The Potential Effects of Propolis against Monosodium Glutamate (MSG) Toxic Effects on Some Biochemical Aspects of Kidney

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Abstract: Monosodium glutamate (MSG) is the most commonly used flavoring agent all over the world. The current study was designed to investigate the protective and therapeutic effect of propolis against monosodium glutamate induced toxic effects on some biological aspects of kidney rats. Accordingly, a total number of fifty male albino rats were divided into five groups. The first group served as control, where the second group was administered propolis at an oral daily dose of 200 mg/kg/b. w. for eight weeks. The third group received MSG 1 g/kg /b. w. for eight weeks. The fourth group (protective group) was first administered propolis alone for 4 weeks, and secondly received MSG in association with propolis for 4 weeks. The fifth group (therapeutic group) was first given MSG alone for 4 weeks and was secondly administered propolis in association with MSG for 4 weeks. At the end of four and eight weeks, blood and kidney tissues were collected to study biochemical parameters and electrophoresis study. MSG administration exerted significant elevation of the mean body weight, absolute and relative kidney weights, serum urea, creatinine, sodium (Na^+), cholesterol, TG, HDL, LDL, VLDL and MDA activities and decrease in potassium (K^+), total protein, albumin and GSH levels. In the electrophoresis study, there was an increase in fraction 1 and 2 and a decrease in fractions 3, 4 and 5 in MSG group, while in the protective group, propolis extract showed significant improvement in the previous fractions. It may be concluded that the results confirm the toxic effect of MSG and the protective effect of propolis, especially when administrated as a protective substance than therapeutic.
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1. Introduction

Monosodium glutamate **(MSG)** is the sodium salt of the non-essential amino acid glutamic acid, one of the most abundant amino acids found in nature. MSG is most commonly used as a flavoring agent all over the world. When MSG is added to food, it provides a flavoring function similar to naturally occurring free glutamate which differ from the four classic tastes of sweet, sour, salt and bitter ***(Egbuonu et al., 2010)***. Despite its taste stimulation and improved appetite enhancement, reports indicate that monosodium glutamate is toxic to human and experimental animals ***(Egbuonu et al., 2010).*** The major adverse reaction of MSG might be either immunological reactions such as urticaria, angioedema, cutaneous allergic reaction and asthma, or non-immunological reaction, which include a variety of symptoms such as headache, myalgia, backache, neck pain, tingling and lushing chest heaviness ***(Freeman, 2006).***

Propolis is a resinous hive product collected by honeybees from many plant sources ***(Tan-No et al., 2006).*** Historically it has been used for various purposes, especially as a medicine ***(Ghisalberti, 1979).*** Flavonoids and phenolics are the major complementary compounds of propolis ***(Ivanovska et al., 1995).*** Flavonoids are thought to be responsible for many of its biological and pharmacological activities including anticancer ***(Padmavathi et al., 2006)***, anti-inflammatory ***(Paulino et al., 2008)***, and antioxidant effects ***(Nieva Moreno et al., 2000).*** The pharmacological effects of bee propolis include reduction of the blood pressure, protection of the liver tissue, protection against stomach ulcer formation and maintenance of serum glucose ***(Kedzia et al., 2007).*** Hepatoprotective, renal protective and therapeutic effects of propolis ethanol extract were also reported ***(Liu et al. 2005)***.

Thus, the present study was designed to examine the possible protective and curative effect of propolis against MSG-induced renal toxicity and oxidative stress in weanling rats.

2. Material and Methods

Fifty weanling male albino rats **(*Rattus norvegicus*)** (75-95 g) were employed in the present study. They were housed in a well ventilated animal house vivarum of Zoology Department, Women collage, Ain Shams University and kept under the same environmental conditions. They were fed to appetite on standard laboratory animal diet and fresh tap water was at all times.

The rats were randomly assigned into five equal groups each containing 10 male rats. The first group ***(Control group)*** was left as normal control. The second group ***(Propolis treated group)*** orally received a daily dose of propolis (200 mg/kg b. w.) for four and eight weeks ***(Bhadauria and Nirala, 2009)***. The third group ***(MSG group)*** was orally administered with 1g/kg b. w. ***(Gomathi and Malarvili, 2009)*** for 4 and 8 weeks. The fourth group ***(Protective group)*** received oral dose of propolis daily for 4 weeks then orally administered propolis and MSG for another four weeks. The fifth group ***(Therapeutic group)*** was treated with oral dose of MSG daily for 4 weeks then orally MSG and propolis for another 4 weeks.

Monosodium glutamate and propolis were purchased from Sigma chemical company (USA).

Biochemical and kidney protein electrophoresis analyses have been assessed. At the end of each experimental period (4 & 8 weeks), blood samples were collected from decapitated animals. The contents of serum urea and creatinine were assayed colorimetrically using commercial kits (Randox Ltd., Co. UK) ***(Fawcett and Scott, 1960 and Seeling and Wust, 1969)***. Sodium (Na^+) and potassium (K^+) analysis were accomplished by emission flame photometry after suitable dilutions ***(Tietz, 1983 and Tietz, 1976)*** respectively. Serum total protein and albumin were assayed colorimetrically using commercial kits (Randox Ltd., Co. UK) ***(Henry et al., 1974 and Doumas et al., 1971)*** respectively**.** Serum total cholesterol ***(Seidel et al., 1983)***, triglycerides ***(Fossati and Prencipe, 1982)***, HDL-cholesterol ***(Stein, 1986)*** were estimated colorimetrically using commercial kits from Randox, Ltd., Co. (UK). LDL-cholesterol was calculated as per Assmann's equation ***(Assmann et al., 1984)***. VLDL-cholesterol was calculated as per Assmann's equation ***(Assman et al., 1984).***

After sacrifice, kidneys were excised at the end of each experimental period and washed with saline solution (0.9 % Na Cl). After washing, the kidneys were homogenized in ice-cold 0.25 M sucrose containing 1 mM diethylenetriamine penta-acetic acid (1:1 w/v). Each sample was then centrifuged for 20 min at 20.000 g. The supernatant was aspirated for measuring the content of reduced GSH ***(Tietze, 1969)*** and MDA ***(Botsoglou et al., 1994)*** by ELISA technique using commercial kits (IBL Gesellschsft, Hamburg, Germany).

Aqueous extracts were prepared from equal weights of kidney of rats of each group as described by ***Jay (1964).*** The method used for electrophoresis was that of ***Davis (1964)*** with ***Syn Gene, 4.01.02.***

Statistical Analysis:

All data were analyzed using the SPSS for windows software, version 10.0. Analysis of variance (ANOVA) which is an indication of the dispersion or difference between more than two means to the calculated standard deviation of this difference was assessed. ***(Tello and crewson, 2003)***.

3. Result:

1- Determination of body weight, kidney weight and relative kidney weight:

The mean body weight of control group rats and those given propolis and MSG increased gradually throughout the experimental period. Yet the percentage of increase in body weight of MSG rats amounted to 6.1 % at the end of experimentation. The data also indicate gradual increase in the mean kidney weights of control and propolis groups throughout the experimental period with no significant differences in relative kidney weight. While, a partial improvement was recorded in mean body weight, kidney weight and relative kidney weight during protective group (Table 1).

Table (1): The protective and therapeutic role of propolis on body weight, kidney weight and relative kidney weight (g) against MSG treated male albino rats

Parameters	Duration \ Group		Control group	Propolis group	MSG group	Protective group	Therapeutic group
Body weight	1st Day	Mean ± S. E. % of change	$86.15^{A}{}_{a}$±1.88	$84.25^{A}{}_{a}$± 1.45 -2.21	$83.74^{A}{}_{a}$±1.48 -2.80	$82.84^{A}{}_{a}$±0.88 -3.84	$83.71^{A}{}_{a}$±2.05 -2.83
	4th week	Mean ± S. E. % of change	$130.60^{A}{}_{b}$±2.73	$132.60^{A}{}_{b}$±6.47 1.53	$148.60^{B}{}_{b}$±3.74 13.78	$128.60^{A}{}_{b}$±5.51 -1.53	$151.80^{B}{}_{b}$±5.19 16.23
	8th week	Mean ± S. E. % of change	$167.20^{A}{}_{c}$±10.70	$162.40^{ACD}{}_{c}$±3.66 -2.87	$177.40^{B}{}_{c}$±3.41 6.10	$159.40^{C}{}_{c}$±5.16 -4.67	$166.00^{AD}{}_{c}$±14.90 -0.72
Kidney weight	4th week	Mean ± S. E. % of change	$0.884^{A}{}_{a}$±0.078	$0.918^{A}{}_{a}$±0.058 3.85	$0.920^{A}{}_{a}$±0.052 4.07	$0.974^{A}{}_{a}$±0.050 10.18	$1.044^{B}{}_{a}$±0.056 18.10
	8th week	Mean ± S. E. % of change	$1.060^{A}{}_{b}$±0.033	$1.004^{A}{}_{b}$±0.021 -5.28	$1.286^{B}{}_{b}$±0.057 21.32	$1.078^{A}{}_{b}$±0.094 1.70	$1.132^{C}{}_{b}$± 0.063 6.79
Relative kidney weight	4th week	Mean ± S. E. % of change	$0.643^{A}{}_{a}$±0.047	$0.690^{A}{}_{a}$±0.011 7.31	$0.619^{A}{}_{a}$±0.028 -3.73	$0.757^{B}{}_{a}$±0.028 17.73	$0.688^{A}{}_{a}$±0.015 6.99
	8th week	Mean ± S. E. % of change	$0.643^{A}{}_{a}$±0.043	$0.619^{A}{}_{a}$±0.004 -3.73	$0.725^{B}{}_{b}$±0.033 12.75	$0.676^{A}{}_{b}$±0.022 5.13	$0.682^{A}{}_{a}$±0.011 6.07

A, B, C, D The groups in the same row with different letters are statistically significant ($p < 0.05$).

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2- Kidney function tests:

Serum urea, creatinine, sodium (Na^+) and potassium (K^+) levels:

Data recorded for the serum urea, creatinine, Na^+ and K^+ are presented by table (2). Normal rats showed more or less constant levels during the course of the study. Moreover, no remarkable changes were reported in propolis rat group. On the other hand, in MSG group, a significant elevation was realized in urea, creatinine and Na^+ levels as compared with control group. In relation to the control rats a significant decrease in the serum K^+ level was reported in the same group.

A considerable time dependent improvement was observed in protected rats group. Furthermore, a highly significant elevation took place in the levels of urea, creatinine and sodium, but significant depression in potassium level in the therapeutic group (group receiving oral dose MSG daily for four weeks then administered oral dose of MSG and propolis for four weeks) during the 4 weeks. A partial decline was recorded through the second interval period of 8 weeks. But, partial recovery occurred in potassium (K^+) level (Table 2).

3- Protein profile testes:

Serum total protein (g/dl) and albumin (g/dl) levels:

On detecting the serum total protein and albumin level, the data are given in table (3). The control and propolis rats group designed more or less constant figures during the study period. In relation to the control rats a significant decrease in total protein level and in albumin level were reported in rats treated with MSG for 8 weeks. Furthermore, a slight decrease took place in serum total protein and albumin level in the protected rats group. Moreover, partial recovery occurred in the therapeutic rats group.

Table (2): The protective and therapeutic role of propolis on serum urea (mg/dl), creatinine (mg/dl), sodium (Na^+)(meq/L) and potassium (K^+)(meq/L) against MSG treated male albino rats.

Parameters	Duration \ Group		Control group	Propolis group	MSG group	Protective group	Therapeutic group
Urea	4th week	Mean ± S. E. % of change	$15.21^{A}{}_{a}\pm0.32$	$15.91^{A}{}_{a}\pm0.39$ 4.602	$30.25^{B}{}_{a}\pm0.16$ 98.882	$16.21^{A}{}_{a}\pm0.68$ 6.575	$29.35^{B}{}_{a}\pm0.64$ 92.965
	8th week	Mean ± S. E. % of change	$15.13^{A}{}_{a}\pm0.51$	$16.01^{A}{}_{a}\pm0.32$ 5.816	$38.66^{B}{}_{b}\pm0.83$ 155.519	$17.54^{A}{}_{a}\pm0.50$ 15.929	$25.12^{C}{}_{b}\pm0.81$ 66.028
Creatinine	4th week	Mean ± S. E. % of change	$0.32^{A}{}_{a}\pm0.10$	$0.31^{A}{}_{a}\pm0.10$ -3.125	$0.85^{B}{}_{a}\pm0.23$ 165.625	$0.33^{A}{}_{a}\pm0.56$ 3.125	$0.82^{B}{}_{a}\pm0.22$ 156.25
	8th week	Mean ± S. E. % of change	$0.35^{A}{}_{a}\pm0.09$	$0.33^{A}{}_{a}\pm0.12$ -5.714	$0.95^{B}{}_{b}\pm0.31$ 171.429	$0.41^{C}{}_{b}\pm0.18$ 17.143	$0.71^{D}{}_{b}\pm0.48$ 102.857
Sodium (Na^+)	4th week	Mean ± S. E. % of change	$133.82^{A}{}_{a}\pm0.56$	$131.70^{A}{}_{a}\pm0.32$ -1.584	$153.31^{B}{}_{a}\pm0.60$ 14.564	$134.56^{A}{}_{a}\pm0.57$ 0.553	$155.20^{B}{}_{a}\pm0.56$ 15.977
	8th week	Mean ± S. E. % of change	$132.70^{A}{}_{a}\pm0.31$	$132.41^{A}{}_{a}\pm0.35$ -0.219	$160.20^{B}{}_{b}\pm0.54$ 20.723	$139.32^{C}{}_{b}\pm0.53$ 4.989	$149.41^{D}{}_{b}\pm0.47$ 12.592
Potassium (K^+)	4th week	Mean ± S. E. % of change	$4.15^{A}{}_{a}\pm0.32$	$4.20^{A}{}_{a}\pm0.29$ 1.205	$2.46^{B}{}_{a}\pm0.90$ -40.723	$4.50^{A}{}_{a}\pm0.91$ 0.843	$2.61^{B}{}_{a}\pm1.0$ -37.108
	8th week	Mean ± S. E. % of change	$4.16^{A}{}_{a}\pm0.40$	$4.14^{A}{}_{a}\pm0.33$ -0.481	$2.03^{B}{}_{b}\pm0.14$ -51.202	$4.21^{A}{}_{a}\pm1.5$ 1.202	$2.93^{C}{}_{a}\pm1.2$ -29.567

A, B, C, D The groups in the same row with different letters are statistically significant ($p < 0.05$).

a, b, c The groups in the same column with different letters are statistically significant ($p < 0.05$).

Table (3): The protective and therapeutic role of propolis on serum total protein and albumin (g/dl) against MSG treated male albino rats.

Parameters	Duration \ Group		Control group	Propolis group	MSG group	Protective group	Therapeutic group
Total protein	4th week	Mean ± S. E. % of change	$6.21^{A}{}_{a}\pm0.13$	$6.19^{A}{}_{a}\pm0.10$ -0.322	$4.51^{B}{}_{a}\pm0.04$ -27.375	$6.21^{A}{}_{a}\pm0.06$ 0.000	$4.31^{B}{}_{a}\pm0.07$ -30.596
	8th week	Mean ± S. E. % of change	$6.24^{A}{}_{a}\pm0.12$	$6.27^{A}{}_{a}\pm0.11$ 0.481	$3.23^{B}{}_{b}\pm0.13$ -48.237	$5.83^{A}{}_{a}\pm0.07$ -6.571	$4.74^{C}{}_{a}\pm0.08$ -24.039
Albumin	4th week	Mean ± S. E. % of change	$186.31^{A}{}_{a}\pm2.41$	$187.92^{A}{}_{a}\pm2.56$ 0.864	$153.73^{B}{}_{a}\pm2.01$ -17.487	$185.21^{A}{}_{a}\pm2.39$ -0.590	$155.22^{B}{}_{a}\pm2.73$ -16.687
	8th week	Mean ± S. E. % of change	$188.70^{A}{}_{a}\pm2.94$	$190.42^{A}{}_{a}\pm2.39$ 0.912	$145.70^{B}{}_{b}\pm2.71$ -22.788	$182.41^{C}{}_{a}\pm2.66$ -3.333	$166.21^{D}{}_{b}\pm2.37$ -11.918

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4- Lipid profile testes:

Serum cholesterol, T G, HDL, LDL and VLDL levels:

From the inspection of the data presented in table (4), no remarkable changes were noted in the level of serum cholesterol, triglyceride (TG), HDL, LDL and VLDL of normal control and propolis rats group. In MSG rats group for 8 weeks, a significant percentage elevation in the level of cholesterol, TG level, in HDL level, LDL level and VLDL level was recorded as compared to control rats (Table 4). Moreover, a marked decrease occurred in lipid profile levels in the protected rats group (Rats receiving oral dose of propolis daily for four weeks then orally treated with propolis and MSG for four weeks).

In relation to MSG rats, it is clear from the data recorded that the best improvement occurred in the protected rats group at 8 weeks. A partial improvement was realized in lipid profile levels in the therapeutic rats group in serum cholesterol, TG, HDL, LDL and VLDL level that was time dependent (Table 4).

Table (4): The protective and therapeutic role of propolis on cholesterol, triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) (mg/dl) against MSG treated male albino rats.

Parameters	Duration \ Group		Control group	Propolis group	MSG group	Protective group	Therapeutic group
Cholesterol	4th week	Mean ± S. E.	55.21^{A}_{a}±0.51	54.31^{A}_{a}±0.20	80.25^{B}_{a}±0.41	53.21^{A}_{a}±0.33	79.21^{B}_{a}±0.35
		% of change		-1.630	45.354	-3.623	43.470
	8th week	Mean ± S. E.	56.32^{AC}_{a}±0.32	53.91^{A}_{a}±0.41	92.29^{B}_{b}±0.32	59.76^{C}_{a}±0.50	75.61^{D}_{a}±0.41
		% of change		-4.279	63.867	6.108	34.251
T. G	4th week	Mean ± S. E.	62.21^{A}_{a}±0.24	58.21^{A}_{a}±0.30	126.43^{B}_{a}±0.90	59.10^{A}_{a}±0.65	123.40^{B}_{a}±0.50
		% of change		-6.430	103.231	-4.999	98.360
	8th week	Mean ± S. E.	60.11^{A}_{a}±0.12	59.13^{A}_{a}±0.22	143.65^{B}_{b}±0.83	65.81^{C}_{b}±0.81	109.45^{D}_{b}±0.81
		% of change		-1.630	138.979	9.483	82.083
HDL	4th week	Mean ± S. E.	15.40^{A}_{a}±0.23	16.24^{A}_{a}±0.21	24.00^{B}_{a}±0.39	15.98^{A}_{a}±0.42	24.23^{B}_{a}±0.34
		% of change		5.455	55.844	3.766	57.338
	8th week	Mean ± S. E.	16.40^{A}_{a}±0.35	17.40^{A}_{a}±0.39	25.58^{B}_{a}±0.23	18.42^{A}_{a}±0.37	22.12^{B}_{a}±0.30
		% of change		6.098	55.976	12.317	34.878
LDL	4th week	Mean ± S. E.	45.85^{A}_{a}±0.32	45.92^{A}_{a}±0.32	59.76^{B}_{a}±0.35	44.59^{A}_{a}±0.40	59.38^{B}_{a}±0.56
		% of change		-3.434	13.117	-7.161	10.705
	8th week	Mean ± S. E.	47.59^{AC}_{a}±0.41	45.56^{A}_{a}±0.39	68.68^{B}_{b}±0.38	50.28^{C}_{b}±0.50	55.97^{D}_{b}±0.49
		% of change		-11.541	36.129	1.004	17.609
VLDL	4th week	Mean ± S. E.	12.44^{A}_{a}±0.58	11.64^{A}_{a}±0.54	25.29^{B}_{a}±0.51	11.82^{A}_{a}±0.58	24.68^{B}_{a}±0.50
		% of change		-6.431	103.296	-4.984	98.392
	8th week	Mean ± S. E.	12.02^{A}_{a}±0.54	11.83^{A}_{a}±0.49	28.73^{B}_{b}±0.58	13.16^{A}_{a}±0.54	20.86^{C}_{b}±0.53
		% of change		-1.581	139.018	9.484	73.544

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a, b, The groups in the same column with different letters are statistically significant ($p < 0.05$).

5- Kidney Tissue (Oxidative stress parameters):

a- Tissue Glutathione (GSH) (µg/g protein) levels:

No remarkable changes were reported after rats were treated with 200 mg/kg b. w. propolis through the experimental duration (Table 5). In MSG rats group, a significant depletion in the content of tissue GSH was recorded. As mentioned in the data of treated rats (protective group) after 8 weeks, GSH levels were nearly similar to that in control group (Table 5). After treatment with MSG and propolis (therapeutic group) a significant decrease in the tissue GSH content occurred after 4 weeks. This level gradually declined after treatment with MSG with propolis, for 8 weeks as compared with control group (Table 5).

b- Tissue lipid peroxidation malondialdhyde (MDA) (mM/100g):

No changes were verified after the administration of propolis (200 mg/kg b. w.) for 4 and 8 weeks (Table 5). On the other hand, in MSG rats group a significant elevation was realized in tissue MDA content as compared. These were later highly significantly increased with lapse of time at the last interval (8 weeks) (Table 5). Furthermore, protection was shown in the MDA content in protective rats group (Table 5).

6- Kidney protein electrophoresis:

Electrophoretic experimental pattern of kidney extract showed five protein fractions. Effect of groups on the protein fractions are the shown in table (6). There was no significant change in the five protein fractions in the group treated with propolis as compared with control group for 8 weeks accept fraction 1 (Table 6 and Fig. 1). In contrast, treatment with MSG for 8 weeks showed reduction or elevation in the factions of the different kidney proteins as shown in table (6) and figure (1). There was an increase in fractions 1 and 2 and a decrease in fractions 3, 4 and 5 in MSG group. In the protective group, the data in table (6) and figure (1) indicated that administration of propolis for four weeks followed by propolis and MSG for an extra 4 weeks

and sacrificed after 8 weeks, managed to protect all protein fractions. On the contrary, in the therapeutic group treated with MSG for 4 weeks followed by administration of MSG and propolis for 4 weeks and sacrificed after 8 weeks, fractions 1 and 2 showed increase, while there was a decrease in fractions 3, 4 and 5 as compared with control group (Table 6 and Fig. 1).

Table (5): The protective and therapeutic role of propolis on glutathione (GSH) (µg/g protein) and malondialdhyde (MDA) (mM/100g) against MSG treated male albino rats.

Parameters	Duration / Group		Control group	Propolis group	MSG group	Protective group	Therapeutic group
GSH	4th week	Mean ± S. E. % of change	$20.23^{A}{}_{a}\pm0.82$	$19.21^{A}{}_{a}\pm0.75$ -5.042	$12.51^{B}{}_{a}\pm0.53$ -38.161	$19.82^{A}{}_{a}\pm0.56$ -2.027	$12.20^{B}{}_{a}\pm0.71$ -38.694
	8th week	Mean ± S. E. % of change	$18.67^{A}{}_{a}\pm0.71$	$18.50^{A}{}_{a}\pm0.81$ -0.911	$8.10^{B}{}_{b}\pm0.60$ -56.615	$18.61^{A}{}_{a}\pm0.47$ -0.312	$14.84^{C}{}_{b}\pm0.54$ -20.514
MDA	4th week	Mean ± S. E. % of change	$0.38^{A}{}_{a}\pm0.12$	$0.40^{A}{}_{a}\pm0.13$ 5.263	$0.69^{B}{}_{a}\pm0.22$ 81.579	$0.36^{A}{}_{a}\pm0.20$ -5.263	$0.72^{B}{}_{a}\pm0.26$ 89.474
	8th week	Mean ± S. E. % of change	$0.40^{A}{}_{a}\pm 0.14$	$0.41^{A}{}_{a}\pm0.15$ 2.500	$1.46^{B}{}_{b}\pm0.25$ 265.000	$0.47^{C}{}_{b}\pm0.21$ 17.500	$0.66^{D}{}_{b}\pm0.31$ 65.000

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Table (6): The protective and therapeutic role of propolis on protein fractions of kidney extract (g/100g protein) against MSG treated male albino rats.

Fraction / Groups		Control group	Propolis group	MSG group	Protective group	Therapeutic group
Fraction 1	% Raw vol.	5.777	7.172	9.842	6.071	10.234
Fraction 2	% Raw vol.	25.506	23.999	36.677	26.207	32.443
Fraction 3	% Raw vol.	21.202	19.663	14.449	18.830	14.896
Fraction 4	% Raw vol.	34.871	36.063	30.774	34.948	31.866
Fraction 5	% Raw vol.	12.643	13.102	8.259	13.945	10.561

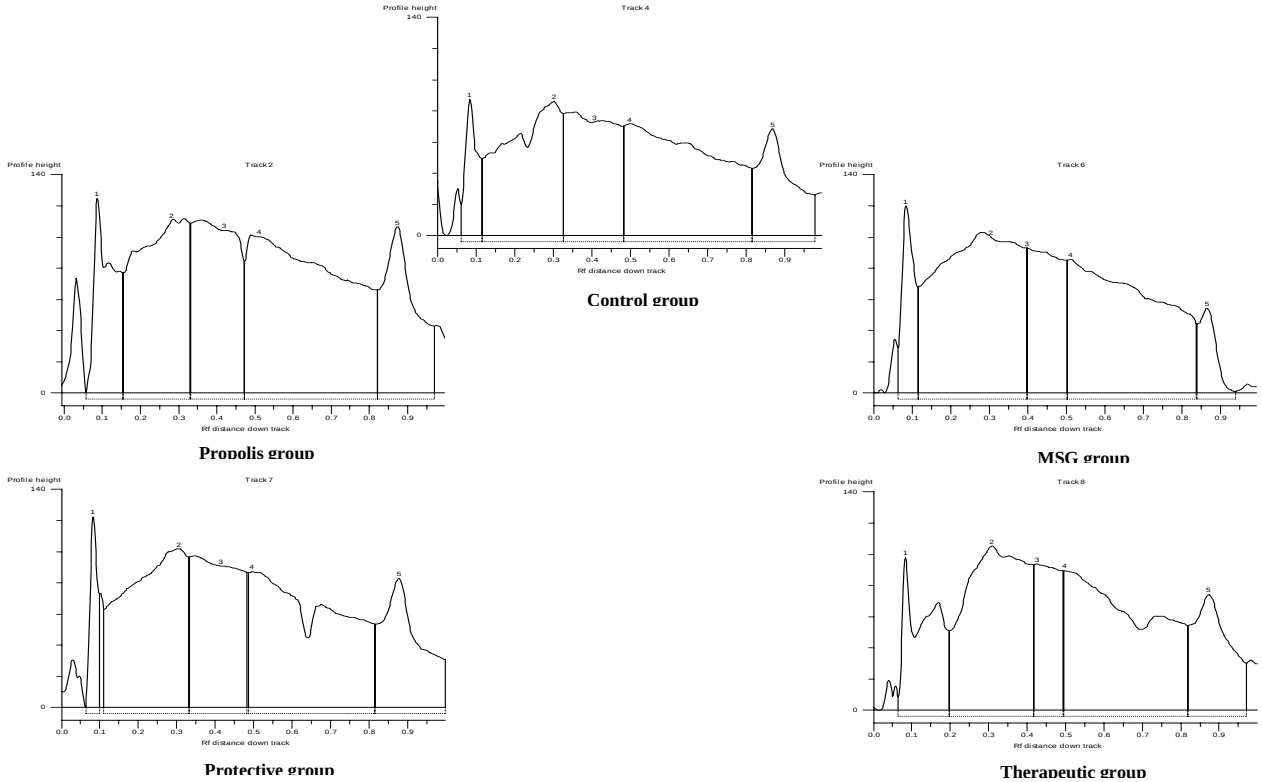

Figure (1): The protective and therapeutic role of propolis on the fractions of protein of kidney extract (g/100g protein) against MSG treated male albino rats.

4. Discussion:

Monosodium glutamate (MSG) is considered one of the most commonly used food enhancer in many types of food. MSG treatment provokes hormonal alterations and specific intestinal changes in smooth muscle reactivity to agonists. The administration of MSG in high concentrations or for long periods of time may cause tissue damage and mediate inflammation. In addition, it triggers the production of reactive oxygen species (ROS) coupled with impaired oxidant/antioxidant balance leading to a state of oxidative stress *(Lei et al., 2005).* Oxidative stress and decreased antioxidative capacity participates in the progression and complications of renal diseases such as hyperlipoproteinemia or cardiovascular diseases *(Gazdikova et al., 2000).*

Propolis or "bee-glue" contains a number of natural active constituents that have been shown to exert a variety of medical properties, such as anti-microbial activity *(Koo et al., 2000)*, protective effect against radiation-induced damage *(El- Ghazaly and Khayyal, 1995)*, anti-mutagenic effect *(Varanda et al., 1999),* anti-hyperalgesic action *(De Campos et al., 1998)* and anti-inflammatory activity *(Ozturk et al., 2000)*. Most of these effects have been related to the anti-oxidant and free radical scavenging properties of propolis *(Basnet et al., 1997).*

The present study showed that, there was significant increase in the final total body weight, kidney weight and relative kidney weight markedly noticed in group of rats treated with MSG. This increase may be due to increased food intake caused by the administration of MSG. Similar results have been reported by *Abass and Abd El-Haleem (2011).*

Earlier report by *Kawakita et al. (2005)* explained that the potential explanation for MSG-obesity link lies in the alteration of regulatory mechanism that affect fat metabolism. It was also found that MSG causes obesity in lab rats by down regulating hypothalamic appetite suppression and, thus, increasing the amount of food consumed *(Hermanussen et al., 2006).* In addition, MSG intake could induce an increase in energy intake *(Bergen et al, 1998)* which could lead to obesity *(Mozes et al., 2004).* Also, *Shibata et al. (1995)* recorded an increase in kidney weights in both sexes of rats given MSG that was considered to be due to Na^+ intake in the regimen.

In the current study, the protective and therapeutic group showed partial decrease in total body weight as compared to the control group. Similarly, both absolute and relative kidney weights manifested partial decrease in protective group while there was an increase in the therapeutic one. Similar results were demonstrated by *Abo-Salem et al. (2009)* who revealed significant amelioration in both body and kidney weights in a dose-dependent manner. Recently, *Garoui et al. (2011)* in their studies on the dietary administration of propolis to cobalt-treated animals showed ameliorated food consumption of lactating rats and induced partial recovery of body and kidney weights of their pups.

Kidney is an organ of the excretory system in the human and high animal bodies. The kidney function can be measured by urea and creatinine clearance.

In the present study, administration of MSG resulted in impairment of some renal biomarkers reflected by the significant increase in urea, creatinine and sodium and decrease in potassium serum levels. These results are in agreement with *Vinodini et al. (2010)* and *Abass and Abd El-Haleem (2011)* who showed an increase in BUN and creatinine that proved that the damages caused by MSG even compromised the kidney function.

Thomas et al. (2009) attributed such increase to increase intake of amino acid, glutamate in the form of monosodium glutamate It has been suggested that an increase in blood urea nitrogen may reflect an accelerated rate of protein catabolism rather than decrease urinary excretion of urea.

Furthermore, the nonphysiologic urea concentrations were associated with increased levels of reactive oxygen species and the oxidative stress marker 8-oxoguanine in cultured cells, probably due to urea potential to increase carbamylation as well as carbonylation *(Zhang et al., 2004).*

Serum sodium ion level was higher in the MSG rats group. The circulating MSG was dissociated in sodium (Na^+) and L-glutamate and crosses the mesothelial peritoneal cells and arrives at the bloodstream *(Walker and Lupien, 2000).*

Kang et al. (2002) reported that hypernatremia is rare but does occur when there is loss of body fluids containing less sodium than plasma along with water intake restriction or if there is excessive sodium intake with limited liquid intake.

On the other hand, serum potassium level was decreased in MSG group, and it might be due to the following reasons: Potassium ions shift between muscle and extracellular fluid, increased renal excretion of potassium, increase in potassium ions uptake of erythrocytes and/or skin *(Ait-Boulahsen et al., 1989)*, or a reduced competition between H^+ and K^+ ions for urinary excretion and thereby increased urinary potassium loss *(Laiken and Fantesil, 1985).*

In the group treated with propolis no remarkable changes in urea, creatinine, sodium and potassium serum levels was detected. While, improvement was observed in protected rats group in the same parameters. Results of the present study are in accordance with the findings of *Newairy et al. (2009*) and *Ramadan et al. (2010).*

The present study corroborates the observations by *Garoui et al. (2011)* who reported that propolis ameliorated the kidney impairment induced by cobalt as suggested by a significant restoration of plasma urea, creatinine levels as well as the creatinine clearance. This might be due to the accelerated regeneration of parenchymal cells under the influence of various bioactive compounds like flavonoids and esters present in propolis that helped to prevent membrane fragility and subsequently decreased the leakage of marker enzymes into circulation *(Bhadauria et al., 2008)*.

Moreover, caffeic acid phenethyl ester (CAPE), a biological active component of propolis was found to improve renal function tests in a rat model with lithium-induced renal tubular damage and oxidative stress *(Bhadauria et al., 2008).* Caffeic acid phenethyl ester, a major compound of propolis might be responsible to protect the increase in blood urea and tubular damage *(Ozen et al., 2004).*

In the present study, no significant difference was determined in total protein and albumin level in propolis group *(Eraslan et al., 2007)*.

The present work on the kidney revealed that the administration of MSG for 4 and 8 weeks induced an obvious depletion in both total protein and albumin contents in the serum as compared to control. The decline in plasma total proteins after treatment with MSG was mainly due to the decrease in albumin *(Attia et al., 2008 and Newairy et al., 2009).* So, the significant decrease in the concentrations of total proteins in rats treated with MSG particularly the albumin could be attributed on one hand to under nutrition and on the other hand to a reduction of the protein synthesis in the liver *(Cherroret et al., 1995).*

In addition, this depletion was attributed to the decreased rate of polypeptide elongation, respiratory depression and decrease of t-RNA in liver *(El-Sherif et al., 2002).*

Propolis extract in protective group showed significant improvement in the activity of both albumin and total protein compared with MSG group. Propolis caused an increase in both activities by maintaining the protein content towards control. These effects could be, at least partly, explained by the anti-oxidant capability of the extract *(Basnet et al., 1997).*

The present investigation showed that propolis in the group administered MSG followed by propolis in association with MSG revealed minimal improvement in protein profile where there was decrease in albumin and total protein. This indicates that propolis was not efficient for use as a therapeutic agent.

In MSG rats group a significant percentage elevation of the levels of cholesterol *(Blackburn et al., 2003 and Obochi et al., 2009)*, TG, HDL, LDL and VLDL level was recorded as compared to control group. Present results are in agreement with *Thomas et al. (2009)* who noticed hyperlipidemia with significantly elevated levels of serum triacylglycerol and cholesterol in MSG group. A shift in glucose metabolism toward lipogenesis might account for the hyperlipidemia in MSG group *(Malik and Ahluwalia, 1994).*

These disturbances in the lipid profile markers were due to the destruction of arcuate nucleus in the hypothalamus as a result of MSG administration which could function in the regulatory manner towards fat metabolism.

The effect of MSG on cholesterol levels could be attributed to the activation of the enzyme, 3-hydroxyl-3-methoxylglutamyl-COA reductase, HMGR, which catalyzed the rate limiting step of cholesterol synthesis (i.e., conversion of HMG-COA to mevalonate), by covalent modification, which converted the phosphorylated state (inactive) to dephosphorylated state (active) *(Obochi et al., 2009)*. The enzyme is most active in the dephosphorylated state *(Bernard et al., 2002)*. This in turn, increased the activity of HMGR, resulting in increased cholesterol synthesis. The activation of HMGR through dephosphorylation also increased the levels of insulin, which stimulated the removal of phosphates from the cells and thereby activated HMGR activity, resulting in increased cholesterol synthesis *(Bernard et al., 2002).*

Insignificant changes were obtained in the propolis rats group throughout the experimental period in the level of serum cholesterol, triglyceride (TG), HDL, LDL and VLDL. Moreover, protection occurred in lipid profile levels in the protective group,while, a partial improvement was recorded in the therapeutic group in serum cholesterol, TG, HDL, LDL and VLDL levels *(Eraslan et al., 2007)*. Decrease in triglyceride and cholesterol levels following propolis intake may be concluded to be directly related to the influence of propolis itself on lipid metabolism.

Similarly, *Bhadauria et al. (2008)* showed dose dependent response and reduced elevated level of triglycerides, total and esterified cholesterol after toxicant exposure. It has been reported that antioxidants and flavonoids can act as inhibitors of lipid peroxidation (LPO) by scavenging polyunsaturated fatty acids peroxy radicals and interrupting the chain reactions *(Pascual et al., 1994)*. It is well-known that phenolic antioxidants can trap initiating radicals and/or propagating peroxyl radicals to break the peroxidation chain reaction to protect the cells from oxidation damage *(Maiti et al., 2005*). CAPE can trap CCl_3 radical and/or CCl_3O_2 radical by donating a hydrogen to the radical to break the free

radical chain reaction that in turn forms a CAPE semiquinone radical, which can react with the second free radical to form the CAPE ortho-quinone *(Fang et al., 2002)*.

In the present investigation, a significant depletion in the content of tissue GSH was designated while a significant elevation was realized in tissue MDA content in MSG rats group as compared with the control group *(Yaqub et al., 2008 and Vinodini et al., 2010)*.

The decrease in GSH presented in the current study might reflect their direct reaction with the reactive oxygen species generated by MSG. Glutamate toxicity involves an imbalance in the hemostasis of cysteine, the precursor of GSH, leading to depletion of intracellular GSH levels and reduced ability to protect against oxidative injury in the cell and ultimately, cell damage. Moreover, lipid peroxidation may eliminate the active sulfhydryl group of GSH and other enzymes.

Oxidative stress and accumulation of free radicals seems to be responsible for MSG toxicity *(Attia et al., 2008)*. The formed free radicals react with polyunsaturated fatty acids in cell membrane producing lipid peroxides and membrane damage. In addition reactive oxygen species (ROS) generated by the toxic effect of MSG might have caused lipid peroxidation and GSH depletion, which are indicators of tissue damage.

NMDA receptors (one of glutamate receptors) have been found in extraneuronal tissues, including pancreatic α cells, the male lower urogenital tract, kidneys, lymphocytes, and megakaryocyte. There is scant evidence regarding its physiological function in extraneuronal tissues, especially in the kidneys. Over stimulation of NMDA receptors can modulate glutamate postsynaptic neurotransmission by generating Ca^{2+} channel openings, and by overloading *(Nagata et al., 1995)* and excessive reactive oxygen species generation *(Conn and Pin, 1997)*. Ischemia, followed by reperfusion, impairs kidneys and contributes to renal dysfunction *(Avshalumov and Rice, 2002)*. Ischemia-reperfusion or hypoxia-reoxygenation injury also evokes burst amounts of reactive oxygen species and Ca^{2+} overload in damaged renal tubules, triggering the entry of these tubular cells into apoptotic and necrotic cell death, and subsequently, to renal dysfunction *(Deng et al., 2002)*.

GSH can diminish oxidative stress either by protecting the detoxifying enzymes by increasing the efficacy of nicotine amide dinucleated phosphate (NADPH), or by helping in the elimination of compounds which produce peroxidation in the cell membranes *(Machlin and Bandich, 1987)*.

In the current work, no remarkable changes were reported after rats were treated with 200mg/kg b. w. propolis in tissue MDA and GSH. Furthermore, protection was shown in protective rats group only and not the therapeutic one *(Ogeturk et al., 2005)*.

A possible mechanism of the protective effects of propolis is that several bioactive compounds present in it might protect oxidative damage by directly neutralizing reactive oxidants, increase the capacity of endogenous antioxidant defense and modulating the cellular redox state *(Moskaug et al., 2005)*. This might be due to the favorable capacity of propolis to pass through the membrane and to accumulate in both hydrophilic and hydrophobic environments for protecting cells against oxidative stress and scavenging free radicals *(Sun et al., 2000)*. Flavonoids and their esters in propolis are pharmacologically active molecules and have been hypothesized to influence the antioxidant activity of propolis *(Lahouel et al., 2004)*.

Propolis can control and modulate the metabolism of lipids leading to decreased outputs of lipid peroxidation and scavenge the free radicals in rats *(Sobocanec et al., 2006)*. The present work revealed minimal improvement in the MDA and GSH content of therapeutic rats group as compared with the control and propolis groups.

In the present study, MSG group showed increase in fractions 1and 2 and decrease in the fractions 3, 4 and 5 of the different kidney saturated protein fractions as compared with control group. This result is in agreement with *Madbouly (2005)* in her study on electrophoresis of liver protein fractions, where treatment of infected mice with mirazid caused decrease of Gamma-globulin of infected group, and induced increases in Beta, Albumin, Prealbumin and Alpha fractions. This decrease and increase in particular protein fractions may be related to the effect of MSG on the specific genes encoding for these fractions as demonstrated in a study by *Radwan (2005)* who revealed that coumarin caused qualitative and quantitative changes in tissues (brain, liver and kidney) protein fractionation pattern of chicken.

Furthermore, *Mansour et al. (2009)* showed that rats treated with profenofos showed a lower concentration of serum proteins and albumin accompanied by decreased globulin alpha 1 and beta along with an increased gamma 2 globulin. After exposure to profenofos α 2, β 1, γ 1 contents were decreased while α 1, β 2, γ 2 globulins were increased. These findings may be related to impact of profenofos towered the hepatic cells and immune system *(Yousef and salama 2009)*.

El-Behairy et al. (2009) investigated the effect of propolis as a prophylactic or therapeutic agent against Rift Valley Fever virus (RVF). The electrophoresis of serum proteins revealed that propolis had a potent antiviral effect as reflected by increased serum protein

concentrations. Also, they concluded that propolis was superior to RVF vaccine when used as a prophylactic and the use of propolis as prophylactic was better than its use as treatment.

Therefore, it may be collectively concluded that because propolis possesses a plethora of minerals, polyphenols and their esters, which may interfere with the formation of highly toxic free radicals to reduce oxidative stress, it can enhance the antioxidant defense mechanism to repair membrane damage.

In view of the findings of the current study, it may be concluded that propolis extract possess the ability to reverse MSG induced kidney oxidative injury as well as to regulate the metabolic enzymatic activities and major cellular components for maintaining proper functioning of the cells and may be considered as a protective agent against MSG induced toxic effects .On the other hand its role in therapy was of only limited value.

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