

## Low Dose Monosodium Glutamate Induced Oxidative Damage and Histopathological Changes on the Renal of Male Rats (Dos Rendah Monosodium Glutamat Mengaruh Kerosakan Oksidatif dan Perubahan Histopatologi Renal Tikus Jantan)

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### ABSTRACT

*Monosodium glutamate (MSG) is a flavour enhancer commonly used in processed food to increase palatability. Several studies have reported that chronic exposure of MSG causes renal fibrosis via oxidative stress mechanism. However, till date, the effects of low dose of MSG on the oxidative stress status and its histopathological observation of renal are still unclear. A total of 18 male Sprague Dawley rats (170 – 200 g) were divided randomly into three groups consisted of the control (received distilled water = 1 ml/kg), MSG 60 (received 60 mg/kg MSG) and MSG 120 (received 120 mg/kg MSG) groups. All of the substances were given via force-feed oral for 28 consecutive days. At the end of the study, all rats were sacrificed and the renal were isolated for biochemical and histological evaluation. The superoxide dismutase (SOD) activity and protein carbonyl (PC) level showed significantly increased ( $p < 0.05$ ) in MSG 60 and MSG 120 group compared to the control group. However, no significant difference was found in glutathione (GSH) and malondialdehyde (MDA) level in all treated groups. The histology observation showed glomerulus shrinkage in MSG 60 and MSG 120 groups. In conclusion, these findings confirmed low dose of MSG-induced oxidative stress and histopathological changes on the renal of male Sprague-dawley rats. Accordingly, care must be taken on the intake of MSG in our daily basis.*

*Keywords: endogenous antioxidant, free radical, oxidative stress*

### ABSTRAK

*Monosodium glutamat (MSG) adalah perasa tambahan yang lazimnya digunakan dalam makanan yang diproses untuk meningkatkan keenakan makanan. Beberapa kajian telah melaporkan bahawa pendedahan kronik MSG boleh menyebabkan renal mengalami fibrosis melalui mekanisme tekanan oksidatif. Namun, sehingga kini, kesan MSG pada dos yang rendah terhadap status tekanan oksidatif dan pemerhatian histopatologi renal masih kurang dilakukan. Sebanyak 18 ekor tikus jantan Sprague Dawley (170 – 200 g) telah dibahagikan secara rawak kepada tiga kumpulan iaitu kumpulan kawalan (menerima air suling = 1 ml/kg), kumpulan MSG 60 (menerima MSG pada dos 60 mg/kg) dan kumpulan MSG 120 (menerima MSG pada dos 120 mg/kg). Kesemua bahan diberikan secara oral paksa selama 28 hari berturut-turut. Pada akhir kajian, semua tikus dikorbankan dan renal diambil bagi penilaian biokimia dan pemerhatian histologi. Aktiviti superoksida dismutase (SOD) dan aras protein karbonil (PC) menunjukkan peningkatan yang signifikan ( $p < 0.05$ ) pada kumpulan MSG 60 dan MSG 120 berbanding dengan kumpulan kawalan. Walau bagaimanapun, tiada perbezaan yang signifikan diperhatikan pada aras glutathione (GSH) dan malondialdehid (MDA) antara kumpulan kajian. Sementara itu, pemerhatian histologi menunjukkan pengecutan glomerulus berlaku pada kumpulan MSG 60 dan MSG 120. Kesimpulannya, hasil kajian mengesahkan MSG pada dos yang rendah mengaruh kerosakan oksidatif dan perubahan histopatologi pada renal tikus jantan Sprague Dawley. Oleh itu, kadar pengambilan MSG pada setiap hari harus diambil perhatian.*

*Kata kunci: Antioksidan endogenous, radikal bebas, tekanan oksidatif*

### INTRODUCTION

Monosodium glutamate (MSG) is one of the food additives commonly used in the Asia including Malaysia. MSG is a naturally occurring sodium salt amino acid that is commonly sold under the trade name A-One, Ajinomoto and Vedan (Egbonu et al. 2009; Waiz et al. 2015). It is used to improve the taste of food and provides a unique flavour (Freeman 2006). It has a unique umami taste, the fifth taste after the four basic tastes on a tongue that is a savoury or meat-like taste (Jinab & Hajeb 2010). The average intake

of MSG was reported at approximately 10 g/day, including those contained in processed foods and its use has been increasing around the world (He et al. 2011). According to Egbonu et al. (2009), improper labelling of MSG in food ingredients lead to high consumption among users.

When MSG is administered orally, it will dissolve in the saliva and dissociate to form glutamate amino acid and sodium (Scinska-Bienkowska et al. 20706). Glutamate is naturally available in high-protein foods such as fish, meat, dairy products, cheese and vegetables like tomatoes and mushrooms (Ramanathan et al. 2007). Glutamate is

the most excitatory neurotransmitters found in the brain. Physiologically, around 40% of this neurotransmitter is released out from the synapses in the central nervous system. Hence the excessive intake of exogenous glutamate may increase the excitatory effects leading to neurotoxicity (Ramanathan et al. 2007).

World Health Organisation (WHO) and Food and Drug Administration (FDA) classified MSG as Generally Recognized as Safe (GRAS) in which MSG is safe to be consumed. However, the usage of MSG still remains controversial due to its side effects on human health (Onyema et al. 2006). One of the effects is the famous Chinese restaurant syndrome that has symptoms like fatigue, diarrhoea, chest pain, vomit, migraine and stomach ache (Beyreuther et al. 2010). MSG has been reported to cause neurotoxic effect leading to brain cell damage, retinal degeneration, endocrine disorders and some pathological conditions such as stroke and epilepsy (Tawfik & Al-Badr 2012). Furthermore, MSG is also able to trigger asthma and various symptoms including headache and dry mouth (Freeman 2006). Beside its neurotoxic effects, the excessive and persistent use of MSG is also reported to cause weight gain in China (He et al. 2011). Furthermore, previous studies also found that repeated exposure of MSG causes oxidative stress to mammalian organs such as testis (Hamza & Al-Harbi 2014), male reproductive accessory organs (Abu Hanipah et al. 2018), brain (Zaidi & Banu 2004), erythrocytes (Ashaolu et al. 2011) and bone marrow (Yahya et al. 2018).

The kidney is vulnerable to oxidative stress due to high in oxidation reactions in mitochondria during detoxification and metabolism process (Daenen et al. 2018). Oxidative stress has been reported to occur in the kidney of rats exposed to MSG chronically by decreasing the endogenous antioxidants level and increasing the lipid peroxidation (Thomas et al. 2009; Paul et al. 2012). Besides, high doses of MSG has been shown to cause renal fibrosis in rats via oxidative stress mechanism (Sharma et al. 2013; Sharma et al. 2014). Oxidative stress is also known as the major culprit involved in advanced stage of kidney disease (CKD) which can accelerate with complications such as inflammation, atherosclerosis, anemia and hypertension (Daenen et al. 2018). All the above aberrations reported in previous studies were from the exposure of high doses of MSG range between 2000-8000 mg/kg of bodyweight and the effect of MSG at low doses on renal oxidative damage is poorly carried out. The chosen doses of MSG in the current study is limited to 120 mg/kg of body weight/day which is based on the daily safe intake (ADI) (WHO 1971). Therefore, the study was conducted to evaluate the effect of low doses of MSG on the oxidative damage and histopathological changes of renal in male Sprague-Dawley rats.

## MATERIALS AND METHODS

### CHEMICALS

MSG was obtained from the local market under the tradename, Ajinomoto. All other chemicals were purchased from Sigma-Aldrich, United States of America except for thiobarbituric acid was purchased from ICN Biomedicals, United States of America.

### ANIMALS AND TREATMENT

Male Sprague-Dawley rats (n=18), weighing between 170 and 200 g were obtained from the Laboratory Animal Resource Unit, Faculty of Medicine, Universiti Kebangsaan Malaysia (UKM), Kuala Lumpur, Malaysia and acclimatized for 7 days. The rats were kept in plastic cages that were exposed at room temperature, 12-hours light and dark cycle throughout the study period. All rats were provided with pellet diet and water ad libitum. The study was conducted under the approval from UKM Animal Ethics Committee (UKMAEC) with resolution number: FSK/2016/IZATUS/23-NOV./807-NOV.-2016-FEB.-2019. The rats were divided randomly into three groups of six rats per group. Group 1 (Control) received 1 ml/kg distilled water while, Group 2 (MSG 60) and 3 (MSG 120) received MSG at dose 60 mg/kg and 120 mg/kg, respectively. The MSG was given orally for 28 consecutive days between 9.00 am to 10.00 am to standardize the daily effects of MSG.

At the end of the study, all rats were fasted overnight, anaesthetised with a single intraperitoneal injection of ketamine and xylazine cocktail (KTX) and sacrificed before the isolation of the kidneys. The kidneys were washed using potassium chloride. The left kidneys were cut and soaked in formalin solution for histology observation. The other parts were minced and homogenized with buffer solution at ratio of 10 g/ml (w/v) at 8000 rpm for 20 minutes at 4°C. The supernatant was collected and kept at -40°C until further biochemical analysis.

### DETERMINATION OF ANTIOXIDANT LEVEL AND OXIDATIVE DAMAGE STATUS

For the determination of antioxidant level, assessment of superoxide dismutase (SOD) activity and glutathione (GSH) level were done using methods of Beyer and Fridovich (1987) and Ellman (1959), respectively. The reaction of superoxide with SOD in the samples led to the nitro blue tetrazolium (NBT) reduction and generated a purple coloured product which was detectable at 560 nm. The SOD activity was expressed as U/mg protein. The GSH level was measured based on the reaction of acid 5, 5'-dithiobis [2-nitrobenzoic] (DTNB) and GSH molecule to form a 5-thionitrobenzoic acid (TNB) and GS-TNB. The formation of a yellow coloured product was then measured at 412 nm. The GSH level was expressed as mmol/mg protein.

Meanwhile, the determination of oxidative damage status involves the assessment of the malondialdehyde (MDA) and protein carbonyl (PC) level to indicate lipid peroxidation and protein oxidation, respectively. The MDA was measured using the methods of Stocks dan Dormandy (1971) that is based on the reaction between thiobarbituric acid and MDA which presence in the sample. The formation of coloured compounds was then measured at 532 nm and the MDA level was expressed as nmol/mg protein. The PC level was measured using methods of Levine et al. (1990). After a serial of protein sedimentation, the protein pellets were dissolved in guanidine hydrochloride and the supernatant was measured at 366 nm. The PC level was expressed as nmol/mg protein.

#### HISTOLOGY OBSERVATION

Histology observation of the kidney was based on the method by Ochei dan Kolhatkar (2006). After the fixation process with 10% formalin, the samples were continued with tissue processing that involves dehydration, washing and impregnation using various concentration of alcohol. Then, the samples were embedded in paraffin wax before sectioning process. The tissue block were cut with the thickness of 5  $\mu$ m. All the slides were dried and stained with hematoxylin & eosin (H&E) staining and were observed using a light microscope under x40 magnification. The histopathological changes observed in the study had been proven by our histopathological expert.

#### STATISTICAL ANALYSIS

All data were analysed using Statistical Package for Social Sciences (SPSS) version 22. The data were tested for normality and examined with one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. All of the results were expressed as mean  $\pm$  SEM with the significant value  $p < 0.05$ .

### RESULTS AND DISCUSSION

#### ANTIOXIDANT LEVEL

Figure 1 showed the SOD activity in all experimental rats. The SOD activity was significantly increased ( $p < 0.05$ ) in MSG 120 and MSG 60 compared to the control group. Besides, there was also a significant increase ( $p < 0.05$ ) between MSG 120 group with MSG 60 group. SOD is the first line of antioxidant defence mechanism that neutralises the oxidant rapidly (Ighodaro & Akinloye 2017). Therefore, the rise in SOD activity in the study might be due to the compensatory mechanism as the enzymatic antioxidant was regulating the increased production of ROS (Ihsan et al. 2011). However, the result contradicted with other previous studies that showed a decreasing activity of SOD in rats treated with high doses of MSG (El-Wahab & Moram 2013; Mourad 2011; Vinodini et al. 2010). The excessive

formation of ROS due to the high concentration of MSG suppressed the abilities of SOD to act as antioxidant thus decreased SOD activity (El-Wahab & Moram 2013).

The GSH level did not show any significant changes ( $p > 0.05$ ) among all the treatment groups as shown in Figure 2. However, the result contradicted with other studies that showed decreased in GSH level of MSG-treated rats (Abdel-Reheim et al. 2014; del Carmen Contini et al. 2017; Zaidi & Banu 2004). The decrease in GSH level in the previous studies was due to the alteration of glutamate-cysteine antiporter system at the cell membrane. The system provided the medium of exchange between intracellular glutamate and the extracellular cysteine which involves in the synthesis of GSH (Bridges et al. 2012; Conrad & Sato 2012; Karihtala & Soini 2007).

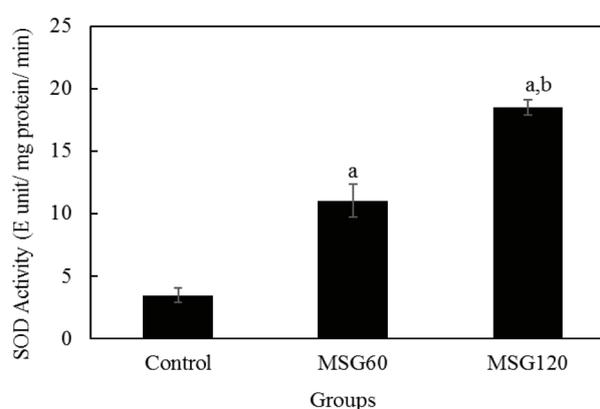


FIGURE 1. The SOD activity of experimental groups. <sup>a</sup> significantly different compared to the control group ( $p < 0.05$ ); <sup>b</sup> significantly different compared to MSG60 group ( $p < 0.05$ )

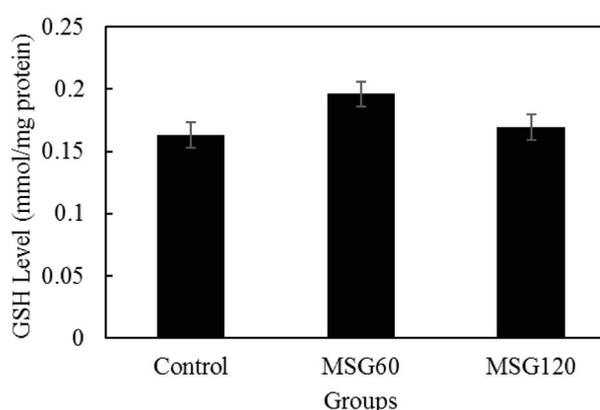


FIGURE 2. The GSH level of experimental groups

#### OXIDATIVE DAMAGE STATUS

The MDA level of experimental rats is shown in Figure 3. MDA level did not show any significant changes ( $p > 0.05$ ) among all treated groups. The finding was contradicting with other studies which found an increment in the MDA level of MSG-treated rats (Abdel-Reheim et al. 2014; Ortiz et al. 2006). High glutamate metabolism led to calcium ion influx ( $Ca^{2+}$ ) in mitochondria thus increased the ROS

production (Adam-Vizi & Starkov 2010). However, in the current study, lipid peroxidation yet not occur in the renal of rats due to the low dose of MSG. However, when compared to MDA, MSG administration had caused significantly increase in PC level ( $p < 0.05$ ) of MSG 120 group and MSG 60 group compared to the control group as shown in Figure 4. Besides that, there was also a significant increase of ( $p < 0.05$ ) PC between MSG 120 group with MSG 60 group. In line with the previous study done by Sharma et al. (2014) who also found an increment of PC in the MSG-treated rats. Some enzymatic proteins such as phosphatase, kinase and the metabolic enzyme are abundantly found in the kidney which these proteins are more susceptible to undergo oxidation compared to the other types of protein (Deavall et al. 2012). This might explain the increased of PC level in the kidney of MSG-treated rats.

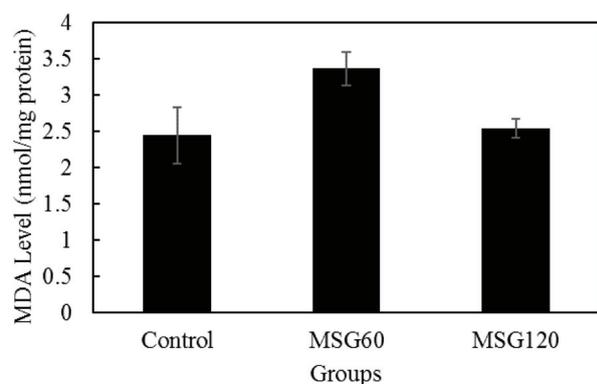


FIGURE 3. The MDA level of experimental groups

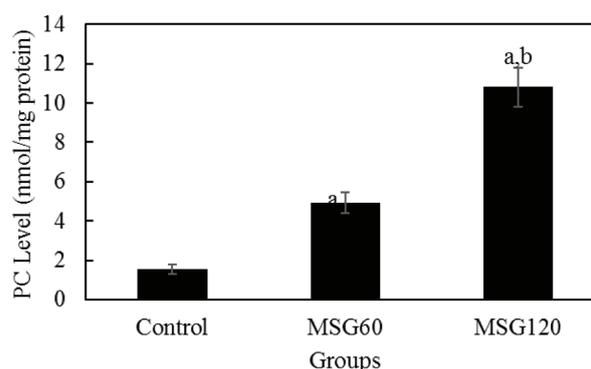


FIGURE 4. The PC level of experimental groups. <sup>a</sup> significantly different compared to the control group ( $p < 0.05$ ); <sup>b</sup> significantly different compared to MSG 60 group ( $p < 0.05$ )

#### HISTOLOGY OBSERVATION

Figure 5 showed the histology observation of the renal in all experimental groups. Normal histology of renal was shown in the control group which was characterised by the intact glomerular (G) structure and surrounded by the capsule of Bowman (BC). The presence of Bowman's space (BS) was also observed. There were proximal convoluted tubule (PCT) and distal convoluted tubule (DCT) layered with simple cuboidal epithelium surrounding the glomerulus. Meanwhile, the glomerulus of MSG 60 and MSG 120 had undergone shrinkage and the Bowman's space was widened based on Figure 1(b) and 1(c), respectively. Shi et al. (2011) reported that the usage of MSG increased the blood pressure

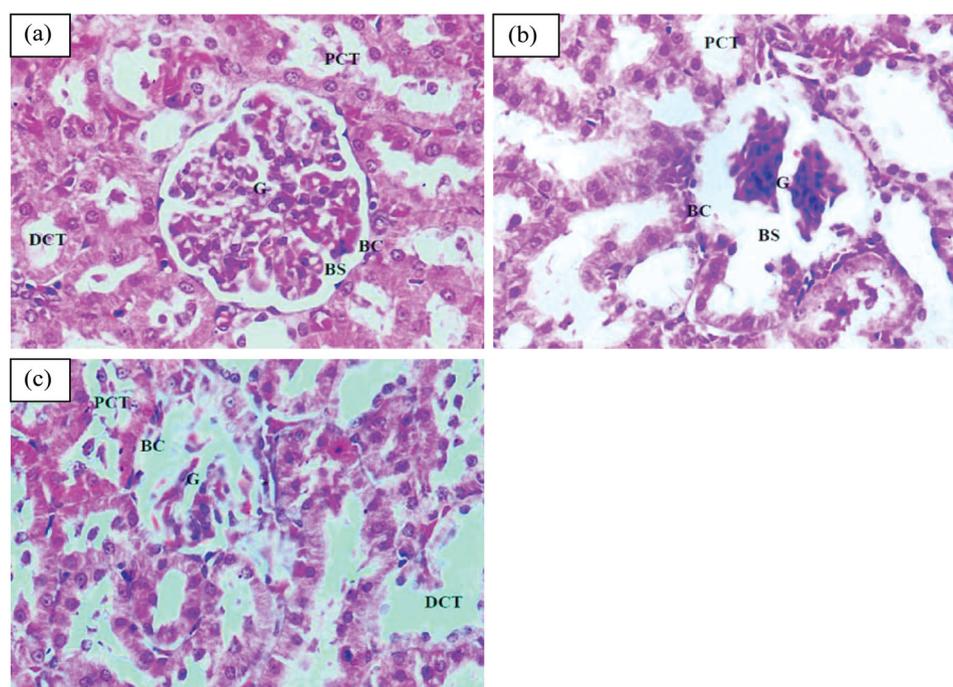


FIGURE 1. The renal histology of all experimental groups (H&E staining; X40 magnification). A normal morphology of renal was shown in control rats which consists of glomerulus, proximal convoluted tubule and distal convoluted tubule. The glomerulus was intact and surrounded by the capsule of Bowman (FIGURE 1a). A glomerulus was shrinkage in MSG60 (FIGURE 1b) and MSG120 groups (FIGURE 1c), respectively. (G: glomerulus; BC: Capsule of Bowman; BS: Space of Bowman; PCT: Proximal Convoluted Tubule; DCT: Distal Convoluted Tubule)

of human adult. Besides that, MSG administration was also found to cause increased of blood pressure in rats leading to alterations in the histology of renal (Onaolapo et al. 2013; Singh et al. 2005). Therefore, the glomerulus shrinkage observed in MSG-treated rats might be due to the increase in blood pressure as the glomerulus abundantly consists of blood capillaries. Automatically the space of Bowman would be increased as the glomerulus shrank.

## CONCLUSION

In conclusion, administration of low dose of MSG for 28 days continuously in experimental rat triggered oxidative stress in the renal as evidenced by the alteration in the enzymatic antioxidant mechanism and protein oxidation. MSG also altered the morphological of the kidney structure. Even at the low dose, MSG can triggered oxidative stress in the renal of the rat.

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