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C Yugandhar
Assistant Professor (Contractual), Department of Veterinary Pathology, College of Veterinary Science, SVVU, Proddatur, Andhra Pradesh, India

RV Ramanamurty
Associate Professor and Head, Department of Veterinary Pathology, College of Veterinary Science, SVVU, Garividi, Andhra Pradesh, India

K Sujatha
Coordinator, Centre for Continuing Veterinary Education and Communication, Sri Venkateswara Veterinary University, Tirupati, Andhra Pradesh, India

N Vinod Kumar
Professor and Head, Department of microbiology, College of Veterinary Science, S.V.V.U, Proddatur, Andhra Pradesh, India

TNVKV Prasad
Senior Scientist, Institute of Frontier Technologies, R.A.R.S, S. V. Agricultural College, Tirupati, Andhra Pradesh, India

U Vinod
Assistant Professor (Contractual), Department of Animal Genetics and Breeding, College of Veterinary Science, SVVU, Tirupati, Andhra Pradesh, India

Corresponding Author:
C Yugandhar
Assistant Professor (Contractual), Department of Veterinary Pathology, College of Veterinary Science, SVVU, Proddatur, Andhra Pradesh, India

Effect of monosodium glutamate salt (Ajinomoto) on oxidative stress in male Wistar albino rats and it's amelioration with ZnO NPs

C Yugandhar, RV Ramanamurty, K Sujatha, N Vinod Kumar, TNVKV Prasad and U Vinod

Abstract
Monosodium Glutamate (MSG) is one of the world's most extensively used food additive in human and livestock diets. Monosodium glutamate (MSG) is the sodium salt of amino acid glutamate, which is the main excitatory neurotransmitter in the body. The present study was carried out to evaluate the potential protective role of ZnO NPs against MSG induced oxidative stress in liver, kidney and testes of male wistar albino rats. For this experiment 48 male wistar albino rats weighing 130-170g Body Weight were procured and devided into 4 groups. Each group having 12 rats. Among four groups, Group I and group III served as negative control and zinc oxide nano particle (ZnO NPs) control respectively. Group II served as monosodium glutamate (MSG) toxic control, where MSG given orally at the dose rate of 5g/kg body weight daily and Group IV served as ZnO NPs ameliorated group where dose given daily (5g/kg b.wt of MSG + 10 mg/kg b.wt of ZnO NPs) for a period of six weeks. All the rats from each group were sacrificed randomly at 6th week after starting the experiment. The study revealed that MSG @ 5 g/ kg b.wt /day orally for 6 weeks was toxic to rats and caused induced adverse effects of oxidative stress changes in various visceral organs by increasing the production of lipid peroxidation and reactive oxygen species (ROS) due to decreased levels of antioxidants. The present study revealed reduced glutathione peroxidise (GPx), super oxide dismutase (SOD) and catalase in liver, kidney and testes were observed in MSG treated rats (Group II). ZnO nanoparticles significantly reduced oxidative damage in liver, kidney and testicular tissues to great extent in MSG induced rats.

Keywords: MSG, ZnO NPs, SOD, CAT, GPx, male albino rats

1. Introduction
Monosodium Glutamate (MSG) is one of the world's most extensively used food additives (E621) (Husarova and Ostatnikova, 2013) [16], particularly in West African and Asian dishes because of its flavor enhancer (Farombi and Onyema, 2006) [10]. Monosodium glutamate (MSG), a white crystalline powder and the sodium salt of a naturally occurring non-essential amino acid, glutamic acid (Furst and Stehle, 2004) [11]. The sodium salt of glutamic acid can produce a unique taste known as fifth taste "umami'', that is different from the four classical tastes like sweet, salty, sour and bitter (Ninomiya, 1998) [19]. MSG contains 78% of glutamic acid, 22% of sodium and water (Samuels, 1999) [23]. Average intake of MSG in European and Asian countries is generally 0.3–0.5 g/day and 1.2–1.7 g/ day, respectively. MSG intake of 16.0 mg/kg of body weight is generally regarded as safe (Beyreuther *et al.*, 2006) [3]. It improves the quality of food intake by stimulating chemosensory perception (Kulkarni *et al.*, 2014) [17].
Glutamate is the main excitatory neurotransmitter in the body. The excess glutamate in brain cause neurotoxicity and act as a potent excite toxin (Olney, 1976) [20]. MSG is a widely used flavor enhancing food additive used mostly in seafood, poultry meats, prepared meals, frozen foods, marinated meats, traditional seasonings like soups or sauces (canned, packed), fresh sausages, chips, snacks, bottled soya and stuffed or seasoned chicken, manufactured meats, some hams, and flavoured tuna, vegetarian burgers and sausages (Bojanic *et al*., 2009) [4]. MSG is produced commercially in modern days by fermentation of starch, sugar, beet sugarcane or molasses (Walker and Lupien, 2000) [27].
According to Food and Drug Administration (FDA) declared that it's safe for limited usage. Excess consumption of MSG can cause cardiac, circulatory, gastrointestinal, muscular, and neurological disorders (Zehra Kazmi *et al.*, 2017) [28]. In addition, could produce symptoms such as headaches, numbness, weakness, sweating, flushing, dizziness, asthma, urticaria,

atopic dermatitis, ventricular arrhythmia, neuropathy and abdominal discomfort (Geha *et al*., 2001) [12]. It has been implicated in male infertility by causing testicular hemorrhage, degeneration and alteration of sperm cell population and morphology (Das and Ghosh, 2010) [7]. Excess of MSG affects the hypothalamus-pituitary axis of the brain, leading to its neuro-excitatatory/neuroendocrine effects and induction of obesity, increased body weight (Egbuonu *et al*., 2010) [8] and adversely affects locomotor activities (Eweka and Om'Iniabohs, 2008) [9]. Glutamate signalling is not only restricted to the CNS also spread in other vital tissues including pancreatic islets, taste buds and cells in the lung, liver, heart, kidney and adrenal as these tissues possess glutamate receptors. Sensory structures of MSG was also present in gastric corpus and signal was mediated by vagus nerve.

The concept of nanotechnology was conceived in 1959 by Richard Feynmann for the first time. It has opened up new panoramas for applications in molecular biology, disease diagnosis, treatment, animal breeding, reproduction, value addition to animal products and biotechnology in revolutionizing almost all the disciplines of veterinary and animal sciences by providing new, small scale tools and materials that are beneficial for living organisms. Nanoparticles (NPs) are used in various fields includes biomedical, gas sensors, drug-delivery systems etc. Out of all other metal nanoparticles, zinc oxide nanoparticles are most important and commonly used (Bedi and Kaur, 2015) [2]. In 21st century nanotechnology is one of the important fields of research because of its distinctive properties (Hamza *et al*., 2021). Zinc is a potent antioxidant and it shows significant properties like anti-inflammatory activity (Costa *et al.*, 2012) [6], scavenging of free radicals or detoxify the free radicals (Hassan *et al.*, 2016) [14] and it protects the cell membrane integrity against oxidative stress damage and improves the antioxidant enzymes levels by reducing the ROS production (Hassan *et al.*, 2014) [15].

Current literature reviewed was found to be specially lacking on the toxicopathological effects of MSG on various visceral organs of rats.

2. Materials and Method

The present toxicopathological research work was carried out to study the effect of monosodium glutamate (Ajinomoto) and possible protective effect of ZnO NPs in male Wistar albino rats. The present study was carryout for oxidative stress in different experimental groups. The experiment was carried out during the period of April 2018 to June 2018 in the Department of Veterinary Pathology, College of Veterinary Science, Tirupati.

2.1 Experimental animals

Male Wistar albino rats with body weight around 150 to 170 g (procured from Sri Venkateswara Agencies, Bangalore) were used for the present experiment. The rats were acclimatized for two weeks in the laboratory conditions before starting the experiment. After two weeks of acclimatization the rats were grouped and housed in standard polypropylene rat cages (four rats in one cage) under standard laboratory hygienic conditions throughout the experiment of 6 weeks. Adlibitum laboratory animal feed (pellet diet) and wholesome drinking water was provided. The approval of the Institutional Animal Ethical Committee (IAEC) was obtained prior to commencement of the experiment.

2.2 Monosodium glutamate salt

The Monosodium glutamate salt was purchased from Loba chemie Pvt. Ltd, Palghar, Maharashtra, product code No. 0395600500 with 99% extra purity.

2.3 Zinc oxide nanoparticles

Zinc oxide nanoparticles (ZnO NPs) powder procured from Nanotechnology Laboratory at Institute of Frontier Technology, Regional Agricultural Research Station, Tirupati. The prepared zinc oxide nanoparticles were characterized by using techniques such as UV-Vis spectrophotometre, FT-IR (Frontier transform infra-red) spectrophotometry, dynamic light scattering and Scanning electron microscopy (SEM). The mean size of 45 nm diameter of nanoparticles were used in present study.

Experimental design

A total of 48 healthy adult male wistar albino rats of 6-7 weeks age were used for the study. These rats were devided randomly into four groups having 12 animals in each group. For this experiment 48 male wistar rats were procured and devided into 4 groups; Group I, Group II, Group III, Group IV. Each group having 12 rats. Among four groups, Group I served as negative control. Group II served as monosodium glutamate (MSG) toxic control, where MSG given orally at the dose rate of 5g/kg body weight daily for a period of six weeks. Group III served as zinc oxide nano particle (ZnONPs) control where ZnO NPs given orally in distilled water at the dose rate of 10mg /kg body weight daily for a period of six weeks. Group IV served as ZnO NPs ameliorated group where dose given daily (5g/kg b.wt of MSG + 10 mg/kg b.wt of ZnO NPs) for a period of six weeks. Rats were clinically monitored throughout the experimental period of 6 weeks and body weights were taken at weekly intervals. At 6th week of after starting the experiment, all the rats from each group were sacrificed.

Oxidative stress

Immediately after sacrifice at 6th week of experimental period, all the tissue pieces of liver, kidney and testes from four groups of rats were collected and stored at -20 °C until use.

Preparation of tissue homogenate

Tissue pieces of liver, kidney and testes were minced separately and homogenized in 0.05 M ice cold phosphate buffer (pH 7.4) by using a virtis homogenizer to make 10% homogenate. The homogenate was mixed with 10% trichloroacetic acid in the ratio of 1: 1, centrifuged at 3000 rpm for 10 min at 4 °C and supernatant was used for estimation of superoxide dismutase (Marklund and Marklund, 1974), catalase (Caliborne, 1985) [5] and glutathione peroxidase (Rotruck *et al.* 1973) [22] in liver, kidney and testes of all rats in all groups.

Statistical analysis

The results were analyzed statistically by performing one-way analysis of variance ANOVA + Turkey- Kramer Multiple Comparisons Test (Snedecor and Cochron, 1994) [25].

3. Results and Discussion

Antioxidant profile

3.1 Glutathione peroxidase (GPX)

Liver, Kidney and Testes

Statistically significant ($p<0.05$) decrease in mean liver, kidney and testes GPx activity was noticed in MSG treated rats (Group II) when compared to the control rats (Group I) (Fig. 1) (Table. 1). These findings were in agreement with Onyema *et al.* (2012), Hassan (2014) [15], Onyema (2016) [14], Singh and Ahluwala (2002) [24]. The decrease in levels of these enzymes might be due to MSG induced generation of reactive oxygen species (ROS) (or) by reducing the

antioxidant cell defense system by depleting glutathione.

A significant improvement was observed in mean liver, kidney and testes GPx activity in ZnO NPs ameliorated rats (Group IV) when compared to the MSG treated rats (Group II) (Fig. 1) (Table. 1). These findings were in agreement with Afifi *et al.,* (2015). Increase in GPx levels in ameliorated group IV might be due to antioxidant property of ZnO NPs protects against oxidative stress by maintaining the cell membrane integrity from oxidative damage (Afifi *et al.,* 2015) and (Hassan *et al.*,2016) [14] or increased Zn concentration in tissue produced from dissociation of ZnO NPs and it is an powerful antioxidant metal and core constituent of antioxidant enzymes like SOD and recognized protector of sulfhydryl group (Afifi *et al.*,2015) and detoxify free radicles by enhancing antioxidant enzymes and also reduce the ROS production (Hassan *et al.,* 2016) [14].

3.2 Superoxide dismutase (SOD)

Liver, Kidney and Testes

There was significant ($p< 0.05$) decrease in mean liver, kidney and testes SOD activity in MSG treated rats (Group II) when compared to the control rats (Group I) (Fig. 2) (Table. 2). These findings were in agreement with Onyema *et al.* (2012), Hassan (2014) [15], Onyema (2016), Singh and Ahluwala (2002) [24]. The decrease in levels of these enzymes might be due to MSG induced generation of reactive oxygen species (ROS) (or) by reducing the antioxidant cell defense system by depleting glutathione.

Statistically significant improvement was noticed in mean liver, kidney and testes SOD activity in ZnO NPs ameliorated rats (Group IV) when compared to the MSG treated rats (Group II) (Fig. 2) (Table. 2). These findings were in agreement with Afifi *et al.,* (2015). Increase in SOD levels in ameliorated group IV might be due to antioxidant property of ZnO NPs protects against oxidative stress by maintaining the cell membrane integrity from oxidative damage (Afifi *et al.,* 2015) and (Hassan *et al.,* 2016) [14] or increased Zn concentration in tissue produced from dissociation of ZnO NPs and it is an powerful antioxidant metal and core constituent of antioxidant enzymes like SOD and recognized protector of sulfhydryl group (Afifi *et al.*,2015) and detoxify free radicles by enhancing antioxidant enzymes and also reduce the ROS production (Hassan *et al.,* 2016) [14].

3.3 Catalase (CAT)

Liver, Kidney and Testes

Statistically significant ($p< 0.05$) decrease in mean liver, kidney and testes catalase activity was noticed in MSG treated rats (Group II) when compared to the control rats (Group I), (Fig. 3) (Table. 3). These findings were in agreement with Onyema *et al.* (2012), Hassan (2014) [15], Onyema (2016), Singh and Ahluwala (2002) [24]. The decrease in levels of these enzymes might be due to MSG induced generation of reactive oxygen species (ROS) (or) by reducing the antioxidant cell defense system by depleting glutathione.

A significant increase in mean liver, kidney and testes catalase activity was noticed in ZnO NPs ameliorated rats (Group IV) when compared to the MSG treated rats (Group II), (Fig. 3) (Table. 3). These findings were in agreement with Afifi *et al.,* (2015). Increase in CAT levels in ameliorated group IV might be due to antioxidant property of ZnO NPs protects against oxidative stress by maintaining the cell membrane integrity from oxidative damage (Afifi *et al.,* 2015) and (Hassan *et al.* 2016) [14] or increased Zn concentration in tissue produced from dissociation of ZnO NPs and it is an powerful antioxidant metal and core constituent of antioxidant enzymes like SOD and recognized protector of sulfhydryl group (Afifi *et al.,* 2015) and detoxify free radicles by enhancing antioxidant enzymes and also reduce the ROS production (Hassan *et al.*, 2016) [14].

Table 1: Mean (±SE) values of Glutathione peroxidase (GPx) (U/min/mg of protein) in rats of different experimental groups

Experimental groups	Mean (±SE) values of (GPx) (Liver) (U/min/mg of protein)	Mean (±SE) values of (GPx) (Kidney) (U/min/mg of protein)	Mean (±SE) values of (GPx) (Testes) (U/min/mg of protein)
Group I (Control)	26.95±0.12247[a]	26.95±0.69402[a]	27.85±0.36742[a]
Group II (MSG)	22.6±0.6532[b]	22.1±0.57155[b]	22.85±0.20412[b]
Group III (ZnONPs)	26.895±0.04082[a]	26.7±0.6532[a]	27.8±0.40825[a]
Group IV (MSG + ZnONPs)	26±0.08165[a]	26.2±0.24495[a]	26.85±0.04082[a]

Mean values with different superscripts differ significantly ($p< 0.05$)
ANOVA, SE = Standard Error

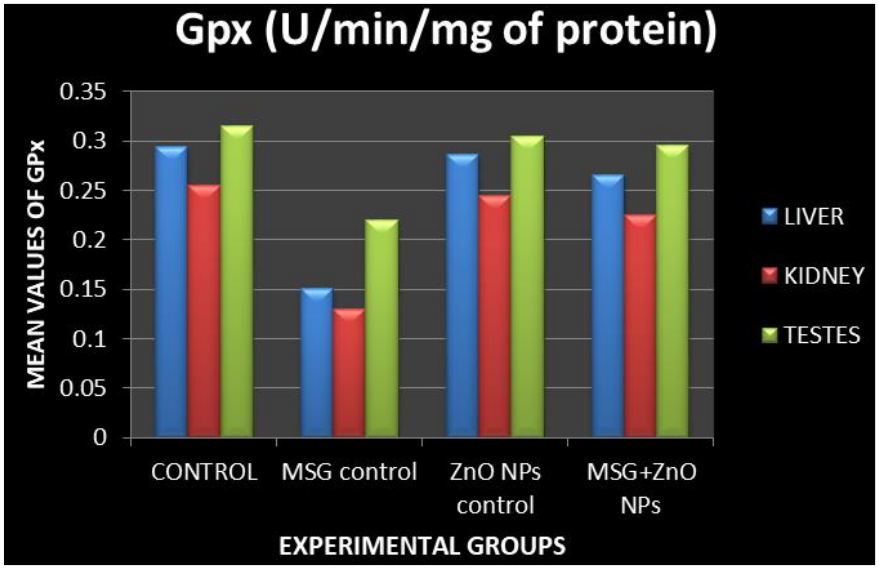

Fig 1: Mean values of Glutathione peroxidase (GPx) (U/min/mg of protein) in rats of different experimental groups

Table 2: Mean (±SE) values of Super oxide dismutase (SOD) (U/min/mg of protein) in rats of different experimental groups

Experimental groups	Mean (±SE) values of (SOD) (Liver) (U/min/mg of protein)	Mean (±SE) values of (SOD) (Kidney) (U/min/mg of protein)	Mean (±SE) values of (SOD) (Testes) (U/min/mg of protein)
Group I (Control)	15.38±0.45724[a]	14.38±0.45724[a]	13.375±0.4654[a]
Group II (MSG)	11.775±0.27353[b]	11.665±0.37151[b]	10.955±0.77159[b]
Group III (ZnONPs)	15.225±0.396[a]	14.575±0.35518[a]	13.175±0.35518[a]
Group IV (MSG+ZnONPs)	14.425±0.36334[a]	13.31±0.25087[a]	12.93±0.80017[a]

Mean values with different superscripts differ significantly ($p< 0.05$)
ANOVA
SE = Standard Error

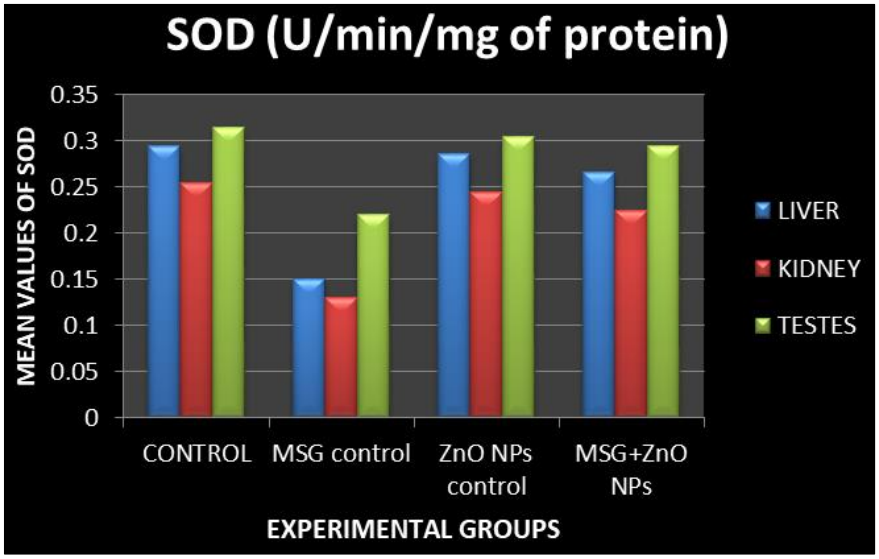

Fig 2: Mean values of Super oxide dismutase (SOD) (U/min/mg of protein) in rats of different experimental groups

Table 3: Mean (±SE) values of Catalase (CAT) (nM of H_2O_2 decomposed/min/mg of protein) in rats of different experimental groups

Experimental groups	Mean (±SE) values of (SOD) (Liver) (nM of H_2O_2 decomposed/min/mg of protein)	Mean (±SE) values of (SOD) (Kidney) (nM of H_2O_2 decomposed/min/mg of protein)	Mean (±SE) values of (SOD) (Testes) (nM of H_2O_2 decomposed/min/mg of protein)
Group I (Control)	0.294±0.02613[a]	0.255±0.02858[a]	0.315±0.0049[a]
Group II (MSG)	0.151±0.02858[b]	0.13±0.01633[b]	0.22±0.0816[b]
Group III (ZnONPs)	0.286±0.02041[a]	0.245±0.02858[a]	0.305±0.01225[a]
Group IV (MSG + ZnONPs)	0.266±0.01225[a]	0.225±0.01225[a]	0.295±0.01225[a]

Mean values with different superscripts differ significantly ($P < 0.05$)
ANOVA
SE = Standard Error

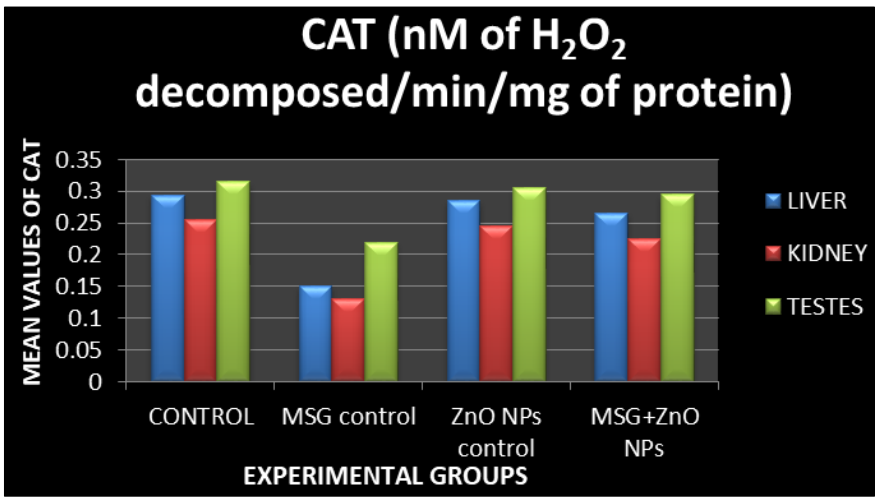

Fig 3: Mean values of Catalase (CAT) (nM of H_2O_2 decomposed/min/mg of protein) in rats of different experimental groups

4. Conclusion

The results of our current investigation showed that oral administration of Monosodium glutamate at dose rate of 5 g/kg b.wt/day orally for 6 weeks caused alterations in oxidative stress parameters in liver, kidney and testes and it was harmful to rats. It was produced numerous abnormalities

in oxidative stress parameters by increasing the formation of reactive oxygen species (ROS) and lipid peroxidation and decreasing antioxidant levels. The results of this investigation suggest that using ZnO NPs on a regular basis in human and veterinary medicine may be effective in protecting against the harmful and toxic effects of MSG.

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