.

Volpi E, Lucidi P, Cruciani C, Monacchia F, Reoldi G, Brunetti P, Bolli G.B and De Feo P(2002). Nicotinamide counteracts alcohol induced impairment of hepatic protein metabolism in humans. J Nutr, 127, 2199-2204.

Wang AM, Ma C, Xie Zh and Shen F (2000). Use of carnosine as a natural anti-senescence drug for human beings. Biochem. (Moscow) 65, 1022-1024.

Williams CF, Lloyd D, Kolarich D, Alagesan K, Duchêne M, Cable J, Williams D, Leitsch D (2012). Disrupted intracellular redox balance of the diplomonad fish parasite Spironucleus vortens by 5-nitroimidazoles and garlic-derived compounds Veterinary Parasitology, 190, 1–2, 23 , 62-73.

Yamano T, Niijima A, Iimori S, Tsuruoka N, Kiso Y, Nagai K (2001). Effect of L-carnosine on the hyperglycemia caused by intracranial injection of 2-deoxy-D-glucose in rats Neuroscience Letters, 313, 1–2, 2 ,78-82.

Yanni AE, Yatzidis HA, Kavantzas NG, Agapitos EV, Perrea DN, Karayannacos PE (2003). Dietary L-asparate and L-glutamate inhibit fatty streak initation in cholesterol-fed rabbit. Nutr. Metab. Cardiovasc. Dis., 13(2), 80-86.

Yeargans GS, and Seidler NW (2003). Carnosine promotes the heat denaturation of glycated protein. Biochem. Biophys. Res. Commun., 300, 75-80.

Yeda SD, Antonio C, Carlos RP, Lea SS, Luciane AF and Ethel LB (2004). Diets rich in saturated and polysaturated fatty acid: metabolic shifting and cardiac health. Nutrition, 20, 230-234.

Yilmaz MI, Baykal Y, Kilic M, Sonmez A, Bulucu F, Aydin A, Sayal A and Kocar IH (2004). Effect of statins on oxidative stress. Biol.Trace Elem. Res., 98, 119-127.

Yoshimatsu H, Chiba S, Tajima D,Akehi Y, Sakata T (2002). Histidine suppresses food intake through its conversion into neuronal histamine. Exp Biol Med.227:63-68.

Yoshimatsu H. Itatevama E, Kondou S, Taiima D, Himeno K, Hidaka S, Kurokawa M, Sakata T (1999). Hypothalamic neuronal histamine as a target of leptin in feeding behavior. Diabetes 48:2286-2291.

Yuvaraj P, Subramoniam A (2009). Hepatoprotective property of Thespesia populnea against carbon tetrachloride induced liver damage in rats. J Basic Clin Physiol Pharmacol. ,20:169-77.

Zagoya JCD, Barron JCA, Vazquez RC, Martinez F, Oropeza AJ (1999). Comparative toxicity of high doses of vastatins currently used by clinicians, in CD-1 male mice fed with a hypercholesterolemic diet. Life Science, 65(9), 947-956.

Zaloga GP, Roberts PR, Black KW, Lin M, Sudo RT and Nelson TE.(1997). Carnosine is a novel peptide modulator of intracellular calcium and contractility in cardiac cells. Am. J. Physiol., 272(41):H462-8.

Zhang X, Song L, Cheng X, Yang Y, Luan B, Jia L, Xu F, Zhang Z (2011). Carnosine pretreatment protects against hypoxia–ischemia brain damage in the neonatal rat model European Journal of Pharmacology, 667, 1–3, 30 , 202-207.

Zhao Y, Liu MY, Wang XL, Liu XL, Yang Y, Zou HB, Sun SM, Yu L, Rosenthal B, Shi HN, Boireau P, Wu XP (2013). Modulation of inflammatory bowel disease in a mouse model following infection with Trichinella spirali. Veterinary Parasitology, 194, 2–4, 20, 211-216.

Zieba R and Wagrowaska-Danilewiez M.(2003). influence of carnosine on the cardiotoxicity of doxorubicin in rabbits,pol.J.pharmacol.55:1079-87.

This work is dedicated to the soul of Kawther M. Soliman, Prof. Dr. of Biochemistry, Faculty of Medicine, Cairo University.