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ROLE OF GARLIC OIL IN MANAGEMENT THE BIOCHEMICAL ALTERATIONS AND OXIDATIVE STRESS INDUCED BY SODIUM NITRITE IN MALE ALBINO RATS

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ABSTRACT

The main purpose of this study was to elucidate the modifying role of garlic oil against the hazard effects of sodium nitrite (a food preservative agent) on some biochemical parameters and oxidative status in male albino rats. The present data observed that the ingestion of sodium nitrite (80 mg/ kg b.wt.) for three months induced a significant increase in serum levels of glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, urea and creatinine. Also, hepatic AST and ALT enzymes activity was increased, whereas a significant decrease was recorded in liver glycogen as well as serum, liver and renal total protein content. Similar decrease was noticed in liver ALP activity, renal urea and creatinine levels. Moreover, the results showed a significant increase in lipid peroxidation assessed as thiobarbituric acid reactive substance (TBARS) in both liver and kidney of sodium nitrite treated rats. In the mean time, glutathione (GSH) content as well as catalase activity were decreased in the same tissues. However, the oral administration of garlic oil at a dose of 5 ml/kg b. wt. showed a marked amelioration of the investigated parameters indicating the protective role of garlic oil.

In conclusion, the chronic administration of sodium nitrite has harmful effects on both biochemical parameters and oxidative status. On the other hand, the garlic oil has a promising role in attenuation the obtained negative effects of sodium nitrite.

Key words: Food preservative - sodium nitrite - garlic oil – biochemical parameters – oxidative status.

INTRODUCTION

Food additives are common in our life and play an important role in the life of human beings [**Kilgore & Li (1980)**]. It has been noticed that, people especially children at the age of nursery usually used food containing additives and colorant with great amounts which attract their attention [**Yamagishi *et al.*, (2006)**]. Sodium nitrite ($NaNO_2$) is considered one of these food additives which has been widely used to preserve cured meat and fish [**Ellen & schuller (1983)**]. It has been reported that $NaNO_2$ has strong mutagenic activity in various systems [**Odashmia (1980)**]. The dangerous point is that nitrite reacts with amines to produce nitros-amines, and with amides to produce nitrosamides [**Choi *et al.*, (2002)**]. The toxic effects of nitrates and nitrites in different mammalian species are well documented and include impairment of reproductive function, hepatotoxicity and methaemogobenemia, impairment of certain defense mechanisms like to the inflamimatory response and tissue injury, growth retardation, carcinogenesis and endocrine disturbance [**Choi (1985); Jahries *et al.*, (1986); Helal & Elsaid (2006); El-Gendy *et al.*, (2007)**]. The wide use of nitrates and nitrites as preservatives in food technology elevates the importance of studying their effects. Also, the question of primary protection of their widely used preservatives deserves a great attention. Recent trends in controlling and treating diseases tend to prefer natural antioxidant compounds rather than synthetic ones [**Neto *et al.*, (2002)**]. The human diet which contains large numbers of natural compounds is more important in protecting the body against the development of adverse effects. One of the first well known plants which possess anticarcinogenic properties is garlic (*Allium sativum* L.) [**Abou Nour & Madbouly (2001) and Gorinstein *et al.*, (2006)**].

Garlic (*Allium sativum* L.) is a common plant used as a food item in all parts of the world and its medical properties have been recognized since ancient times. Garlic has been reported to display antibacterial, anticarcinogenic, hypolipidemic, hypoglycemic, antifungal and antiatherosclerotic properties [**Bordia & Verma (1980) and Hussain *et al.*, (1990)**]. Also garlic is one of the antioxidants that defend against free radicals damage [**Hey, (2002); Banerjee *et al.*, (2003) and Pari *et al.*, (2007)**].

Therefore, the present study aims to investigate the hazard impacts of sodium nitrite on biochemical and oxidative parameters in

male rats, in addition to clarify the possible protective role of garlic oil for counteracting the progress of such dangerous effects.

MATERIAL AND METHODS

I- Experimental animals:

Male Albino Rats *(Rattus rattus)* weighing about 100-120 g were used in this study. The animals were kept under good ventilation and received a balanced diet and water *ad libitum* through out the experimental period.

II- Drugs:

1. Sodium nitrite ($NaNO_2$):

Sodium nitrite was obtained from *El-Nasr* Company for chemicals, Egypt. It was applied as a freshly prepared and given orally at a dose of 80 mg/ kg body weight as previously recommended by [**Kohn *et al.* (2002)**].

2. Garlic oil (GO):

Garlic oil was purchased from *El-Captain* Company (Cap. Pharm., Egypt. Licence of Ministry of Health no.2849/2002. It was given orally at a dose of 5 ml / kg body weight according to **Chen *et al.* (2003).**

III-Animal groups:

Experimental animals were divided into four main groups, six rats for each as follow:

1- Control rats group:

Rats were received normal laboratory diet without any treatment.

2- Garlic oil treated rats group:

Rats were supplied with normal laboratory diet and received orally garlic oil at a dose of 5 ml/ kg body weight for 3 months.

3- Sodium nitrite treated rats group:

Rats were supplied with normal laboratory diet and received orally sodium nitrite at dose of 80 mg/ kg body weight for 3 months.

4- Sodium nitrite + garlic oil treated rats group:

Rats were given orally garlic oil and simultaneously administered with sodium nitrite at the same mentioned doses besides the same normal laboratory diet for the same period (3 months).

At the end of the experimental period, overnight fasted animals were sacrificed and blood samples were collected in clean centrifuge tubes. Serum was separated from coagulant blood by centrifugation at 860 g for 20 min, and then quickly frozen at -20°C for biochemical analysis. Small pieces of liver and kidney tissues were separated as rapidly as possible, weighed and homogenized in ice cold water and frozen at -20°C for subsequent measurements.

IV - Biochemical analysis:

Serum glucose level was estimated according to the method of **[Trinder (1969)]** using Biomerieux reagent kits. Liver glycogen content was estimated according to the method described by **[Van-Handle (1965)]**. Serum alanine aminotransfrase (ALT) and aspartate aminotransfrease (AST) enzymes activity was determined according to the method described by **[Reitman & Frankel (1957)]**, whereas, alkaline phoasphatase (ALP) activity was estimated by the method of **[Belfield & Goldberg (1971)]**. Total protein and bilirubin concentrations were estimated using Diamond Diagnostic Kits as described by **[Henry (1964) and Jendrassik & Graf (1938)]**, respectively. Urea and creatinine levels were measured using Diamond diagnostic Kits based on the methods of **[Palton & Crouch (1977) and Henry (1974)]**, respectively. The product of lipid peroxidation, thiobarbituric acid reactive substances (TBARS), was determined as described by **[Esteribauer & Cheesman (1990)]**. Glutathione (GSH) content was estimated by the method of **[Prins & Loose (1969)]**, while the activity of catalase was assayed according to the method of **[Aebi (1983)]**.

V- Statistical analysis:

The present data were analyzed using **SPSS** program (Statical Pucteage for Social Science) version 11. For comparison of different experimental rat groups, one way analysis of variance (ANOVA) was used followed by Aonst Tukey test as described by **[Snedecor & Cochran (1982)]**. The results were expressed as means $\pm$ SE and % of change. Values of $P< 0.05$ were considered statistically significant.

RESULTS

In the present study, the observed data recorded that, the oral administration of garlic oil alone did not induce pronounced changes in the most biochemical, oxidative and antioxidant parameters.

Data represented in Table 1 showed a significant increase in serum glucose, bilirubin, urea and creatinine levels as well as the enzymes (AST, ALT, ALP) activity, while total protein content observed a significant decrease in $NaNO_2$-intoxicated rats compared to control rats. However, the administration of garlic oil as a protective agent can ameliorate the disturbances induced by sodium nitrite as expressed by a significant increase of serum total protein content in addition to a significant decrease of serum glucose, bilirubin, urea and creatinine levels as well as the investigated enzymes activity if compared to $NaNO_2$- intoxicated rats.

As shown in Table 2, a statistically significant decrease of hepatic glycogen and total protein contents as well as the activity of the enzymes; ALT and AST of $NaNO_2$-intoxicated rats was observed. Similar significant decrease was noticed in the levels of renal urea, creatinine and total protein of $NaNO_2$-intoxicated rats. While hepatic ALP activity was significantly increased if compared to control rats. On the other hand, the administration of garlic oil showed a marked improvement in both hepatic and renal function parameters.

Moreover, the present results indicated that TBARS concentration was significantly increased, while GSH content as well as catalase activity were significantly decreased in both liver and kidney of $NaNO_2$-intoxicated rats (Table 3) comparing to control rats. Meanwhile, the presence of garlic oil with $NaNO_2$ caused reduction in TBARS concentration and elevation in the level of GSH as well as the activity of catalase if compared with $NaNO_2$- intoxicated rats.

Concerning ANOVA analysis of the investigated parameters it was revealed that the general effect between groups was significant throughout the experiment.

Table (1): Serum biochemical parameters in control and different treated groups.

Parameters	Animal Groups				ANOVA	
	Control	Garlic Oil (GO)	$NaNO_2$	$NaNO_2$ +GO	F	P
Glucose (mg/dl)	102.4±1.5	93.5±2.5[a] -8.7*	207.3±1.5[a] +102.3*	105.9±1.1[b] +3.4*&-48.9**	934.1	P<0.05 S
AST (U/ml)	88.8±1.6	88.6±1.5 -0.2*	138.2±2.1[a] +55.6*	115.1±0.8[a&b] +29.6*&-16.7**	224.8	P<0.05 S
ALT (U/ml)	22+0.84	20.8+0.64 -5.5*	32.2+1.1[a] +46.4*	26+0.63[a&b] +18.2*&-19.3**	38.4	P<0.05 S
ALP (K.Arm.U/100 ml)	21.5+0.8	19.9+0.8 -7.4*	27.8+0.7[a] +29.3*	22.5+0.2[b] +4.7*&-19.1**	70.8	P<0.05 S
Bilirubin (mg/dl)	0.29+0.006	0.28+0.002 -3.4*	0.47+0.005[a] +58*	0.34+0.005[a&b] +15.4* & -27**	425.4	P<0.05 S
Total protein (g/dl)	6.8+0.17	7.1+0.45 +4.4*	4.9+0.16[a] -27.9*	6.7+0.19[b] -1.5*&+36.7**	3.5	P<0.05 S
Urea (mg/dl)	37.9+0.45	36.5+0.52 -3.7*	49.8+0.93[a] +31.4*	38.1+0.47[b] +0.53* &-23.5**	97.4	P<0.05 S
Creatinine (mg/dl)	1.52±0.11	1.48±0.08 -2.6*	1.98±0.14[a] +35.5*	1.22±0.04[b] -20* & -38.4**	12.0	P<0.05 S

Results are presented as means ± SE (n=5) and % of change.

a: Significantly different compared to control group.

b: Significantly different compared to $NaNO_2$-intoxicated rats group

*: % of change compared with control group.

**: % of change compared with $NaNO_2$-intoxicated rats group.

S: Significant change at P<0.05.

ANOVA among the fourth groups: P>0.05 non-significant and P<0.05 significant: F = F Tabulated P = Probability

Table (2): Hepatic and renal biochemical parameters in control and different treated groups.

Parameters		Animal Groups				ANOVA	
		Control	Garlic Oil (GO)	$NaNO_2$	$NaNO_2$ +GO	F	P
Liver	Glycogen (mg/100g)	36.7±1.6	42.4±1.5[a] +13.6*	12±0.5[a] -67.9*	19±1.5[a&b] -49.2* & +58.3**	115.4	P<0.05 S
	AST (U/mg)	11.4±0.20	11.7±0.10 +2.6*	10.1±0.21[a] -11.4*	11.6±0.24[b] +1.8* & +14.9**	98.2	P<0.05 S
	ALT (U/mg)	2.7±0.09	2.9±0.13 +7.4*	2.1±0.05[a] -22.2*	2.6±0.05[b] -3.7* &+23.8**	110.9	P<0.05 S
	ALP (K.Arm.U/g)	170.4±2.1	168.2±1.0 -1.3*	271.2±2.1[a] +59.2*	233.4±1.7[a&b] +37*& -13.9**	1633.1	P<0.05 S
	Total protein (g/100g)	34.5±0.8	33.4±0.6 -3.2*	31.2±0.5[a] -9.6*	29.6±0.6[a] -14.2* & -5.1**	13.1	P<0.05 S
Kidney	Urea (mg/100g)	34.3±14.4	35.5±12.6 +3.5*	24.5±13.9[a] -28.6*	27.1±13.3[a&b] -21* & +10.7**	1770.5	P<0.05 S
	Creatinine (mg/g)	1.02± 0.01	1.04±0.02 +2.0*	0.95±0.02[a] -6.9*	1.13±0.01[a&b] +10.8* & 18.9**	25.1	P<0.05 S
	Total protein (g/100g)	42.4±1.5	42.6±2.2 +0.5*	21.1±1.4[a] -50.2*	39±1.2[b] -8.0* & +84.8**	40.8	P<0.05 S

Results are presented as means ± SE (n=5) and % of change.

a: Significantly different compared to control group.

b: Significantly different compared to $NaNO_2$-intoxicated rats group

*: % of change compared with control group.

**: % of change compared with $NaNO_2$-intoxicated rats group.

S: Significant change at P<0.05.

ANOVA among the fourth groups: P>0.05 non-significant and P<0.05 significant: F = F Tabulated P = Probability

Table (3): Hepatic and renal oxidative stress and antioxidant parameters in control and different treated groups.

Parameters		Animal Groups				ANOVA	
		Control	Garlic Oil (GO)	$NaNO_2$	$NaNO_2$ +GO	F	P
Liver	TBARS (nmol/g)	102.5±1.3	70.4±2.2[a] -31.3*	253.6±2.9[a] +147.4*	148.4±1.3[a&b] +44.8*&- 41.5**	1580.5	P<0.05 S
	GSH (mg/g)	0.65±0.02	0.69±0.01 +6.2*	0.52±0.01[a] -20*	0.66±0.01[b] +1.5* & +27**	35.8	P<0.05 S
	CAT (KU/mg)	0.17±0.01	0.19±0.01 +11.8*	0.05±0.01[a] -70.6*	0.08±0.01[a&b] -52.9* & +60**	66.3	P<0.05 S
Kidney	TBARS (nmol/g)	176.6±1.4	139.7±2[a] -20.9*	234±7.6[a] +32.5*	203.1±0.6[a&b] +15* & -13.2**	99.8	P<0.05 S
	GSH (mg/g)	0.76±0.01	0.77±0.02 +1.3*	0.63±0.02[a] -17.1*	0.75±0.01[b] -1.3* & +19**	20.5	P<0.05 S
	CAT (KU/mg)	0.14±0.01	0.15±0.01 +7*	0.06±0.01[a] -57*	0.10±0.01[a&b] -28.6*&+66.7**	23.7	P<0.05 S

Results are presented as means ± SE (n=5) and % of change.

a: Significantly different compared to control group.

b: Significantly different compared to $NaNO_2$-intoxicated rats group

.*: % of change compared with control group.

**: % of change compared with $NaNO_2$-intoxicated rats group.

S: Significant change at P<0.05.

ANOVA among the fourth groups: P>0.05 non-significant and P<0.05 significant: F = F Tabulated P = Probability

DISCUSSION

The addition of $NaNO_2$ and other food additives to our foods, may react with amines of the foods in stomach and produces nitrosamines, or produces large numbers of free radicals. Such products may increase lipid peroxidation which can cause many harmful hazards to the different body organs especially liver and kidney **[Choi *et al.*, (2002)]**. On the other hand, the dietary natural antioxidant may prevent or

reduce such hazards. These protecting actions can be explained by the capacity of these antioxidants to scavenge free radicals, which are responsible for the oxidative damage of lipid, protein and nucleic acid **[Aruoma (1998) and Mathew & Biju (2008)].** So the interest of the present study has been focused on the role of garlic oil as a protective agent against the hazard effects of sodium nitrite in male rats.

The present study showed a significant increase in serum glucose concentration and decrease in liver glycogen content of sodium nitrite treated group. These findings may be due to the nitrite stimulation of the rate of gluconeogenesis **[Wiechetek *et al.*, (1992)]**. Increased blood glucose level may be resulted from glucose shifting from tissue to blood or to an impairment of glucose mobilization. **[Helal & Abdel Rahman (2005); El-Nagar (2006) and Shalaby *et al.*, (2006)].**

Furthermore, the disturbance in metabolic processes leading to hyperglycemia due to exposure to oxidative stress which may be resulted from nitroso-compounds that may alter the antioxidant system **[Anil *et al.*, (2005)]**. However, the amelioration in serum glucose and liver glycogen after administration with garlic oil as a protective agent was recorded in this study. The hypoglycemic effect of garlic oil may be due to the ability of its organosulfur compounds in the enhancement of insulin secretion **[Liu *et al.*, (2005) and Eidi *et al.*, (2006)]**. In addition, the present study showed a reduction in total protein content in $NaNO_2$ - intoxicated rats. These results indicated the harmful effect of nitrite on the biosynthesis of protein **[Eremin & Yocharina (1981)]**. This finding may be attributed to the stimulatory effect of the nitrite on the thyroid and adrenal glands that leads to block of protein synthesis while fast breakdown occurs. This leads to an increase of free amino acids and to a decrease of protein turnover **[Yanni *et al.*, (1991)]**. Also, this result may be attributed also to the NO release which affects on the protein synthesis **[Kolpakov *et al.*, (1995)]**. On the other hand, the co-administration of garlic oil with $NaNO_2$ ameliorates the observed change in total protein content. This finding may be due to the increasing in the immunoglobulin level and total globulin concentration **[Shalaby *et al.*, (2006)]**.

The present data suggested an increase in bilirubin concentration as well as AST, ALT and ALP enzymes activities in serum of $NaNO_2$ treated rats group. These results could be attributed to some toxicological effects of nitrosocompounds formed in the acidic environment of the rat stomach and causing severe hepatic necrosis, which may lead to increase in the activity of these enzymes **[El-Naggar (2000)]**. Meanwhile, a

beneficial effect was appeared by garlic oil treatment as indicated by the inhibition of serum AST, ALT and ALP enzymes activity and bilirubin concentration. These results may be attributed to the role of garlic oil in stabilized cell membrane and protect the liver against deleterious agents and free radical-mediated toxic damages to the liver cells [**Shalaby *et al.*, (2006)**].

Also, the present work showed an elevation in serum urea and creatinine concentrations and reduction in renal urea and creatinine concentrations of $NaNO_2$ treated rats. These results may be due to induced impairment of kidney functions [**Ahmed & Mannaa (2000) and Al-Ayed (2000)**]. The adverse effects of nitrite on kidney might be due to nitric oxide formations which cause kidney dysfunction [**Ismail *et al.*, (2003)**] or could be attributed to the change in the threshold of tubular reabsorption, renal blood flow and glomerular filtration rate [**Zurovsky & Haber (1995)**]. On the other hand, garlic oil treatment has a good protective effect on kidney functions as evidenced by decreasing serum urea and creatinine concentration and increasing their concentration in the kidney tissues. It seems likely that garlic can protect kidney tissue against oxidative damage result in an improvement in kidney functions. Also, the marked improvement in the examined parameters of the kidney functions may be attributed to the antioxidant properties of garlic that made it possible to scavenge free radicals, reducing the level of nitric oxide and consequently decrease the level of lipid peroxidation [**Pari & Murugavel (2007)**].

Furthermore, an increase in lipid peroxidation resulted in both kidney and liver in $NaNO_2$-intoxicated rats could be attributed to the oxidative cytotoxicity of nitrite [**Patsoukis & Georgiou (2007)**]. However, the treatment with garlic was effective in preventing the occurred oxidative stress as achieved by decreasing lipid peroxidation. The marked reduction in lipid peroxidation may be due to direct effect of the garlic constituents as free radical scavengers [**Pedraza-Chaverrí *et al.*, (2000) and Anwar & Meki (2003)**], and to its antioxidant effects as well as the effect of diallyl disulphide (DADS) and diallyl trisulphide (DATS) which are present in garlic oil [**Wu *et al.*, (2001); Sener *et al.*, (2003) and Pari *et al.*, (2007)**].

Concerning the antioxidant status, the present study showed decreasing in glutathione content and catalase enzyme activity in both liver and kidney of sodium nitrite treated group. These results may be attributed to the observed increase in lipid peroxidation which resulted in

the oxidation reactions [**Shahjahan *et al.*, (2005)**]. However, the administration of garlic oil can improve the antioxidant defense mechanism as manifested by increasing both glutathione and catalase levels. This finding may be attributed to the antioxidant effects of diallyl disulfide (DADS) and diallyl trisulfide (DATS) [**Harunobu (2006)**] and their ability in modulating the oxidative stress, enhancing the antioxidant and detoxifying enzyme system [**Wu *et al.*, (2001); Saravanan & Prakash (2004) and Popova & Popove (2005)**].

In conclusion, from the results achieved it can be concluded that the administration of garlic oil has a beneficial role in overcoming the occurred adverse effects of chronic ingestion of sodium nitrite probably through its excellent antioxidant properties and highly nutritional values.

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دور زيت الثوم في ضبط التغيرات البيوكميائية والإجهاد التأكسدى المستحدث بنيتريت الصوديوم في ذكور الجرذان البيضاء

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يتناول الكثير من الناس بعض الأطعمة التى تحتوى على مواد حافظه مثل نيتريت الصوديوم دون تفكير فى خطورة هذه المواد لأن نيتريت الصوديوم قد يتفاعل مع المركبات الأمينية الموجودة فى المعدة لينتج مركبات النيتروزأمين أو ينتج عدد كبير من الشوارد الحرة التى قد تزيد من عملية أكسدة الدهون مسببة العديد من الأمراض.

ولقد أصبح الإعتماد على المصادر الطبيعية المضادة للأكسدة محل اهتمام الدراسات الحديثه الأن وبناء على ذلك بنيت فكرة هذه الدراسة والتي تعتبرمحاولة لتقييم التأثيرالسلبى لنيتريت الصوديوم على بعض المعايير البيوكميائية ومضادات الأكسدة فى ذكور الجرذان، بالإضافة إلى توضيح الدور المحتمل لزيت الثوم للوقاية من مثل هذه الاثار.

وقد أسفرت النتائج على أن تناول الجرذان لنيتريت الصوديوم (٨٠ مجم لكل كجم من وزن الجسم) لمدة ثلاثة شهور على التوالى قد تسبب فى العديد من التغييرات البيوكيمائية التي تمثلت فى إرتفاع مستوى جلوكوز مصل الدم مصحوبا بانخفاض محتوى جليكوجين الكبد. بالإضافة لخلل واضح فى وظائف كل من الكبد والكلى نتيجة لما أثبتته النتائج من زيادة نشاط بعض الإنزيمات مثل ALP, ALT, AST وإرتفاع مستوى البيليروبين واليوريا والكرياتينين فى مصل الدم مع انخفاض فى مستوى البروتين الكلى فى مصل الدم والكبد والكلى. هذا وبالإضافة لما سبق فقد أكدت النتائج أيضا وجود ضغط تأكسدى وخلل فى الجهاز المضاد للأكسدة نتيجة لوجود ارتفاع فى نواتج التأكسد الفوقى للدهون فى الكبد والكلى وانخفاض مضادات الأكسدة الممثلة فى CAT و GSH .

وعلى الجانب الأخر لوحظ أن تعاطي الجرذان لزيت الثوم (5 مللي لكل كجم من وزن الجسم) بجانب نيتريت الصوديوم قد أسفر عن تحسن ملحوظ فى معظم القياسات السابق ذكرها. ولذلك توصى الدراسة بالحد من تناول الإضافات الغذائية ذات التأثيرات الضارة على أعضاء الجسم الحيوية. كما توصى بكثرة تناول المواد الغذائية الطبيعية التى لها قيمة غذائية عالية لتقليل التأثيرات السيئة لمثل هذه الإضافات الغذائية.