Protective role of rockect seed (*Eruca sativa*) extract against monosodium glutamate induceed hepato-renal toxicity in male rats

ABSTRACT

Background and Objective: Monosodium glutamate (MSG) is identified as Ac'cent that is used in the food industry as a flavor enhancer with an umami taste that intensifies the meaty, savory flavor of food. The present study aimed at evaluating the protective and ameliorative role of rocket seeds extract against monosodium glutamate induced hepatic renal toxicity and oxidative stress in male rat. **Materials and Methods**: A total of 60 male adult albino rats were equally divided into six groups (G1, Control; G2, rocket seeds (RS); G3, ACCENT or MSG; G4, Co- treated (RS+MSG); G5, Post- treated (MSG+RS); G6, Self-treated MSG). **Results:** Current results revealed that; a significant increase in serum ALT, AST, ALP, AFP, Urea, Creatinine, potassium ions, chloride ions, cholesterol, triglyceride, HDL, and LDL levels in MSG as compared to control and RS groups. In contrast; a significant decrease in serum albumin, total proteins, catalase, GSH and SOD in liver and kidney homogenates in MSG as compared to control and RS groups. Co- or post treatment of MSG with rocket seeds improved this change in liver and kidney functions, with best results for co- treatment than post and self treatment. **Conclusion:** These findings suggested that misuse of monosodium glutamate may contribute to a continuous hepatic and renal damage. This shows that the desired dose of monosodium glutamate can safely be used with grapes seed in improving hepatic and renal damage in monosodium glutamate in young rats.

Key words: Monosodium glutamate, ACCENT, Rocket seeds, Liver and kidney, rats.

1. INTRODUCTION

Glutamate is one of the most plenteous amino acids in nature and it is a reinforcement of l-glutamic ruinous is spoken to be a trademark supplement in different sustenance [1]. Different as of now composed sustenances are especially speaking to potential customers fundamentally in context on their normal flavors. In that capacity it's nothing frightening that the sustenance business managing these thing sections shows incredible vitality for the utilization of sustenance or sustenance fixings passing on the regular umami taste and flavor upgrade frameworks [2]. Seasoning can anticipate an immense dietary movement, especially in sustenances that are not astoundingly delicious, by giving the vital intrigue [3]. MSG is used to give a "significant", "inviting", or "brothy" taste to sustenances by enlivening the glutamate receptors on the tongue [1]. There are glutamate receptors in various bits of the body, amazingly the cerebrum, where glutamate is a neural connection.

Monosodium glutamate (MSG) is perceived as Ac'cent is a flavor enhancer called glutamate. The uncommon and subtle taste Ac'cent produces is grouped "umami" in Japan [4]. Monosodium glutamate is a regularly happening sodium salt of glutamic destructive which was from the outset mixed from wheat gluten but at this point made in business sums by bacterial development [5]. MSG is used in both home and diner cooking and it is a run of the mill fragment of Asian eating regimens [6] It is communicated that the taste quality enlivened

by MSG and other related substances was exceptional and was not a blend of fundamental taste attributes, to be explicit, sweet, sharp, salty, extreme [7].

As indicated Asia was the biggest maker of monosodium glutamate, represented roughly 94% of universes MSG creation limit. Popularity, financial, inexhaustible work and its utilization in feed stocks may be the purpose for its huge scale creation in Asia. Taiwan, Indonesia, China, Thailand and Vietnam were the significant MSG makers.

The use of complementary and alternative medicine has been a marked increase in recent decades [8,9,10,11,12,13,14]. Many plants products have significant antioxidant activities, which play important roles in cancer treatment. Medicinal plants may serve as a vital source of potentially useful new compounds for the development of effective therapy to combat a variety of liver and kidney problems [14-17].

Rocket seeds (Eruca sativa Mill. or Eruca vesicaria L.) broadly spread all over the world and is commonly consumed fresh (leafs or sprouts) for its classic spicy taste. Rocket seeds are too used for the creation of oil and for appreciated pungent tang sprouts [18]. The seeds contain approximately 45% erucic acid and about 9% gadoleic acid (C20:1) [19]. Plantlet regeneration via somatic embryogenesis [20] have been reported for Eruca sativa.

The rocket seeds contain carotenoids, vitamin C, flavonoids such as appiin and luteolin and glucosinolates the precursors of isothiocyanates and sulfaraphene [21], volatile oils like myristicin, apiole and βphellandrene [22,23]. Glucosinolates were found to have several biological activities including anticarcinogenic, antifungal, antibacterial plus their antioxidant action [24]. The rocket seeds contain also contain Zn, Cu, Fe, Mg, Mn and other elements [25], which increase immune response and the reproductive performance. Carotenoids can protect phagocytic cells from antioxidative damage, enhance T and B lymphocyte proliferative responses and increase the production of certain interleukins [26]. Given the wide usage of monosodium glutamate as flavor enhancer it is basic to look at this occurrence of it's over use for long time and its effect on liver and kidney. Likewise, the purpose of this assessment is to show the alterations in some hematological and biochemical and oxidative weight parameters after the medications of male rats with ACCENT.

2. MATERIAL AND METHODS

2.1. Experimental animals

The experiment was performed on 60 male albino rats (Rattus norvigicus) weighing 150 g (±10) and of 9-10 weeks' age. They were obtained from animal house of National Research Center (Dokki, Giza, Egypt). The rats were housed in suitable plastic cages for one week before the experimental work for acclimation with anew room conditions and maintained on a standard rodent diet, with water available ad libitum. During the experiment animal behaviour were noticed and body weight at the beginning and the end of experiment were measured. Animal maintenance and treatments were conducted in accordance with the Faculty of Science, Tanta University guide for animal, as approved by Institutional Animal Care and Use Committee (IACUC-SCI-TU-0074).

2.2. Experimental design

A total of 60 male adults rats were equally divided into six groups and the experiment lasted for 8 weeks on which constant weight of diet was given for each rat. Group 1, control includes animals that not given any drug; group 2, includes rats that receive rocket seeds (intragastrically, 30 mg/kg body weight/day); group 3, include animals that receive ACCENT (intragastrically, 50 mg/Kg body weight/day) for 4 weeks. In contrast; group 4 (co-treated) include rats receive ACCENT and rocket seed at the same time for 4 weeks while group 5 (post treated) include rats receive ACCENT for 4 weeks and then treated with rocket seed for another 4 weeks. Group 6 (self-treated) include rats receive ACCENT for 4 weeks and not treated with any drug for another 4 weeks.

2.3. Determination of Serum Enzymes

At the end of the experimental period, animals were fasted overnight and blood samples were individually collected from the eyes by retro-orbital puncture using blood capillary tubes without heparin as per requirement under mild ether anesthesia for for clinical chemistry examinations. Blood samples were incubated at room temperature for 10 minutes and left to clot then centrifuged at 3000 r.p.m for 10 min and the serum were collected, serum was separated and kept in clean stopper plastic vial at –80°C until the analysis of serum parameters [27].

2.3.1. Serum liver functions enzymes

Serum aspartate transaminase (AST) and alanine transaminase (ALT) activities were assessed in the sera as per Al-Rasheed et al. [28] respectively while serum alkaline phosphatase (ALP) levels was evaluated by Moustafa et al. [15]. Serum albumin and globulin was assessed by Basuony et al. [29] while serum total proteins level was evaluated by Tousson et al. [30].

2.3.2. Electrolytes and Kidney Functions Biomarkers

Serum urea and creatinine were determined in the mouse sera according to Tousson et al. [31]. The approach proposed by El-Masry et al. [17] was followed to measure the levels of serum electrolytes (Potassium, sodium, calcium and chloride ions) using commercial kits (Sensa core electrolyte, India).

2.3.3. Serum lipid profiles

Test kits of (StanBio, USA) were used for the determination of plasma lipid profile including total cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) according to Salama et al. [32,33].

2.4. Statistical analysis:

Data were expressed as mean values ± SE and statistical analysis was performed using unpaired t-test to assess significant differences among treatment groups. The criterion for statistical significance was set at $p<0.05$ for the biochemical data. All statistical analyses were performed using SPSS statistical version 21 software package (SPSS® Inc., USA).

3. RESULTS

The dose of rocket seeds (Eruca sativa) did not initiate any side effects for the animals, where as various side effects were observed in animals treated with ACCENT such as facial pressure, chest pain, rapid heartbeat, headache, difficulty breathing for asthmatics, weakness, nausea and Numbness.

Results in Table (1) revealed a significant increase ($P <0.05$) in ALT, AST and alkaline phosphatase activities. In contrast; significant decrease in total protein and albumin levels in the AC'CENT and self-treated group compared with the control group. Treatment of AC'CENT induced toxicity with rocket seeds as co- and post treatments improved liver function parameters and Co-treatment induced best results as compared to post treatments.

Figure (1) revealed that; serum AFP levels in ACCENT and self-treated groups revealed significant increase compared with control group. In contrast a significant decrease in AFP levels in treated ACCENT with rocket seeds groups (G4, G5) when compared to ACCENT and self-treated groups.

Table (1): Changes in serum Liver function (ALT, AST, and alkaline phosphatase, total protein and albumin) levels in experimental groups.

	G1	G2	G3	G4	G5	G6
ALT (U/L)	31.67 ± 0.988****	28.17 ± 1.11****	55.67 ± 1.14	45.33 ±1.25****	42 ± 0.77****	49.67 ± 1.49**
AST (U/L)	118.3 ± 1.26****	111.3 ± 1.71****	178.8 ± 3.57	147.2 ±3.72****	140± 1.34****	161.2 ± 2.02***
ALP (U/L)	127.2 ± 1.424****	117.7 ± 1.229****	200.2 ± 3.825	139.2 ±1.014****	153.3± 2.01****	167.3± 2.36****
T. protein (g/dl)	6.49± 0.03****	6.49± 0.04****	4.91 ± 0.10	5.92± 0.14****	5.49± 0.08***	5.02 ± 0.08^{NS}
Alb (g/dl)	4.37± 0.05****	4.54 ± 0.03****	3.36 ± 0.07	4.25± 0.04****	3.95± 0.052****	3.67 ± 0.09**

The significance of difference was analyzed by one – way ANOVA (compare all vs. ACCENT group) using computer program. Values are expressed as means ± SEM. one – way ANOVA was significant at $P < 0.05$. where, G1, control group; G2, Rocket seeds group; G3, ACCENT group; G4, co- treated group; G5, post-treated group; G6, self-treated groups.

Table (2) exhibits that; kidney function (urea, creatinine) levels in serum were significant increase (P <0.05) in the ACCENT and self-treated groups when compared with the control group. In contrast a significant decrease in urea, creatinine levels in treated ACCENT with Rocket seed groups (G4, G5) when compared with ACCENT (G3) and self-treated (G6) groups. Also, no significant in their levels in self-treated ACCENT group (G6) compared with ACCENT group (G3).

Table (2) revealed that; in potassium and chloride ions levels were significant increase (P <0.05) Ii contrast; no changes were detected in sodium and calcium ions levels in the ACCENT and self-treated groups when compared with the control group. Treatment of ACCENT with rocket seeds as co- and post treatments improved these changes in electrolytes and Co-treatment induced best results as compared to post treatments.

Table (3) exhibits that; a significant (P <0.05) increase in cholesterol, triglycerides, LDL, and HDL were detected in ACCENT and self-treated groups when compared with the control group. In contrast a significant decrease in in cholesterol, triglycerides, LDL, and HDL levels in treated ACCENT with Rocket seed groups (G4, G5) when compared with ACCENT (G3) and self-treated (G6) groups. Also, no significant in their levels in self-treated ACCENT group (G6) when compared with ACCENT group (G3).

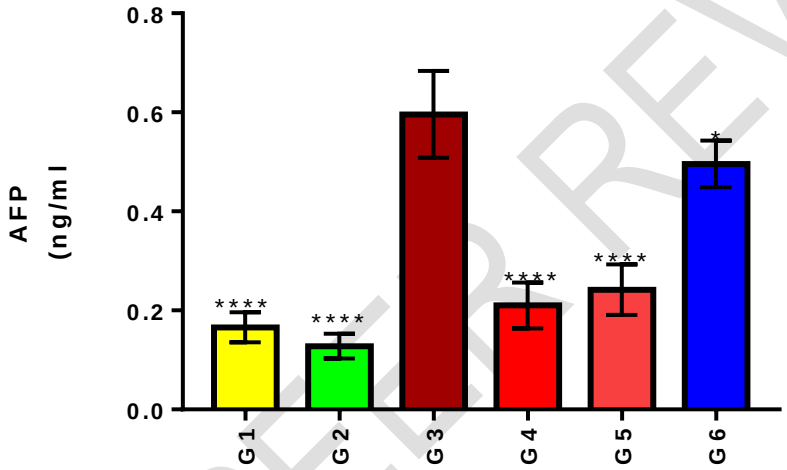

Figure (1): Changes in serum AFP in different groups. Where G1, Control group; G2, Rocket seeds group; G3, ACCENT group; G4, Co-treated ACCENT group with Rocket seeds ; G5, Post-treated ACCENT group with Rocket seeds ; G6, Self-treated ACCENT group.

Table (2): Changes in serum Kidney function (urea, creatinine) levels and electrolytes (potassium, chloride, calcium and sodium ions) in experimental groups.

	G1	G2	G3	G4	G5	G6
Urea (mg/dl)	22.83 ± 0.82****	22.2 ± 0.85 ****	40.63 ± 0.52	32.33 ± 1.08****	33.25 ± 0.72****	39.55 ± 0.48NS
Creatinine (mg/dl)	0.53 ± 0.03****	0.42 ± 0.026****	0.99 ± 0.04	0.73 ± 0.029****	0.72 ± 0.011****	0.94 ± 0.037NS
K+ (mEq/L)	4.472 ± 0.139***	4.337 ± 0.146****	5.305 ± 0.167	4.537 ± 0.129**	4.568 ± 0.114**	5.097 ± 0.053NS
Cl- (mEq/L)	100.1 ± 0.459****	100.5 ± 0.418****	109.8 ± 0.969	103.7 ± 1.474***	103.2 ± 0.790***	106.6 ± 1.166NS
Ca++ (mEq/L)	1.103 ± 0.018NS	1.215 ± 0.058NS	1.152 ± 0.025	1.148 ± 0.02NS	1.152 ± 0.025NS	1.14 ± 0.014NS
Na+ (mEq/L)	136.2 ± 0.603NS	137.4 ± 0.5175**	135 ± 0.5582	135.7 ± 0.3535NS	136 ± 0.3232NS	135.5 ± 0.2167NS

The significance of difference was analyzed by one – way ANOVA (compare all vs. ACCENT group) using computer program. Values are expressed as means ± SEM. one – way ANOVA was significant at P < 0.05.

where, G1, control group; G2, Rocket seeds group; G3, ACCENT group; G4, co- treated group; G5, post-treated group; G6, self-treated groups.

Table 3: Changes in serum lipid profiles (cholesterol, TG, HDL and LDL) levels in experimental groups.

	G1	G2	G3	G4	G5	G6
Cholst (mg/dl)	109.2+ 3.45	105.2 ± 2.82****	152.8 ± 3.22	113.4 ± 3.54****	121.8 ± 1.83****	138.8 ± 1.93**
Tg (mg/dl)	95.4 ± 3.50****	99.2 ± 2.29****	150 ± 3.82	109.4 ± 2.06****	123.4 ± 3.04****	135 ± 3.02**
HDL (mg/dl)	69.24 ± 1.94**	66.4 ± 1.71***	79.28 ± 1.56	72.46 ± 2.39	66.1 ± 1.89***	68.76 ± 0.71**
LDL (mg/dl)	20.88 ± 1.25****	18.98± 1.98****	43.52 ± 2.28	19.06 ± 1.54****	28.62 ± 1.42****	43.04 ± 1.72^{NS}

The significance of difference was analyzed by one – way ANOVA (compare all vs. ACCENT group) using computer program. Values are expressed as means ± SEM. one – way ANOVA was significant at P < 0.05. where, G1, control group; G2, Rocket seeds group; G3, ACCENT group; G4, co- treated group; G5, post-treated group; G6, self-treated groups. NSP=0.1234; *P=0.0332; **P=0.0021; ***P=0.0002; ****P<0.0001

4. Discussion

Monosodium Glutamate or Accent (MSG) is one of the world's most extensively used food additives which are ingested as part of commercially processed foods. Monosodium glutamate is the sodium salt of glutamic acid, is added to food, it provides a flavoring function similar to the naturally occurring free glutamate which differ from the four classic tastes of sweet, sour, salty and bitter the serious side effects of monosodium glutamate (MSG) are many and may not be reversible. Many industrially prepared foods are particularly attractive to potential consumers primarily because of their typical flavors. Several studies in animals have shown that MSG is toxic to the various organs such as the liver, brain, thymus, and kidneys [2,7].

Therefore, it's no surprise that the food industry dealing with these product segments shows great interest in the use of food or food ingredients carrying the typical umami taste and flavor enhancement systems. Therefore; the present study was designed to investigate the role of rocket seeds (Eruca sativa) extract in improving renal and hepatic toxicity induced by monosodium glutamate.

In the current study; ALT, AST and ALP activities were significantly increase in serum of rats treated with MSG as compared to control group (P <0.05), while; serum albumin and total proteins were significantly decrease in rat treated with MSG as compared to control group (P <0.05). These results were in agreement with the data of Oscar et al. [34]) who reported that MSG administration will increase the enzyme activity (ALT and AST) which indicated that there was hepatocellular injury.

These consequences were in pact with the information of Onyema et al. [35] who well-versed that ACCENT direction will rise the enzyme activity (ALT and AST) which revealed that there was hepatocellular injury. Albumin and total protein levels decrease in ACCENT group compared with control group which might suggest cellular leakage and function alimpairment of hepatic cell membranes [16,36], and on the other hand, decreased levels of albumin, and total proteins. Current results agree with Tawfik and, Al-Badr [37] who reported that; monosodium glutamate administration induced adverse effects of on liver functions in adult rats. Our study agrees with Eweka [7] who informed that; accent caused dilatations of the central vein of the liver associated to the liver sections of the control sets.

The results of the experiments conducted revealed that, unlike the control group, rats given MSG exhibited, on the one hand, higher levels of ALT, AST and ALP, such results were consistent with those obtained by [34], who concluded the occurrence of hepatocellular damage based on MSG-induced elevation in the levels of ALT and AST. There is also agreement between the present study and those by [38, 35] with regard to the

fact that rats administered with MSG had higher serum ALT levels, most likely based on the observation that hepatic oxidative stress was caused by MSG. In a similar way, [39] found that rats injected with MSG displayed increased AST and ALT levels accompanied by hepatocyte deterioration.

Mansour et al. [40] confirmed this result and referred that the elevation of these enzymes in plasma due to the leakage of ALT and AST from the liver cystol into the blood. Moreover, Al-Mamary et al. [41] reported that the high concentration activity of serum ALT probably be a marker of hepatic damage. This elevation might be mainly to the production of free radical caused damage of plasma membranes and mitochondrial resulting in release of this enzyme [42]. The high concentration activity of GGT in MSG group is corroborated with previous study of Onyema et al. [35] who reported that MSG caused oxidative stress resulting in liver damage.

The result seemingly agrees with the reports of Onyema et al. [35] that the activity of serum ALT increased in male rats that were fed MSG probably due to the finding that MSG induced oxidative stress in the liver. Thus, it could be concluded that MSG may be hepatotoxic at a low dose, hence should be avoided during the treatment of liver disorders, the use of MSG even at low doses should not be encouraged because of the possible health implications. The reduction of albumin in the MSG treated rabbits is similar to the finding by [37] who reported that MSG group showed reduced in serum albumin levels lower than control group.

In the current study, serum total proteins, and albumin were significantly increased while serum ALT, AST and ALP were significantly decreased in all prophylactic groups and also in treated group of Eruca sativa seeds compared to MSG group. In the same line, Ahmed [43] indicated the ability of Eruca sativa oil to stimulate the regeneration of hepatic tissue which increased protein synthesis in damaged liver and improved the functional statues of the liver cells.

There was an extremely significant increase in Alpha-fetoprotein (AFP) concentration in rats treated with accent equated to control and Tawfek et al. [44] confirm that. Oxidative stress is produced by the extreme manufacture or a declined removal of free radicals in cells, the widely held of which are oxygen radicals and additional reactive oxygen species (ROS) [45].

The circulating MSG was dissociated in sodium (Na+) and L-glutamate. The L-glutamate crosses the mesothelial peritoneal cells and arrives at the bloodstream by means of a transport system using ATP. A part of the L-glutamate in the cell conjugates, in order to be eliminated, and another part is transformed into glutamine. When this occurs, the cells try to repair some of the damages by using enzymes that are present in the smooth endoplasmic reticulum but the cell is not able to completely remove the excess glutamine.

The serum urea nitrogen is a measure of renal function. Normally, the serum urea nitrogen level rises in heart failure, dehydration, or a high protein diet and low urea nitrogen level can be seen in renal damage or in liver diseases. A change in serum creatinine level is also an indicator of kidney function. Therefore, in the present study serum creatinine was determined to find out the effect of MSG on renal functional markers such as serum creatinine, and serum urea nitrogen.

On the other hand, no changes were detected in calcium and sodium ions after treatment of rats with MSG and this depletion were increase after treated with grape seeds. These results are in harmony with previous studies which reported that MSG. The significant increase in creatinine content of the serum following the administration of MSG may be attributed to compromise of the renal functional capacity [12]. MSG might have either interfered with creatinine metabolism leading to increased synthesis or the tissues might have compromised all or part of its functional capacity of tubular excretion. Current results agree with Tawfik and Al-Badr [37] who reported that; monosodium glutamate administration induced adverse effects of on kidney functions in adult rats. The association between dietary factors, including MSG and the risk of kidney disease, has been hypothesized in numerous studies. The kidneys are highly sensitive to ischemia, toxic insults, and other chemicals [27]. In very general terms a rising level of creatinine significance an increasing problem with poorly performing kidneys [46]. Hence there is possible link between MSG and renal impairment. However, elevation in chloride and potassium ions in contrast no significant variation recorded in calcium and sodium ions after treatment of rats with MSG.

Rocket seeds (Eruca sativa Mill. or Eruca vesicaria L.) broadly spread all over the world and is commonly consumed fresh (leafs or sprouts) for its classic spicy taste. Rocket seeds are too used for the creation of oil and for appreciated pungent tang sprouts [18]. It is widely used in traditional medicines and has a noble standing as a therapy of renal ailments [47].

Ahluwalia and Malik [48] confirm as in this study that the significant increases seen in the serum concentrations of total lipids, triglycerides, HDL and LDL in ACCENT group. Too initiate increase in cholesterol level [49]. In prophylactic groups, Eruca sativa significantly decreased serum cholesterol,

triglycerides and low density lipoprotein cholesterol levels while the mean values of high density lipoprotein cholesterol and HDL-C/LDL-C ratio were significantly increased.

The activities of liver function enzymes tended to decrease indicating improved liver function tests. Such reduction of liver enzyme activities and also reduction of total protein and urea concentration exhibit healthy effect of dietary rocket due to high content of sulphur and antioxidant status as reported by Alam et al. [47].

Medicinal plant has nutrient compositions that are essential for the physiological functions of human body. Such nutrients and biochemical's like carbohydrates, fats and proteins play an important role in satisfying human needs for energy and life. Minerals are essential for human nutrition and must be obtained from diet [50]. The improvements in nutritional and growth results represented in table 3 were related to the chemical composition of Eruca seeds and phytochemical analysis. Seeds contain various nutrients which are required for food or feed purposes [51]. Rocket and other Cruciferous vegetables contain a group of anticancer compounds known as glucosinolates, these compounds exert antioxidant activity and are potent stimulator of natural detoxifying enzymes in the body ,such compound exert secretary, anti-ulcer and cytoprotective properties in the ethanolic extract of the plant in rats [52].

CONCLUSIONS

This study suggests that continuous consumption of MSG in the dosage range tested herein May result in varying degrees of liver and kidney injury, depending on the concentration Administered. It is important to note that the amount of MSG used in many previously Published studies were very high, in contrast to the present study which showed evidence of organ injury at relatively lower doses administered chronically over a period of time. Our data suggests that further research is warranted to examine the safety profile of this widely used food additive.

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