Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 180 (2023) 105-118 EISSN 2392-2192

Assessment of the effect of monosodium glutamate on oxidative stress and cancer in male and female rats

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ABSTRACT

Monosodium glutamate (MSG) is one of the commonly used food-additives in commercial foods and it is known to be responsible for various human disorders. We evaluated the effect of low and high doses of monosodium glutamate (MSG) on oxidative stress in both female and male rats, and its pathological role in various cancer types. A total of 120 wistar rats (60 female and 60 male) were used for this. The rats were divided equally into 3 groups (40 rats each) representing the various experimental durations (2, 4, and 6 months). Each of these groups were further divided equally into 8 subgroups containing 5 rats each, labeled as follows: female rats orally administered daily 1000, 2000, 3000 mg/kg body weight MSG representing low (LD), medium (MD) and high (HD) dose of MSG respectively while the control group was fed normal rat chow and water; also, the male rats were given the same treatments. The superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) levels were significantly decreased and the MDA levels increased in the male and female rats by the doses of MSG following short term and long term administration. Furthermore, the markers of pancreatic cancer (CA-19-9), colorectal cancer (CEA), ovarian cancer (CA-125) and prostate cancer (PSA) were significantly increased after administration of the various doses of MSG in the rats. All the doses of MSG negatively compromised the antioxidant defence system in both genders and enhanced the progression of colorectal, pancreatic, prostate and ovarian cancers without gender disparity. Although MSG offers enormous benefits to the food industry, continuous use of this food additive can have

(Received 01 April 2023; Accepted 02 May 2023; Date of Publication 06 May 2023)

detrimental effects on human health. Thus, the use of MSG in foods should be mitigated or if possible not used at all.

***Keywords*:** Monosodium glutamate, antioxidant enzymes, cancer markers, malondialdehyde

1. INTRODUCTION

Monosodium glutamate (MSG, $C_5H_8NO_4$, Na, CAS No. 142-47-2, Molecular Weight 169.11) is a sodium salt of naturally occurring (non essential) glutamic acid (Singh and Ahluwalia, 2003). MSG has been extensively used for a very long time as a flavor enhancer all over the world. MSG has a meaty taste caused by the contaminants that occur in crude glutamates, with a sweet-salty taste when in larger quantity, and 1% or more is subject to the generation of sweetish taste. Its solubility in water is 385,000 mg/L at 25°C (Budavari, 1989; O'Neil, 2001; Rim, 2017). Increased cellular levels of ROS elicit deleterious effects on biological molecules suchlike protein, lipid, DNA and RNA. The attack of ROS on macromolecules is one of the several mechanisms of oxidative stress. Oxidative stress play major role in the development of several pathological conditions suchlike cardiovascular diseases, diabetes mellitus, inflammatory disease, cancer, cataracts, Alzheimer's disease, autism and aging. There are elevations in the levels of ROS in conditions of environmental stress and cell dysfunction, and this eventually leads to the impairment of the body cells (Giles and Jacob, 2012; Geier et al., 2009a; Geier et al., 2009b). The role of MSG in the initiation of oxidative stress has been extensively reported (Fuentealba et al., 1994; Ahluwalia et al., 1996; Singh et al., 2003; Farombi and Onyema, 2006; Pavlovic et al., 2007; Egbuonu, 2022; Kesherwani et al., 2022; Kesherwani et al., 2022). Cancer is a disorder that is associated with body cells proliferation caused by failures in cellular modulation and inhibition in the progression of the cell cycle, leading to the generation of malignant tumor cells and possibly getting to the metastatic stage (Tyagi et al., 2017). The total number of deaths caused by cancer increased by 17% between 2005 and 2015 and is still on the rise till date (GBD, 2015). The cancer causing efficacy of MSG is palpable and has been confirmed in various studies (Al Hargan et al., 2003; Egbuonu et al., 2010; Hata et al., 2012; Ali et al., 2014; Boonnate et al., 2015; Oladipo et al., 2015). Cancer is currently regarded as the most death causing pathological disorder worldwide (Ohiagu et al., 2021). When antioxidant activities are overwhelmed by the actions of radicals, the antioxidant defence system is perturbed, giving rise to the emergence of various human pathological conditions (Chikezie et al., 2015; Dorcas, et al., 2022). Thus, the estimation of the cellular redox status and perturbation levels as well as the possible occurrence of cancer in various organs of the body is of great importance. The present study therefore assessed the effect of long and short term administration of MSG on antioxidant enzymes activities as well as malondialdehyde levels in both female and male rats, and its pathological role in colorectal, pancreatic, prostate and ovarian cancers.

2. METHODS

Sample Procurement and Preparation

Ajinomoto, which is a brand of monosodium glutamate (MSG) manufactured by Ajinomoto co., inc. Tokyo, Japan was purchased from Relief Market Owerri Imo State, Nigeria.

Aqueous extracts were obtained on weekly basis for a total period of 181 days within which the feeding was carried out in this study.

Animal Husbandry

A total of 120 weanly Wistar rats (70-78g) were obtained from Biochemistry Department, Federal University of Technology, Owerri, Imo State. The rats were allowed to acclimatize for 14 days, maintained *ad libitum* on water and growers mash. The rats were equally divided into three groups of 40 rats each, representing the various experimental durations of 2, 4, and 6 months. Each of these groups consisting of 40 rats were further divided equally into 8 subgroups each containing 5 rats, labelled, and orally administered according to the established LD_{50} as shown in Table 1 below. After completion of the feeding duration, the animals were sacrificed by cervical decapitation under mild anaesthesia of ethyl ether. Both blood (collected by cardiac puncture) and sera was prepared for analysis to be carried out.

Table 1. Dosing schedule of rats with MSG

Groups	Administration
1	Female rats administered daily 1000 mg/kg b.w (low dose) MSG
2	Female rats administered daily 2000 mg/kg b.w (medium dose) MSG
3	Female rats administered daily with 3000 mg/kg b.w (high dose) MSG
4	Female rats fed normal rat chow and water
5	Male rats administered daily 1000 mg/kg b.w (low dose) MSG
6	Male rats administered daily 2000 mg/kg b.w (medium dose) MSG
7	Male rats administered daily with 3000 mg/kg b.w (high dose) MSG
8	Male rats fed normal rat chow and water

Determination of Malondialdehyde (MDA)

According to Ohkawa et al. (1979), 0.5 ml of normal saline was pipetted into a test tube containing 0.5 ml of the serum sample. About 2 ml of thiobariturіc acid (TBA)/trichloroacetic acid (TCA) mixture was added, allowed to boil for 1 hour, cooled to room temperature, and centrifuged at 4000 rpm for 5 min. The clear supernatant was read at 535 nm. The concentration of MDA (nmol/ml) was calculated by using the following formula:

Concentration of the test = Abs(test) – Abs (blank) / 1.56 X 1000000

Determination of Catalase (CAT) activity

The CAT was determined using the method by Aebi (1984). 2.5 ml of distilled water was pipetted into test tube containing 0.5 ml H_2O_2, and about 40 µl sample was added and mixed

thoroughly. Rate of decomposition of H_2O_2 was read at 240 nm at 30 sec interval for 5 mins. CAT activity was calculated as follows:

(Decrease in absorbance X 100/1) divided by protein amount in mg divided by time in min.

Superoxide Dismutase (SOD) activity

The SOD activity was determined according to the method described by Marklund (1980). Sample extract (20 ml) and 2.5 ml of 0.05 M carbonate buffer (pH 10.2) were mixed together and equilibrated in the spectrophotometer. In addition, 0.3 ml of 0.3 mM freshly prepared adrenaline was added and mixed by inversion. The increase in absorbance at 480 nm was monitored spectrophotometrically at 30 seconds intervals for 3mins.

Glutathione peroxidase (GSH-Px) activity

The GSH-Px activity was determined through the modification of Paglia and Valentine (1967) method. The reaction medium was made up of potassium phosphate buffer 171 mM, sodium azide 4.28 mM, EDTA 2.14 mM, reduced glutathione 6 mM, NADPH 0.9 mM, and glutathione reductase 2 U.mL–1. The reaction occured at 22 °C (±1), starting with the addition of H_2O_2 0.72 mM. The absorbance of the samples was measured at 340 nm using a spectrophotometer. The measurements were taken every 15 seconds for 300 seconds. The GSH-Px enzymatic activity was expressed in enzymatic units per mL of sample ($U.mL^{-1}$).

Determination of Pancreatic Cancer Markers (CA 19-9)

The serum Pancreatic Cancer Markers (CA 19-9) were determined with a CA-19-9 ELISA kit according to the manufacturer's instructions (Accubind Elisa Microwells, Monobind Inc. Lakeforest, USA). Precisely 25 µl of the serum reference calibrator was pipetted into an assigned well and 100 µl of the biotinylated labeled antibody was added to each well. Afterwards the microplate was gently swirled for 30 secs and incubated at room temperature for 30 mins. Next, the contents of the microplate was decanted by using an adsorbent paper to blot dry, then 350 µl of the wash buffer was added and decanted by blot drying four more times.

In a similar order of addition of the reagents, 100 µl of the Ca 19-9 Tracer reagent was added to all wells, covered and incubated at room temperature for forty five (45) minutes. Next, the contents of the microplate was decanted again by using an adsorbent paper to blot dry, then 350 µl of the wash buffer was added and decanted by blot drying five more times.

In a similar order of addition of the reagents, 100 µl of the working signal reagent was added to all wells, covered and incubated at room temperature for five (5) minutes. The Relative Light Units for each well was thus read, and a plot of the Relative Light Unit for the sample, against the corresponding reference was used to estimate the CA19-9 concentration expressed as ng/ml.

Determination of Colorectal Cancer Markers (CEA)

The serum colorectal cancer markers (CEA) were determined with a CEA ELISA kit according to the manufacturer's instructions (Accubind Elisa Microwells, Monobind Inc. Lakeforest, USA). Precisely 25µl of the serum reference calibrator was pippeted into an assigned well and 100 µl of the CEA Tracer Reagent was added to each well. Afterwards the microplate was gently swirled for 30 secs and incubated at room temperature for 45 mins. Next,

the contents of the microplate was decanted by using an adsorbent paper to blot dry, then 350 µl of the wash buffer was added and decanted by blot drying four more times.

In a similar order of addition of the reagents, 100 µl of the working signal reagent was added to all wells and incubated for fifteen (5) minutes at room temperature. The Relative Light Units for each well was thus read, and a plot of the Relative Light Unit for the sample, against the corresponding reference was used to estimate the CEA concentration expressed as ng/ml.

Determination of Ovarian Cancer Markers (CA-125)

The serum ovarian cancer markers (CA-125) were determined with a CA-125 ELISA kit according to the manufacturer's instructions (Accubind Elisa Microwells, Monobind Inc. Lakeforest, USA). Precisely 25 µl of the serum reference calibrator was pippeted into an assigned well and 100 µl of the CA-125 Tracer Reagent was added to each well. Afterwards the microplate was gently swirled for 30secs and incubated at room temperature for 45 mins. Next, the contents of the microplate was decanted by using an adsorbent paper to blot dry, then 350µl of the wash buffer was added and decanted by blot drying four more times.

In a similar order of addition of the reagents, 100 µl of the working signal reagent was added to all wells and incubated for fifteen (5) minutes at room temperature. The Relative Light Units for each well was thus read, and a plot of the Relative Light Unit for the sample, against the corresponding reference was used to estimate the CA-125 concentration expressed as ng/ml.

Statistical Analysis

All data generated were subjected to statistical analysis. Values were reported as Mean ± Standard deviation (S.D) while one-way ANOVA was used to test for differences among treatment groups using Statistical Package for Social Sciences (SPSS) version 20 at 95% confidence interval ($p < 0.05$).

3. RESULTS

Antioxidant enzymes activities and malondialdehyde levels of female and male rats administered monosodium glutamate

The levels of superoxide dismutase, catalase, glutathione peroxidase and malondialdehyde of the female and male rats administered monosodium glutamate for 2, 4, and 6 months are shown in Table 2. The result showed that the administration of LD, MD and HD of MSG significantly ($p<0.05$) decreased the CAT levels in the female rats after 2, 4 and 6 months administration and in the male rats after 4 and 6 months administration respectively when compared with the control.

Only the administration of the HD of the MSG after 2 months significantly ($p<0.05$) decreased the CAT level in the male rats in comparison with the control.

All the doses of MSG significantly ($p<0.05$) decreased the SOD levels in the male rats after 2 and 4 months administration and in the female rats after 2 months administration respectively when compared with the control.

Similarly, the MD and HD of the MSG significantly ($p<0.05$) decreased the SOD levels in the male rats after 6 months administration and in the male rats after 4 and 6 months administration respectively in comparison with the control.

The administration of LD, MD and HD of MSG significantly ($p<0.05$) decreased the levels of GPx in the female rats after 2, 4 and 6 months as well as in the male rats after 4 and 6 months administration while only the MD and HD of MSG significantly ($p<0.05$) decreased the levels of GPx in the male rats after 2 months administration in comparison with the control.

No significant effect was observed on the MDA levels of the female rats administered the various MSG doses for 2 months, while the LD, MD and HD administration to the female rats for 4 and 6 months significantly ($p<0.05$) increased the MDA levels when compared with the control. All the doses of MSG significantly ($p<0.05$) increased the MDA levels after 4 months administration in the male rats; similarly, the MDA levels was also significantly ($p<0.05$) increased after MD and HD administration for 6 months while only the HD significantly ($p<0.05$) increased the MDA levels in the male rats for 2 months administration in comparison with the control.

Table 2. Superoxide dismutase, catalase, glutathione peroxidase and malondialdehyde levels of female and male rats administered monosodium glutamate

DURATION	GROUPS	SOD (U/gHb)	CAT (U/gHb)	GPx (U/L)	MDA (nmol/ml)
FEMALES					
2 MONTHS					
	C	20320.00±1583.91[a]	45.85±1.34[a]	76.70±2.26[a]	22.00±5.65[a]
	LD	16645.50±1378.15[b]	35.15±2.61[b]	63.45±2.19[b]	23.00±4.24[a]
	MD	16402.00±562.85[b]	25.85±2.47[c]	55.70±0.98[c]	25.50±6.36[a]
	HD	8880.50±1074.09[c]	25.40±5.09[c]	44.10±5.79[d]	20.00±4.24[a]
4 MONTHS					
	C	20835.00±739.63[ai]	47.50±2.12[a]	76.05±5.30[a]	35.00±2.82[b]
	LD	18103.00±506.28[b]	32.50±3.53[b]	66.95±4.45[b]	55.00±4.24[c]
	MD	16818.50±1144.80[b]	29.00±4.24[c]	54.40±5.51[c]	51.00±1.41[c]
	HD	11248.50±1646.85[c]	27.50±0.70[c]	50.85±2.05[c]	81.00±4.24[d]
6 MONTHS					
	C	38049.50±2358.20[d]	45.85±1.34[a]	70.70±2.26[a]	31.41±3.53[a]
	LD	34350.00±5389.56[dl]	35.15±2.61[b]	54.45±4.15[b]	40.00±4.24[b]
	MD	29948.50±2137.58[el]	25.85±2.47[c]	47.62±3.04[d]	52.50±6.36[c]
	HD	27647.00±1927.57[e]	25.40±5.09[c]	40.31±2.11[d]	93.00±4.24[e]

MALES					
2 MONTHS					
	C	19014.50±303.34^{fa}	28.00±4.24^{dc}	84.75±3.74^{e}	19.00±4.24^{a}
	LD	12820.50±2093.74^{g}	29.00±4.24^{df}	79.35±3.60^{ea}	18.00±1.41^{a}
	MD	12798.00±704.27^{g}	30.50±4.94^{df}	67.30±4.52^{fgb}	24.50±6.36^{a}
	HD	7973.50±504.16^{hc}	23.00±4.24^{c}	62.30±5.65^{fb}	36.50±4.94^{b}
4 MONTHS					
	C	23165.00±2787.41^{i}	44.00±4.24^{eg}	92.65±5.02^{g}	31.50±3.53^{d}
	LD	22791.00±2647.40^{i}	33.50±3.53^{f}	82.95±2.33^{e}	35.00±1.41^{b}
	MD	19061.00±311.12^{fa}	29.50±6.36^{df}	67.50±4.66^{fb}	40.00±2.82^{b}
	HD	15197.00±688.72^{j}	24.00±5.65^{dc}	70.15±3.32^{fb}	48.00±2.82^{c}
6 MONTHS					
	C	47060.50±1694.93^{k}	48.65±2.61^{e}	81.85±1.76^{e}	36.50±2.12^{b}
	LD	46037.00±4821.05^{k}	42.00±1.55^{g}	71.95±3.88^{ga}	40.50±2.12^{b}
	MD	32480.00±2539.92^{l}	33.20±2.54^{f}	61.95±2.61^{f}	52.50±3.53^{c}
	HD	33392.00±2527.19^{l}	26.15±2.89^{c}	52.45±2.19^{hb}	61.00±4.24^{e}

Values are means ± standard deviations, n=5. Values with different superscript letter(s) (a-l) down the column are significantly different ($p < 0.05$). SOD – Superoxide dismutase, CAT – Catalase, GPx – Glutathione peroxidise, MDA – Malondialdehyde

Cancer markers of female and male rats administered monosodium glutamate

Table 3 shows the cancer markers of female and male rats administered monosodium glutamate. No significant ($p>0.05$) change was observed in the levels of colorectal cancer markers (CEA) of the female rats as well as the male rats administered MSG for 2 months for all the doses.

The MD and HD MSG significantly elevated ($p<0.05$) the CEA levels when administered for 4 months in the female and male rats. After 6 months administration, all the doses significantly increased ($p>0.05$) the level of CEA after 6 months in the female rats while only the MD and HD significantly increased ($p<0.05$) the level of CEA in the male rats when compared with the control.

All the doses of MSG significantly increased ($p<0.05$) the level of pancreatic cancer marker (CA – 19-9) for 2, 4 and 6 months administration in both the female and male rats in comparison with the control.

The administration of LD, MD and HD of the MSG for 2 months caused no significant change ($p>0.05$) in the levels of the ovarian cancer marker (CA-125) while the MD and HD of the MSG significantly increased ($p<0.05$) the ovarian cancer marker levels after 4 months administration in the female rats when compared with the control. Furthermore, all the three doses of the MSG significantly increased ($p<0.05$) the ovarian cancer marker levels in the female rats after administration for 6 months when compared with the control.

The administration of MD and HD of MSG for 2 and 4 months significantly ($p<0.05$) increased the prostate specific antigen (PSA) levels while after 6 months, all the doses significantly ($p<0.05$) elevated the PSA concentration when compared with the control level.

Table 3. Levels of cancer markers of the female and male rats administered monosodium glutamate

DURATION	GROUPS	CEA (U/ml)	CA-19-9 (U/ml)	
FEMALES				
				CA-125 (U/ml)
2 MONTHS				
	C	0.75 ± 0.10^{a}	0.30 ± 0.02^{a}	0.80 ± 0.14^{a}
	LD	0.70 ± 0.17^{a}	1.10 ± 0.49^{b}	0.85 ± 0.21^{a}
	MD	0.70 ± 0.14^{a}	1.85 ± 0.23^{c}	0.75 ± 0.21^{ae}
	HD	0.75 ± 0.11^{a}	1.50 ± 0.25^{c}	0.95 ± 0.49^{a}
4 MONTHS				
	C	0.85 ± 0.07^{a}	0.65 ± 0.05^{d}	0.90 ± 0.28^{a}
	LD	0.85 ± 0.21^{a}	1.95 ± 0.07^{c}	1.05 ± 0.21^{a}
	MD	1.15 ± 0.07^{c}	1.85 ± 0.20^{c}	1.55 ± 0.21^{b}
	HD	1.60 ± 0.14^{de}	1.85 ± 0.07^{c}	1.85 ± 0.07^{bc}
6 MONTHS				
	C	1.45 ± 0.21^{d}	0.85 ± 0.07^{e}	2.10 ± 0.28^{c}
	LD	1.95 ± 0.21^{ef}	1.60 ± 0.01^{c}	3.80 ± 0.14^{d}
	MD	2.15 ± 0.21^{f}	2.45 ± 0.03^{f}	3.75 ± 0.21^{d}
	HD	2.60 ± 0.28^{g}	2.50 ± 0.01^{f}	4.00 ± 0.28^{d}

MALES				
				PSA (ng/ml)
2 MONTHS				
	C	0.75±0.07^{ha}	0.25±0.02^{ga}	0.31±0.00^{a}
	LD	0.75±0.07^{ha}	1.55±0.03^{hc}	0.36±0.18^{a}
	MD	0.75±0.07^{ha}	1.75±0.07^{hc}	0.48±0.14^{bd}
	HD	0.70±0.14^{ha}	1.45±0.21^{hjc}	0.52±0.12^{b}
4 MONTHS				
	C	0.95±0.21^{iac}	0.30±0.11^{id}	0.23±0.01^{c}
	LD	0.80±0.14^{ha}	1.05±0.49^{j}	0.20±0.01^{c}
	MD	1.30±0.42^{jcd}	1.35±0.37^{hj}	0.33±0.02^{a}
	HD	1.45±0.35^{jcd}	1.40±0.23^{hj}	0.44±0.03^{d}
6 MONTHS				
	C	1.35±0.49^{jd}	0.70±0.01ie	0.20±0.01^{c}
	LD	1.55±0.07^{jd}	1.65±0.21^{hc}	0.34±0.00^{a}
	MD	2.10±0.28^{kf}	1.70±0.14^{hc}	0.36±0.00^{a}
	HD	2.40±0.42^{kgf}	1.85±0.07^{hc}	0.49±0.02^{b}

Values are means ± standard deviations n=5. Values with different superscript letter(s) (a-k) down the column are significantly different ($p < 0.05$). CEA – Colorectal cancer marker, CA – 19-9 – Pancreatic cancer marker, CA-125 – Ovarian cancer marker, PSA – Prostate specific antigen

4. DISCUSSION

Monosodium glutamate (MSG) is one of the commonly used food-additives in commercial foods. MSG is extensively used and it is found in a high number of ingredients used daily in various homes as well as in processed foods seen in every market or grocery store (Niaz et al., 2018). MSG has been reported to be responsible for various human disorders including oxidative stress and cancer, however, oxidative stress is an inducer of cancer. Currently, cancer is the leading cause of death globally and there is a daily rise in the number of deaths caused by cancer (Ohiagu et al., 2021). Oxidative stress leads to DNA, protein, and/or lipid damage; chromosomal instability; genetic mutation as well as cell growth modulation; which eventually results in cancer (Klaunig et al., 2010).

Different disease conditions such as cardiovascular diseases, diabetes mellitus, tissue inflammation, sickle cell anaemia, cancer, cataracts, alzheimer's disease, autism, aging have been reported to be associated with increased generation of free radicals in conjunction with alteration in antioxidant defense capabilities; indicating the contributive role of reactive oxygen species in the onset, escalation and pathological complications of diseases (Yakubu et al., 2004; Shaikh and Shrivastava, 2014).

From this study, the MSG-induced suppression of the antioxidant enzymes was profound. The findings of this study showed that even minimal amounts of MSG for two months compromised the antioxidant defence system. Superoxide dismutase catalyzes the dismutation of superoxide anion to hydrogen peroxide, for further detoxification to water by CAT (Mukherjee et al., 2003). The decrease in activity of SOD after treatment with MSG in this present study implied that the synthesized antioxidant enzyme had been suppressed. The decreased activity of CAT in the MSG treated animals is an indication of alteration of CAT activity in the degradation of hydrogen peroxide. Toxic hydroxyl radicals which contribute significantly to oxidative stress can be generated from hydrogen peroxide (Kaushik and Kaur, 2003; Pavlovic et al., 2007). The report of Kesherwani et al. (2022) and Egbuonu (2022) corresponds to the findings of this study for the SOD and CAT levels.

From the results, the GPx activities were affected after administration of low and medium dose of MSG both at long and short periods, whereas the MDA levels were distorted majorly with administration beyond 2 months. Similarly, the lowest dose of MSG used in the study by Ahluwalia et al. (1996), 4 mg/kg body weight, significantly increased GPx activities and lipid peroxidation. Also, Kesherwani et al. (2022) reported significant higher level of MDA after administration of 100 mg/kg bodyweight of MSG, which was considered as low dose in their study. This simply indicated that cellular components were at risk with prolonged administration of MSG. GPx is regarded as one of the key enzymes for the detoxification of reactive oxygen species. Fuentealba et al. (1994) posited that glutathione levels become altered in advanced exposure to toxicants. MDA is an end-product of lipid peroxidation triggered by ROS (Pavlovic et al., 2007). Lipid peroxidation causes the alterations in the polyunsaturated fatty acids of the cellular membrane and thus decreases the fluidity of the membrane, which is required for the proper functioning of the cell (Latha and Babu, 2001). Increase in the levels of malondialdehyde (MDA) especially after prolonged consumption of MSG even at low doses provides clues as to the degree of lipid peroxidation caused. The findings of this study also implied that even prolonged low level consumption of MSG, predisposes the body to cellular damage and excessive lipid peroxidation.

Carcinoembryonic Antigen (CEA) is a recommended prognostic biomarker in colorectal cancer for the diagnosis of tumor and assessing the extent of response to therapy. Elevated levels of CEA is a typical indication of the progression of colorectal cancer (Campos-da-Paz et al., 2018). MSG elevated the colorectal cancer marker, CEA, after prolonged administration in this study. This means that moderate amounts when administered in short duration was not carcinogenic with regards to colorectal cancer while continuous use of MSG predisposes the individual to possible occurrence of coloerectal cancer. The study by Hata et al. (2012) reported that obese and diabetic mice subjected to MSG treatment were highly susceptible to azoxymethane-induced colorectal carcinogenesis. Al Hargan et al. (2003) studied cancer cell viability using MTT assay and they reported a significant increase in the number of viable cells after treatment with MSG for 24 h using different concentrations (0.5, 1.0, 10, 50, and 100 mM), and they finally concluded that MSG confers a pro-proliferative effect on colorectal

cancer cells. Carbohydrate antigen 19-9 (CA19-9) is the most current and effective widely used pancreatic cancer biomarker (Kim et al., 2020; Humphris et al., 2012; Goonetilleke et al., 2007). From the findings of this study, MSG increased the concentrations of the pancreatic cancer marker, CA19-9, irrespective of the dose, duration, and sex. This meant that MSG consumption is a major predisposing factor to pancreatitis. Similar observations were made by Boonnate et al. (2015) who posited that daily MSG dietary consumption was associated with enhanced β-cell hemorrhages and fibrosis. The findings by Leshchenko et al. (2012) showed that continuous prolonged intake of monosodium glutamate causes serious damages to the pancreas.

Ovarian cancer has been reported as the leading cause of death in women diagnosed with gynecological cancers. Generally, it is considered as the fifth most frequent cause of death in women (Arora et al., 2020). The serum levels of Cancer Antigen 125 (CA125), also referred to as Carbohydrate Antigen 125 are increased in 50% of early-stage tumours, which are mostly type I ovarian cancers and 92% of advanced-stage tumours, which are mostly type II ovarian cancers (Van Haaften-Day et al., 2001; Charkhchi et al., 2020). In the present study, MSG-induced increase of the ovarian cancer marker, CA-125, in a dose and duration dependent manner.

The levels of CA-125 increased as the feeding duration stretched to 6 months especially with the medium and high doses. This observation agreed with the report of Ali et al. (2014) who showed that MSG-treated rats showed degenerative changes of the ovary with many atretic follicles and vacuolated stroma. The study by Oladipo et al. (2015) reported the deleterious effects of MSG at high doses in the ovaries of Sprague-dawley rats by inducing considerable structural changes including degenerated follicles, oocytes and medulla with vacuoles having congested blood vessels in these ovaries.

Screening for prostate cancer using serum prostate-specific antigen (PSA) is crucial for the detection of the emergence of prostate cancer at an early and intervenable stage which is amenable to curative treatment and amelioration of the occurrence of disease-specific mortality (Lin et al., 2008; Vickers, 2017; Ilic et al., 2008). This study investigated the potentials of MSG to cause alterations in the PSA levels of Wistar rats. In this study, both medium and high dose MSG elevated the PSA levels when compared to the control rats even at the shortest duration of time. The study by Egbuonu et al. (2010) revealed the potential of MSG in altering the functional capacity of the prostate as it significantly elevated the level of the biomarker, prostatic acid phosphatase. MSG mitigated the reproductive ability of male mice in the study carried out by Pizzi et al. (1977).

5. CONCLUSIONS

All the doses of MSG including 1000 mg/kg b.w, 2000 mg/kg b.w and 3000 mg/kg b.w for low, medium and high doses respectively used in this study compromised the antioxidant defence system in both genders by suppressing the activities of the antioxidant enzymes and increasing the level of malondialdehyde, an indication of excessive lipid peroxidation. Furthermore, MSG also enhanced the progression of colorectal cancer and pancreatic cancer without gender disparity as well as prostate cancer and ovarian cancer in male and female rats respectively. Although MSG offers enormous benefits to the food industry, continuous use of this food additive can have detrimental effects on human health. Thus, the use of MSG in foods should be mitigated or if possible not used at all.

Acknowledgement

The authors are grateful for the technical assistance offered by Mr. C.O. Kabiri, Senior Laboratory Technologist, Department of Biochemistry, Faculty of Science, Imo State University Owerri, Nigeria.

References

[1] Ahluwalia P, Tewari K, Choudhary P. Studies on the effects of monosodium glutamate (MSG) on oxidative stress in erythrocytes of adult male mice. *Toxicol Lett.* 1996; 84(3): 161-5

[2] Al Hargan A, Daghestani MH, Harrath AH. Alterations in APC, BECN1, and TP53 gene expression levels in colon cancer cells caused by monosodium glutamate. *Braz J Biol*. 2023; vol. 83, e246970

[3] Ali AA, El-Seify GH, El Haroun HM, Mohammed Soliman MA. Effect of monosodium glutamate on the ovaries of adult female albino rats and the possible protective role of green tea. *Menoufia Med J.* 2014; 27: 793-800

[4] Arora T, Mullangi S, Lekkala MR. Ovarian Cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan

[5] Boonnate P, Waraasawapati S, Hipkaeo W, Pethlert S, Sharma A, Selmi C, Prasongwattana V, Cha'on U. Monosodium Glutamate Dietary Consumption Decreases Pancreatic β-Cell Mass in Adult Wistar Rats. *PLoS One* 2015; 10(6): e0131595

[6] Budavari S. in The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals (Merck and Co., USA, 1989).

[7] Campos-da-Paz M, Dórea JG, Galdino AS, Lacava ZGM, de Fatima Menezes Almeida Santos M. Carcinoembryonic Antigen (CEA) and Hepatic Metastasis in Colorectal Cancer: Update on Biomarker for Clinical and Biotechnological Approaches. *Recent Pat Biotechnol.* 2018; 12(4): 269-279

[8] Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and Ovarian Cancer: A Comprehensive Review. *Cancers*. 2020; 12(12): 3730

[9] Chikezie PC, Ojiako OA, Ogbuji AC. Oxidative stress in diabetes mellitus. *Int J Biol Chem.* 2015; 9(3): 92-109

[10] Dorcas Aanuoluwapo Adeleke, Peace Abiodun Olajide, Oluwakemi Semiloore Omowumi, Darasimi Deborah Okunlola, Anjolaoluwa Maryann Taiwo, Babatunde Oluwafemi Adetuyi, Effect of Monosodium Glutamate on the Body System. *World News of Natural Sciences* 44 (2022) 1-23

[11] Egbuonu ACC, Ejikeme PM, Obasi LN. Monosodium glutamate: Potentials at inducing prostate pathologies in male Wistar rats. *AJB.* 2010, 9(36); 5950-54

[12] Egbuonu ACC. Antioxidant Outcomes of L-arginine on Monosodium Glutamate-induced Oxidative Stress in Rats' Testes. *NJBMB.* 2022; 37(2):128–132

[13] Farombi EO, Onyema OO (2006) Monosodium glutamate-induced oxidative damage and genotoxicity in the rat: modulatory role of vitamin C, vitamin E and quercetin. *Hum Exp Toxicol.* 25: 251–259

[14] GBD (2015). Mortality and causes of death collaborators: global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the global burden of disease study 2015. *Lancet.* 388(10053): 1459–1544

[15] Geier DA, Kern JK, Garver CR, Adams JB, Audhya T, Nataf R, Geier MR. Biomarkers of environmental toxicity and susceptibility in autism. *J Neurol Sci.* 2009b; 280(1-2): 101-8

[16] Geier DA, Kern JK, Garver CR, Adams JB, Audhya T, Geier MR. A prospective study of transsulfuration biomarkers in autistic disorders. *Neurochem Res.* 2009a; 34(2): 386-93

[17] Giles GI, Jacob C. Reactive sulfur species: an emerging concept in oxidative stress. *Biol Chem.* 2002; 383: 375–88

[18] Goonetilleke K, Siriwardena A. Systematic review of carbohydrate antigen (CA19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol.* 2007; 33: 266–70

[19] Hata K, Kubota M, Shimizu M, Moriwaki H, Kuno T, Tanaka T, Hara A, Hirose Y. Monosodium glutamate-induced diabetic mice are susceptible to azoxymethane-induced colon tumorigenesis. *Carcinogenesis.* 2012; 33(3): 702-7

[20] Humphris JL, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, Colvin EK, Nagrial A, Chin VT, Chantrill LA, Samra JS, Gill AJ, Kench JG, Merrett ND, Das A, Musgrove EA, Sutherland RL, Biankin AV; NSW Pancreatic Cancer Network. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol.* 2012; 23(7): 1713-22

[21] Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, Agoritsas T, Dahm P. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. *BMJ.* 2018; 362: k3519

[22] Kaushik S, Kaur J. Chronic cold exposure affects the antioxidant defense system in various rat tissues. *Clin Chim Acta.* 2003; 333: 69–77

[23] Kesherwani, R., Bhoumik, S., Kumar, R. *et al.* Monosodium Glutamate Even at Low Dose May Affect Oxidative Stress, Inflammation and Neurodegeneration in Rats. *Ind J Clin Biochem* (2022). https://doi.org/10.1007/s12291-022-01077-1

[24] Kim H, Kang KN, Shin YS, Byun Y, Han Y, Kwon W, Kim CW, Jang JY. Biomarker Panel for the Diagnosis of Pancreatic Ductal Adenocarcinoma. *Cancers (Basel)*. 2020; 12(6): 1443

[25] Latha B, Babu M. The involvement of free radicals in burn injury: a review. *Burns.* 2001; 27: 309–17

[26] Leshchenko IV, Shevchuk VH, Falalieieva TM, Beregova TV. The influence of long-term monosodium glutamate feeding on the structure of rats pancreas. *Fiziol Zh.* 2012; 58(2): 59-65

[27] Lin K, Lipsitz R, Miller T, Janakiraman S, U.S. Preventive Services Task Force Benefits and harms of prostate-specific antigen screening for prostate cancer: an

evidence update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2008; 149: 192-9

[28] Niaz K, Zaplatic E, Spoor J. Extensive use of monosodium glutamate: A threat to public health? *EXCLI J.* 2018; 17: 273-78

[29] O'Neil, M. J. in The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals 13th Edn (White-house Station, USA, 2001).

[30] Ohiagu FO, Chikezie PC, Chikezie CM, Enyoh CE. Anticancer activity of Nigerian medicinal plants: a review. *FJPS.* 2021; 7: 70

[31] Oladipo I C, Adebayo EA, Kuye, OM. Effects of Monosodium Glutamate in Ovaries of Female Sprague-Dawley Rats. *Int J Curr Microbiol App Sci.* 2015; 4(5): 737-745

[32] Pavlovic V, Pavlovic D, Kocic G, Sokolovic D, Jevtovic-Stoimenov T, Cekic S, Velickovic D. Effect of monosodium glutamate on oxidative stress and apoptosis in rat thymus. *Mol Cell Biochem.* 2007; 303(1-2): 161–6

[33] Pizzi WJ, Barnhart JE, Fanslow DJ. Monosodium glutamate admlinistration to the newborn reduces reproductive ability in female and male mice. *Science.* 1977; 196(4288): 452-4

[34] Rim K.-T. Toxicological evaluation of MSG for the manufacturing workers' health: A literature review. *Toxicol Environ Health Sci.* 2017; 9(1): 1–11

[35] Shaikh H, Shrivastava VK. Effects of streptozotocin induced diabetes mellitus type 1 on the rat brain antioxidant status and activity of acetyl-cholinesterase: a novel and potential treatment by Vitex negundo. *Int J Pharm Pharm Sci*. 2014; 6(10): 252-6

[36] Singh K, Ahluwalia P. Studies on the Effect of Monosodium Glutamate [MSG] Administration on Some Antioxidant Enzymes in the Arterial Tissue of Adult Male Mice. *J Nutr Sci Vitaminol,* 2003; 49: 145-8

[37] Singh P, Mann KA, Mangat HK, Kaur G. Prolonged glutamate excitotoxicity: effects on mitochondrial antioxidants and antioxidant enzymes. *Mol Cell Biochem.* 2003; 243(1-2): 139-45

[38] Tyagi N, Sharma GN, Shrivastava B, Saxena P, Kumar N. Medicinal plants: used in anti-cancer treatment. *Int J Res Dev Pharm L Sci.* 2017; 6(5): 2732–39

[39] Van Haaften-Day C, Shen Y, Xu F, Yu Y, Berchuck A, Havrilesky LJ, de Bruijn HWA, van der Zee AGJ, Bast RC, Hacker NF. OVXL, macrophage-colony stimulating factor, and CA-125-II as tumor markers for epithelial ovarian carcinoma a critical appraisal. *Cancer.* 2001, 92: 2837–44

[40] Vickers AJ. Prostate cancer screening: time to question how to optimize the ratio of benefits and harms. *Ann Intern Med.* 2017; 167: 509-10

[41] Yakubu MA, Sofola OA, Igbo I, Oyekan AO. Link between free radicals and protein kinase C in glucose-induced alteration of vascular dilation. *Life Sci.* 2004; 75(24): 2921-2932