Original Research Article

Amelioration of monosodium glutamate- induced testicular damage and infertility in male rats by water melon and cantaloupe seeds extract and juices

ABSTRACT

Aims: Monosodium glutamate (MSG) is extensively used as food additive and flavor enhancer, there is a growing concern that this may affect the male reproductive system and fertility. The objective of this study is to investigate the effect of MSG on fertility and testes of mature male rats and the ameliorative role of water melon and cantaloupe (seeds extract and juices).

Study design: Thirty-six male Sprague - Dawely rats (150-180g) were randomly assigned into six groups (n=6). Group (1): orally administered with distilled water. Group (2): orally administered with 60mg/kg of MSG. Groups (3 and 4): orally administered with 60mg/kg of MSG + 200mg/kg of water melon seeds extract and juice respectively. Groups (5 and 6): orally administered with 60mg/kg of MSG + 200mg/kg of cantaloupe seeds extract and juice respectively.

Results: Results showed that administration of MSG for 6 weeks caused *abnormalities of semen characteristics, increased DNA damage and up-regulation of caspase3 expression in the testes tissue. Also, the levels of plasma sex hormones were decreased and the oxidant-antioxidant status was disturbed, moreover, MSG caused alteration in the histopathological structures of testicular tissue. Administration of seeds extract or juices of water melon and cantaloupe almost corrected the biochemical and histopathological alteration produced by MSG.*

Conclusion: this study concluded that water melon and cantaloupe seeds and juice extracts have an ameliorative role against MSG-induced testicular damage and infertility in rats.

Keywords: Monosodium glutamate, Testes, male infertility, watermelon, cantaloupe, *Citrullus lanatus, Cucumis Melo L.*, antioxidant.

1. INTRODUCTION:

Monosodium glutamate (MSG), a white crystalline powder, is the sodium salt of a naturally occurring non-essential amino acid, glutamic acid. MSG contains 78% of glutamic acid, 22% of sodium and water. Glutamate is the main component of many proteins and peptides of most tissues [1]. Moreover, glutamate occurs naturally in various foods including poultry, cheeses, meat broths, seafood and vegetables. MSG is a widely used flavor enhancing food additive. When MSG is added to food, it provides a flavoring function similar to the naturally occurring free glutamate which differs from the four classic tastes of sweet, sour, salty and bitter [2]. Commercial production of MSG requires large vast of harmless bacteria to convert glutamate from sugars or starches into glutamic acid. This acid is then allowed to evaporate, and the remaining

brownish white or white crystals are sold as pure MSG [3]. It is present in a wide variety of processed foods including prepared meals, flavored chips and snacks, marinated meats, flavored tuna, soups or sauces (canned, packed), bottled soy or oriental sauces, fresh sausages, and stuffed or seasoned chicken, vegetarian burgers, luncheon chicken and turkey and sausages. It may be present in packaged foods without appearing on the label [4].
Various studies have shown that Monosodium glutamate is neurotoxic, nephrotoxic, hepatotoxic, and gonadotoxic [5, 6 ,7]. These molecules can contribute to the oxidative stress. Moreover, MSG has a toxic effect on the testis by causing a significant oligozoospermia and increases abnormal sperm morphology. It has been implicated in male infertility by causing testicular hemorrhage, degeneration and alteration of sperm cell population and morphology [8].

Plant extracts have been used as medicines, nutrition, and other industrial purpose. The natural products today symbolize safety in contrast to the synthetic drugs. A melon belongs to the family Cucurbitaceae with an edible fruit. Melons have their origin in Africa and southwest Asia, but they later started appearing in Europe at the end of the Roman Empire [9].

The Watermelon (Citrullus lanatus) is a member of the family Cucurbitaceae. The juice or pulp from watermelon is used for human consumption, while rind and seeds are major solid wastes. The rind is utilized for products such as pickles and preserves, as well as for extraction of pectin) [10]. Melon fruit contains large quantities of seeds. The kernels are sometimes used as dressing for bread, cake, sweetmeats and snack foods, often in place of almonds and pistachio. The seeds can be cooked and dried and served as snacks e.g. Egypt, Iran and might also be cooked, ground (West Africa) and fermented for use as a flavor enhancer in gravies and soups [11]. Watermelon is one of such medicinal plant that has attracted scientific interest due to its bioactivities. C. lanatus sp. is a natural source of antioxidants such as beta-carotene, vitamin C, citrulline, B vitamins, especially B1 and B6, as well as minerals such as potassium and magnesium. Watermelon juice with red flesh is an excellent source of lycopene, having about 40% higher lycopene content than raw tomatoes [12]. The tissue protective effects of watermelon juice have been previously reported. The anti-inflammatory, antioxidant, anti-ulcerogenic and anti-diabetic effects of watermelon have also been documented [13, 14]. The constituents of watermelon juice are known for their free radical scavenging activities and antioxidant effects [15]. These functional ingredients act as protection against chronic health problems like cancer and cardiovascular disorders [16].

Cantaloupe melon (Cucumis melo L.) also belongs to Cucurbitaceae family. This fruit is one of the most consumed crops worldwide due to its sweetness, juicy taste, pleasing flavor, and it is known for nutritive and medicinal properties of pulp. It is rich in important vitamins, such as riboflavin, thiamine and folic acid. It is also a good source of pro-vitamin A and vitamin C [17]. It has been shown to possess useful medicinal properties such as analgesic, anti-inflammatory, anti-oxidant, anti-ulcer, anti-cancer, anti-microbial, diuretic, anti-diabetic, and anti-fertility activity [18].

During fruit consumption and industrial processing, a large quantity of waste materials is produced, such as melon peels and seeds. These by-products are still rich in phytochemicals, such as polyphenols, carotenoids, and other biologically active components, which have a positive influence on health and preventing aging effects. Among all, polyphenol compounds show antioxidant activity, delaying or inhibiting the oxidation of lipids and other molecules, so protecting cells from damage by reactive oxygen species (ROS) [19].

The main objective of the present work is to study the protective effect of water melon and Cantaloupe melon juices and aqueous seed extracts against testicular toxicity induced by MSG.

2. MATERIAL AND METHODS:

2.1. Animals:

Adult male albino rats (Sprague-Dawely strain) weighing 150-180 g were obtained from El -Salam Farm, Giza, Egypt. The experiment was carried out in the Animal House of the Medical Research Center, Ain Shams University, Cairo, Egypt. Thirty-six rats were individually housed in stainless steel cages with constant controlled environments of temperature 25°C ± 5°C, air humidity 55%±10% and 12/12 hours light/dark cycle and offered the standard commercial pellet diet and drinking water *ad libitum* for one week as adaptation period, then all rats were kept on commercial pellet diet and drinking water ad- libitum to the end of the experiment (6 weeks).

2.2. Chemicals:

Monosodium-glutamate (C5H9NO4·Na) was purchased from Top Chem company, Cairo, Egypt.

2.3. Plant materials:

The fruits of water melon and cantaloupe were purchased from the ministry of agriculture, Cairo, Egypt. The watermelon and cantaloupe fruits were washed, the flesh isolated from the rind and the seeds were removed. Juices of watermelon and cantaloupe were prepared from chopped fruits using household juice extractor.

The healthy-looking seeds collected from watermelon and cantaloupes were oven-dried at 35°C, to a constant weight. The dried seeds were reduced into fine powder using a laboratory grinding hand mill. The powder was soaked in water for48hours at the ratio of 1g to 20ml of water. Mixture was stirred at 1hour interval and kept overnight. Mixture was separated by filtering it to get a clear solution. The extract was concentrated using a Rotary evaporator. The concentrated water extracts of watermelon and cantaloupe seeds were stored in sealed bottles in refrigerator at 4°C until used [20].

2.4. Experimental design:

Animals were randomly assigned into six groups of (n = 6), as follow:

Group1 (control group): Rats were orally given distilled water by gastric tube daily.

Group 2(MSG): Rats orally given 60 mg/kg b.wt of MSG by gastric tube daily.

Group 3(WMS): Rats orally given 60 mg/kg b.wt of MSG +200 mg/kg b.wt of watermelon seeds extract by gastric tube daily.

Group 4(WMJ): Rats orally given 60 mg/kg b.wt of MSG +200 mg/kg b.wt of watermelon juice by gastric tube daily.

Group5 (CPS): Rats orally given 60 mg/kg b.wt of MSG + 200 mg/kg b.wt of cantaloupe seeds extract by gastric tube daily.

Group 6(CPJ): Rats orally given 60 mg/kg b.wt of MSG + 200 mg/kg b.wt of cantaloupe juice by gastric tube daily.

2.5. Samples collection:

After 6 weeks of treatment, the animals were fasted for 24 hours prior to sacrifice. Animals were anaesthetized using ether and blood was collected from hepatic portal vein into heparinized tubes and centrifuged at 1500 rpm for 15 min for obtaining plasma. The testes along with the caudal epididymis and seminal vesicles were removed and washed with saline solution and dried. The caudal epididymis was separated from the testes and lacerated to collect the semen with a microscope glass slide for analysis of sperm characteristic. The seminal vesicles and one testis from each rat were immediately fixed in 10% formalin solution for microscopic examination, while the second one stored frozen at -20°C until used for the tissue biochemical analysis.

2.6. Semen Analysis:

The total number of sperms was counted using counting chamber (haemocytometer), expressed as number of sperm cells in millions/ml. The fluid from the caudal epididymis was diluted with saline solution to 0.5 ml, in order to determine sperm motility, which was expressed in percentage (%). Abnormal features of sperm morphology were observed and categorized as tail defects, neck and middle piece defects, and head defects; then the findings were expressed as percentage (%) of morphologically abnormal sperm.

2.7. Comet assay for determination of DNA damage in testes tissue:

0.5 g of crushed samples were transferred to 1 ml ice-cold PBS., this suspension was stirred for 5 min then filtered. Cell suspension was mixed with low-melting agarose (0.8% in PBS). 100 μl of this mixture was spread on pre-coated slides. The coated slides were immersed in lyses buffer (0.045 M TBE, pH 8.4, containing 2.5% SDS) for 15 min. The slides were placed in electrophoresis chamber containing the same TBE buffer, but devoid of SDS. The extent of DNA migration for each sample was determined by image capture and scoring of 50 cells at ×400 magnification using Komet 5 image analysis software developed by Kinetic Imaging, Ltd (Liverpool, UK).The comets tails lengths were measured from the middle of the nucleus to the end of the tail with 40x increase for the count and measure the size of the comet. For visualization of DNA damage, observations are made of EtBr-stained DNA using a 40x objective on a fluorescent microscope according to [21].

2.8. Determination of caspase-3 in testes tissue:

100 mg of tissue was rinsed with PBS, homogenized in 1 ml PBS and stored overnight at -20°C. After two freeze-thaw cycles that break the cell membranes, the homogenates were centrifuged for 5 minutes at 5000×g, 2-8 °C, the supernatant was removed and assayed immediately using ELISA kit (No. CSB-E08857r).

2.9. Determination of sex hormones:

Testosterone hormone was determined in plasma using ELISA kit number K7418-100.Luteinizing hormone (LH) was determined in plasma using ELIZA kit (No. CSB-E12654r).

2.10. Assessment of oxidant -antioxidant Status:

Lipid Peroxidation byproduct, malondialdehyde (MDA), was estimated in plasma using Colorimetric/Fluorometric Assay Kit (No. K739-100) according method described by [22]. The non-enzymatic antioxidant, reduced glutathione (GSH), was determined in whole blood using NWK-GSH01 assay kit according to [23].

2.11. Microscopic Examination of testes and seminal vesicles:

Specimens from testes and seminal vesicles were fixed in 10% formalin, after fixation, tissues were embedded in paraffin. Sections of µm were stained with hematoxylin and eosin stain and examined under the light microscope [24].

2.12. Statistical analysis:

The data was analyzed using the Statistical Package for Social Science program (S.P.S.S. 9). One-way analysis of variance (ANOVA) was used. Results were expressed as mean ± Standard deviation (S.D.), differences considered significant when P≤0.05 according to [25].

3. RESULTS

3. 1. Effect of water melon and cantaloupe (seeds and juices) on semen analysis in experimental groups:

The results of epididymal semen analysis of rats from all groups are summarized in **Table (1).**As shown in the table, the total sperm count and the percent of motile sperm were significantly (P≤0.05) reduced in the MSG-administered rats compared to control group, the count and motility were increased in the treated groups (WMS, WMJ, CPS and CPJ) compared to MSG control group.

Morphological analysis of semen samples revealed a significant(P≤0.05) higher percentage of spermatozoa with abnormal morphology in rats orally administered with MSG compared to control , the recorded morphological abnormalities include, tail defects (coiled tail, short tail or double tails), head defects (no head, double heads) or middle piece defects (Large swollen midpiece or absent neck).There was a significant (P≤0.05) decrease in the percent of abnormal sperm in the treated groups compared to MSG control group.

Compared with the control group, there was a significant(P≤0.05) decrease in the sperm vitality in MSG-administered rats, on the other hand, treatment of rats with WMS, WMJ, CPS and CPJ was significantly increased the percent of (alive/ dead) sperm.

Table (1): Sperm parameters of control and experimental groups:

Groups	Sperm count (×106sperm/ml)	Sperm motility (% of motile sperm)	Sperm morphology (% of abnormal sperm)	Sperm vitality (alive/dead %)
Control	94.833±10.00a	83.50 ± 3.61a	10.66±2.50a	85.16±2.04a
MSG	60.11± 10.60b	49.66 ± 7.89b	40.16±3.71b	51.00±4.33b
WMS	87.68 ± 6.83a, c	77.50 ± 2.51c	21.83±1.94c	71.16±2.92c

WMJ	79.66 ± 6.86c, d	74.00 ± 3.22c	31.66±3.26d	67.00±3.22d
CPS	76.83 ± 5.81d	73.16 ± 4.79c	30.83±2.31d	70.66±2.87c
CPJ	78.33 ± 5.71d	65.00 ± 6.19d	23.66±2.73c	69.66±2.25c, d

*Values*are *expressed as means ± S.D., n= 6, There was no significant difference between means have the same letter in the same column (P≤0.05)*

3.2. Effect of water melon and cantaloupe (seeds and juices) on Comet assay and caspase-3 in testes tissues in experimental groups:

The percent of DNA damage in testes tissue was significantly increased (P≤0.05) in rats administered with MSG compared to rats in the control group, this was clear from the increased percent of tailed DNA and decreased percent of untailed DNA, also MSG induced statistically significant (P≤0.05) increase in the average of tail DNA, tail length and tail moment. These elevations in the comet assay parameters and DNA damage was alleviated by administration of water melon and cantaloupe (seeds extract and juices)

There was a significant (P≤0.05) increase in caspase 3 activity in MSG control group, furthermore, administration of water melon and cantaloupe (seeds extract and juices) along with MSG caused lowering of caspase 3 expression as shown in **(table 2).**

Table (2): Comet assay and caspase 3 in the testis's tissues of control and experimental groups:

Groups	Tailed (%)	Untailed (%)	Tail DNA (%)	Tail length (µm)	Tail moment (Units)	Caspase3 (ng/100mg)
Control	3.15 ±0 .14a	97.20 ± 0.14a	0.93 ± 0.01a	1.62 ± 0.08a	1.43 ± 0.06a	2.02 ± 1.01a
MSG	14.00 ±0.81b	86.09 ± 0.68b	3.12 ± 0.15b	3.58 ± 0.27b	10.27 ± 0.97b	7.84 ± 0.57b
WMS	10.35 ± 0.35c	89.57 ± 0.34c	2.56 ± 0.19c	2.69 ± 0.09c, d	6.09 ± 1.63c	5.52 ± 0.13c
WMJ	9.60 ± 0.50d	90.51 ± 0.34d	2.62 ± 0.13c	2.80 ± 0.02c	7.71± 0.03d	5.33 ± 0.34c, d
CPS	8.20 ± 0.02e	92.32 ± 0.16e	2.55 ± 0.02c	2.58 ± 0.02d	6.59 ± 0.03c, d	4.91 ± 0.16d
CPJ	9.78±0.59c, d	90.73±0.14d	2.67±0.03c	2.47 ± 0.03d	7.13 ± 0.15d	5.02 ±0.23c, d

Values are expressed as means ± S.D., n= 6, There was no significant difference between means have the same letter in the same column (P≤0.05)

3.3. Effect of *water melon and cantaloupe (seeds and juices) on plasma* sex hormones in experimental groups:

Oral administration of MSG for 6 weeks caused significant (P≤0.05) decrease in testosterone and LH hormones in plasma compared to control group. On the other hand, administration of water melon and cantaloupe (seeds extract and juices) along with MSG significantly increased the levels of sex hormones (testosterone and LH) when compared with the MSG group **(table 3).**

Table (3): Plasma sex hormones of control and experimental groups:

Groups	Testosterone (ng/ml)	LH (mIU/ml)
Control	4.48 ± 0.11a	2.20 ± 0.09a

MSG	2.22 ± 0.05b	1.10 ± 0.10b
WMS	3.00 ± 0.06c	1.39 ± 0.02c, b
WMJ	3.45 ± 0.08d	2.08 ± 1.21a, e
CPS	3.52 ±0.15d	1.74 ± 0.03a, c
CPJ	2.83 ± 0.11e	1.64 ± 0.04a, b,c,e

Values are expressed as means ± S.D., n= 6, There was no significant difference between means have the same letter in the same column (P≤0.05)

3.4. Effect of water melon and cantaloupe (seeds and juices) on oxidant -antioxidant Status in experimental groups:

From the results presented in (table 4) it is clear that MDA level was significantly elevated (P≤0.05) and GSH was decreased in MSG treated group as compared with normal control group which indicate disturbance in the oxidant-antioxidant status. Meanwhile, groups treated with MSG co-administered with water melon and cantaloupe (seeds extract and juices) afforded significant decrease in the level of MDA and increase in GSH when compared with the group that administered MSG only.

Table (4): Plasma GSH and MDA of control and experimental groups:

Groups	GSH (Mmol/ml)	MDA (nmol/ml)
Control	26.33 ± 0.59a	2.43 ± 0.09a
MSG	14.53 ± 0.38b	8.01 ± 0.62b
WMS	16.65 ± 0.34c	5.54 ± 0.26c
WMJ	16.57 ± 0.41c	5.31 ± 0.20c, d
CPS	18.28 ± 0.20d	4.96 ± 0.10d
CPJ	17.17 ± 0.46e	4.97 ± 0.24d

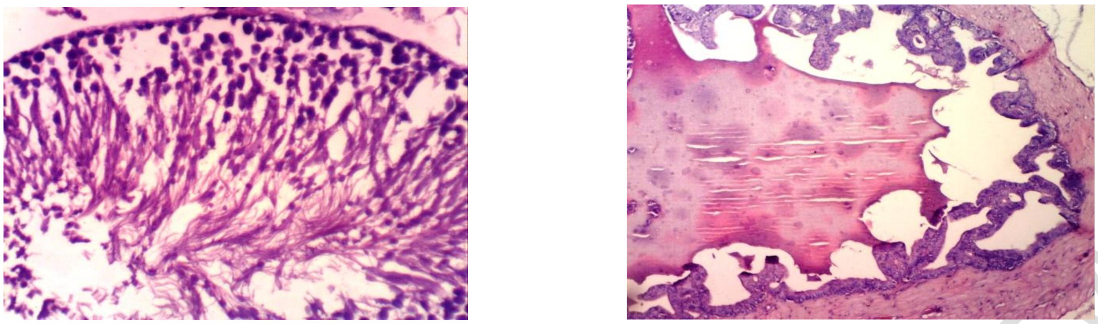
Values are expressed as means ± S.D., n= 6, There was no significant difference between means have the same letter in the same column (P≤0.05)

3.5. Microscopic examination of testes and seminal vesicles:

The microscopic examination of testes and seminal vesicles of rats illustrated that, the testicular section from control group showed normal histological structure of seminiferous tubule with normal spermatogoneal cells and complete spermatogenesis (Figure 1 A) and seminal vesicles revealed no histopathological alterations (Figure 1 B). On the other hand, examined testicular sections from MSG-administered rats revealed congestion of interstitial blood vessel and degeneration of spermatogoneal cells lining seminiferous tubules (Figure 2A), also MSG administration caused hyperplasia and vacuolation of epithelial lining and congestion of blood vessel in the serosa of the seminal vescles (Figure 2B).

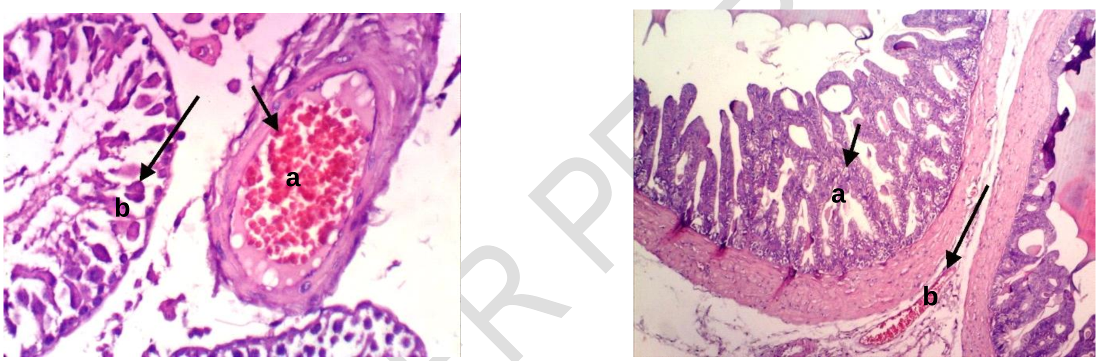
Testes of rats from WMS group showed no histopathological changes and complete spermatogenesis with sperm production (Figure 3 A), while the seminal vesicles revealed some hyperplasia of epithelial lining (Figure 3B). The testicular tissue of WMJ group revealed some degeneration of spermatogoneal cells lining seminiferous tubules (Figure 4 A). Also, the seminal vesicles showed few hyperplasia of epithelial lining (Figure 4B).

Examined testes sections from rats orally administered with CPS showed no histopathological changes and complete spermatogenesis with sperm production (Figure 5 A), meanwhile, the seminal vesicles revealed some hyperplasia of epithelial lining (Figure 5B). Few examined sections of testes from CPJ showed congestion of interstitial blood vessel (Figure 6A). While, seminal vesicles revealed no histopathological changes (Figure 6B).



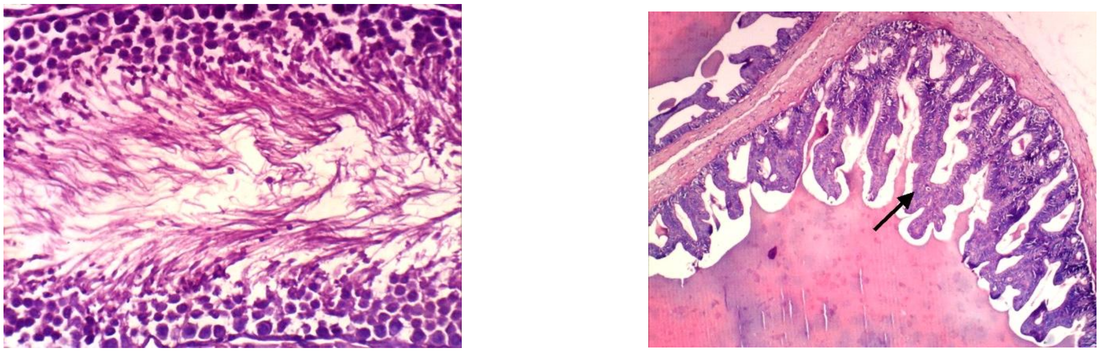
1A **1 B**

Figure (1): **(1A)** - Testicular section of control rats showing normal histological structure .
(1B) - Seminal vesicles of control rats revealed no histopathological alterations (H & E X 400).



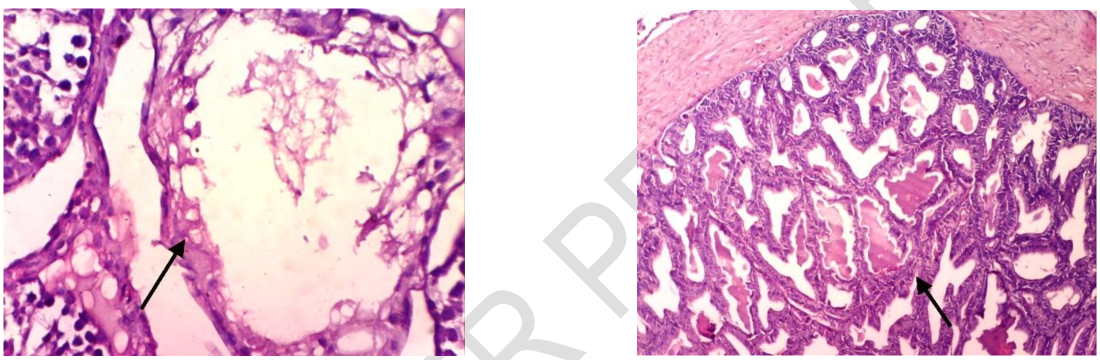
2A **2B**

Figure (2): **(2A)** - Testicular section of MSG rats showing congestion of interstitial blood vessel **(a)** and degeneration of spermatogoneal cells lining seminiferous tubules **(b).** **(2B)** - Seminal vesicles of MSG rats showing hyperplasia and vacuolation of epithelial lining**(a)** and congestion of blood vessel in the serosa of the seminal vesicles **(b)** (H & E X 400).



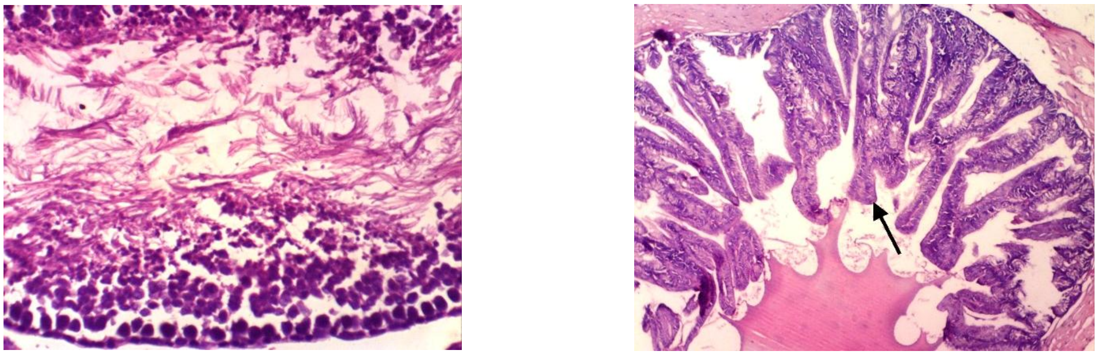
3A **3B**

Figure (3): (3A) - Testicular section of WMS rats showing no histopathological changes and complete spermatogenesis with sperm production. **(3B) -** seminal vesicles of WMS rats showing some hyperplasia of epithelial lining (H & E X 400).



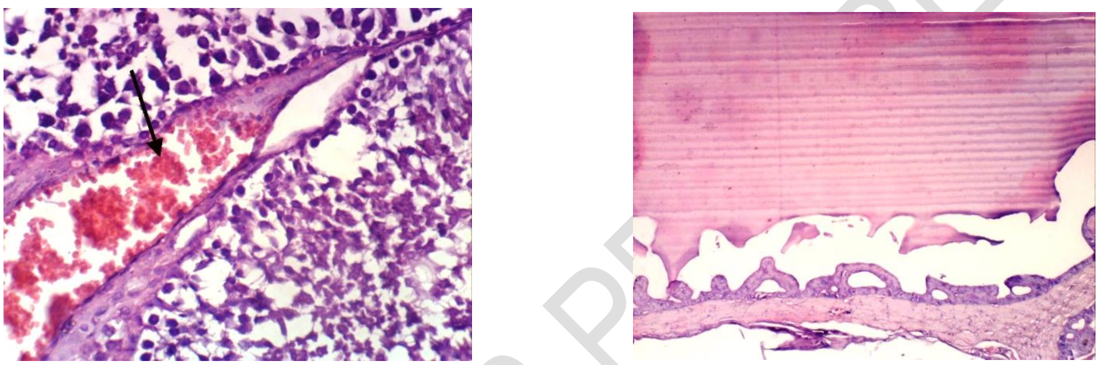
4A **4B**

Figure (4): (4A) - Testicular section of WMJ rats showing some degeneration of spermatogoneal cells lining seminiferous tubules . **(4B) -** seminal vesicles of WMJ ra ts showing few hyperplasia of epithelial lining (H & E X 400).



5A **5B**

Figure (5): (5A) - Testicular section of CPS rats showing no histopathological changes and complete spermatogenesis with sperm production . **(5B) -** seminal vesicles of CP S rats showing few hyperplasia of epithelial lining (H & E X 400).



6A **6B**

Figure (6): (6A) - Testicular section of CPJ rats showing congestion of interstitial blood vessel . **(6B) -** seminal vesicles of CPJ rats showing no histopathological changes (H & E X 400).

DISCUSSION:

Monosodium glutamate is a common flavor enhancer in nutritional industries, **Moore, (2003)** illustrated that MSG is known to affect the structure and function of male reproductive system and showed to be toxic to the testes of human and experimental animals **[26].** The present study was designed to investigate the ameliorative effect of water melon and cantaloupe (seeds extract and juices) against mono sodium glutamate-induced testicular injury and infertility in male rats.

The present study indicates that exposure to MSG caused reduction of sperm count, motility and vitality, moreover, increment of the percent of morphologically abnormal sperm**.** These results agree with the previous reports which indicated that administration of MSG resulted in damage to the testes and reduced in viability and efficiency of the sperm due to distortion of the sperm characteristics, this can be a major cause of infertility in males, induction of oxidative stress has been suggested to be the major mechanism by which MSG induced cellular degenerative changes **[27, 28]**. Also, there was a significant reduction in the caudal epididymal sperm reserves of the rats that received MSG relative to the control rats. **Ismail (2012),** showed that the decreased caudal epididymal sperm counts observed in the MSG-administered rats may be the end result of a considerable decline in the influence of testosterone on spermatogenesis in these rats **[29]. Onakewhor et al, (1998)** reported that consumption of MSG causes oligozoospermia, increased abnormal sperm morphology, and various degenerative changes. It has deleterious effects on the Sertoli cells and Leydig cells of the testes and adversely affects spermatogenesis **[30],** spermiogenesis and testosterone production in adult male rats **[31].**

Some mechanisms by which MSG inhibited the spermatogenesis are explained in the previous studies, **Takarada *et al.,* (2004)** proved the presence of functional glutamate transporters and receptors in testes of rat, so that, testes are considered to be target organ for MSG **[32]. Giovabattisa *et al.,* (2003)** stipulates that MSG have neurotoxin effects on the function of hypothalamus-pitutary-gonadal system and this affect the male reproduction. The ability of MSG to damage nerve cells of the hypothalamus is a central cause of alteration in the neural control of reproductive hormone secretion via the hypothalamic-pituitary-gonadal regulatory axis **[33].** These alterations in reproductive hormone secretion may adversely affect the reproductive capacity of the affected animals **[29].** Another mechanism reported that exposure to MSG resulted in a decrease in the testicular Ascorbic acid level that could lead to oxidative damage of rat testes **[7].**

DNA damage in the testes tissue was significantly observed in this study as measured by comet assay. The average of tail DNA, tail length and tail moment were found to be increased in testicular tissues of rats treated by MSG**.** DNA damage measured using the comet assay in human spermatozoa has been shown to be associated with infertility **[34].**MSG has a toxic effect on many body organs by altering ionic permeability of neural membrane and induces persistent depolarization **[35].**

Apoptosis is a physiological process that controls the numbers of cells in the testicular tissue and removes the defective germ cells during spermatogenesis. However, excessive apoptosis causes destruction of male reproductive function **[36].** We detected apoptotic cells in testicular tissue by using the caspase-3 activity. Because caspases trigger a cascade of proteolytic cleavage events and are considered central players in all apoptotic events in mammals, we selected a caspase activation test. Among these cysteine proteases, caspase-3 is believed to be one of the most commonly involved in the execution of apoptosis in various cell types and a key protease activated during the early stages of apoptosis. Also, oxidative stress could play a critical role in the induction of apoptosis and a higher susceptibility of sperm DNA to denaturation and fragmentation **[37].**

In present study, MSG administration elevated caspase-3 expression in the testicular tissue relative to the control indicating that MSG increase apoptosis in the rat testis**.** These results were in harmony with several studies who observed elevation in caspase-3 expression in the liver and testes of MSG-treated rats **[4, 38].** Caspase-3 is the key inducer of apoptosis, so activation of Caspase-3 induce apoptotic processes and destroy numerous cellular structures, leading to cell death **[39].** Caspases are a family of endoproteases, which have critical links in cell regulatory cascades controlling inflammation and cell death. They are produced as inert zymogens then activated when the cell receives apoptotic stimuli. So that, they are used as markers for cellular damages in many diseases **[40].**

Testes are an important organ responsible for the production of sperms and testosterone hormone, which is necessary for maintenance of secondary sexual characters and spermatogenesis **[41].** Gonadotropins (FSH, LH) and testosterone are the prime regulators of germ cell development. LH stimulates the production of testosterone in Leydig cells, which act on the Sertoli and peritubular cells of the seminiferous tubules and stimulates spermatogenesis **[42].** So, FSH, LH and testosterone evaluation are useful in the management of male infertility **[43].**

MSG administration caused reduction in LH and testosterone levels. ***S*akr and Badawy, (2013)** concluded that daily administration with MSG to male rats for 4 weeks significantly reduced the serum levels of testosterone and LH **[44].**

Franc *et al.,* (2006) reported that the central nervous system of MSG-treated rats showed neurogenic functional changes in the hypothalamus that induced a reduction in levels of LH and testosterone **[45]. Boodnard *et al.* (2001)** explained that the low serum testosterone and LH levels associated with MSG may be due to destruction of neurons in the hypothalamus **[46].** This destruction can result in disturbance of the hypothalamic-pituitary-testes axis that regulate the steroidogenesis of testicular Leydig cells leading to decrease in serum testosterone level. Moreover, MSG lowered serum cholesterol level, which is a precursor of steroid hormones including testosterone hormone leading to lowering its level **[47].** This may explain the decrease of plasma testosterone and LH levels recorded in the present work.

Also, oral administration of MSG caused increase in lipid peroxidation markers as MDA and decrease in free radical scavenging enzymes such as reduced glutathione (GSH). Lipid peroxidation is one of the main manifestations of oxidative damage and has been found to play an important role in the toxicity of many xenobiotic. It was evaluated by assessment of TBARS (MDA). Free radicals are known to attack the highly unsaturated fatty acids of the cell membrane and induce lipid peroxidation which considered a key process in many pathological events **[48].**

Reduced glutathione (GSH) is a potent endogenous antioxidant that helps protecting the body cells from a number of noxious stimuli including reactive oxygen species (ROS) **[49].** Reduced levels of GSH in this study confirm an increased susceptibility to oxidative damage and this observation is in agreement with the reports that inverse relationship exists between lipid peroxides and glutathione status. Glutathione depletion of 20% to 30% can impair the cell defense against the toxic action of xenobiotics and may lead to cell injury/death via damage to lipids, proteins and DNA. Therefore, it may cause loss of enzymatic activity and structural integrity of enzymes and activate inflammatory processes **[50,51].**

It was reported that the toxic effects of MSG lead to alterations in the structural integrity of mitochondrial inner membrane, resulting in the depletion of mitochondrial GSH levels and increased formation of hydrogen peroxide by the mitochondrial electron transport chain**[51].**We suggested that the major reason for damage of testicular tissues is the increasing level of lipid peroxidation and decrease efficiency of the antioxidant system. The increased lipid peroxidation caused oxidative damage to sperms DNA, impair motility and have a significant effect on the development of spermatozoa.

In our study co-administration of water melon and cantaloupe (seeds extract and juices) to MSG-treated rats improved semen quality and quantity**,** ameliorated the testicular damage of DNA and apoptosis process in testicular tissue, increased the plasma levels of sex hormones (testosterone and LH) and there was also a significant decrease in lipid peroxidation and an increase in the content of GSH

Watermelon and cantaloupe juices and seeds are rich sources of phenolics, α- tocopherol, carotenoids and vitamin C**. Watermelon (*Citrullus lanatus)*** is very rich in phytonutrients such as lycopene a forerunner of β-carotene and a carotenoid which have antioxidant capacity in scavenging ROS **[52].** It was reported that high consumption of fruits and vegetables containing lycopene is associated with reduced incidence of some types of prostate cancer, furthermore, provoke sexual and reproductive system **[53].** The mechanisms by which watermelon seeds extract protect against experimentally induced testicular damage may be due to rich source of vitamin C, thiamine, flavonoids and a high level of polyphenolic compounds present in the plant.

The protective effect of water melon seeds extract against MSG-induced testicular injury in male rats, reported in this study agree with that reported by **[54],** who concluded that, the extract of water melon seeds has ameliorative potentials on male reproductive system by increased sperm motility, well defined cellularity of the testis, increased sperm viability, decreased sperm morphological alterations, increased sperm count and increased testosterone level. Furthermore, the results of **Khaki *et al.,* (2013)** showed increase in sperm viability, motility and population of male rats received water melon seeds extract for 4 weeks so they concluded that it has a positive effect on male infertility **[55].**

Cantaloupe *(Cucumis melo L.)* is one of the most consumed fresh fruits worldwide and its residue, peel and seeds, is commonly discarded, the plant is rich in beneficial compounds such as resveratrol, lycopene and astaxanthin, and phenolic acids **[56,57].** The presence of phenolic compounds possibly explains the antioxidant potential found in both melon juice and seed extract **[58].**The phytochemical study of *Cucumis melo* seeds extract made by **Arora *et al.,*(2011)** showed the presence of flavonoids, trepenoids, alkaloids and phenolic compounds, these phyto compounds are responsible for the antioxidant and anti-inflammatory effects of cantaloupe, thus its seeds can be used to treat diseases caused by free radicals**[59].** Furthermore, this paper investigates for the first time the ameliorative effects of cantaloupe (seeds extract and juices) against MSG -induced infertility in male rats. We suggested that the high content of antioxidant and phytocompounds are responsible for this effect.

The ability of aqueous extract of watermelon seeds and juice to decrease MDA level may be due to its metal chelating capacity and the presence of lycopene in its phytochemical constituent. Melon is reported to have high lycopene content, a lipophilic antioxidant that is present in high concentration in the testis and in the seminal plasma. Its lipophilic nature enables it to accumulate in cell membranes and lipoproteins, thus exerting a more noticeable effect on components of such a cell. It also traps free radicals and halts the propagative chain reactions, reducing the ROS burden and alleviating oxidative stress, thus preventing oxidative damage to lipids, proteins and DNA **[60].** Lycopene utilizes redox defense mechanism to fight against free radicals that could cause infertility. Testes is believed to be an organ that store lycopene in human **[61].** Lycopene strongly inhibits the induction of oxidative stress by chain-breaking, trapping free radical and to lesser extent by interacting with ROS or chelating metal ions. Similarly, the impacts of lycopene on GSH might be returned to inhibition of GSH oxidation. Also, high percent of conjugated double bonds on lycopene help in quenching free radical anions render it a potent free radical scavenger **[62].**

Moreover, Saponin that was found to be present in the seed extracts functions majorly at stimulating an increase in the body's natural endogenous testosterone levels which helps to maintain testosterone levels **[54].** Also, Astaxanthin, a very potent antioxidant was reported to have positive effects on the reproductive system and particularly on infertility. the Astaxanthin has positive effects on sperm parameters and fertility by increasing inhibin B secretion by Sertoli cells. Astaxanthin has not only improved sperm morphology but also significantly increased the number and motility of spermatozoa **[63].**

β-carotenes have protective effect on testicular seminiferous tubules. One explanation for this protection is that β-carotene is a lipophilic substance and passes easily through biological membranes, a property that gives β-carotene an advantage in rapidly entering the cells. The second possible mechanism is that β-carotene plays an important role in the protection of cellular membranes and lipoprotein against oxidative damage. It is possible that the provitamin A activity of β-carotene had an effective role in this protection. A third favorable mechanism is the antiapoptotic effect of β-carotene, which may be protective against the direct toxicity on testis tissue. Also, production of ROS may mediate a signal for apoptotic cell. The prevention of apoptosis by β-carotene has been suggested to depend mainly on singlet oxygen–quenching properties and its ability to trap peroxyl radicals. Our study strongly showed that oxidative stress and apoptotic cell death might play an important role in MSG-induced testicular damage **[37].** The present study suggests that β –carotene as active component of juices and seeds has a potent protective effect on MSG-induced oxidative testicular damage and apoptotic cell death in rats.

On the other hand, vitamin C a low molecular weight compound is a potent antioxidant that is capable of protecting the testis against oxidative stress due to increased generation of free radicals such as H_20_2. The beneficial effects of vitamin C are attributed mainly to its antioxidant properties **[64].** The constituents of watermelon juice are known for their free radical scavenging activities and antioxidant effects which illustrate their ameliorative effect against MSG presented in this study. Watermelon contains high amount of Vitamin C, it has been reported that vitamin C protects human spermatozoa against endogenous oxidative damage by neutralizing hydroxyl, superoxide and hydrogen peroxide radicals and preventing sperm agglutination. Therefore, it is possible that the Vitamin C content of juices helped to ameliorate the production of peroxidation thus leading to improvement in morphology and viability of spermatozoa of treated rats. MSG is known to adversely affect the production of testosterone by disrupting the hypothalamic-pituitary-testicular axis through oxidative stress and inducing cellular toxicity **[65].**

A great deal of changes that recorded in the present investigations are in accordance to the histological studies that were carried out on the testes of MSG- administered animals. **Alalwani, (2014)** and **Khayal *et al.,* (2018)** found that administration of MSG to young male rats caused several tissue alterations of the seminiferous tubules, they showed severely slight to moderate damaged seminiferous tubules as hyaline material involved and widening of the spaces between seminiferous tubules and congestion of blood vessels. The congestion of blood vessels may be due to the inhibition of prostaglandins synthesis, since these compounds are known to be involved in the regulation of testicular blood flow **[66,67]**. **Abd-Ella and Mohamed, (2016)** indicated that testes of rats treated with MSG displayed variable degree of histopathological alterations like blood hemorrhage, appearance of different vacuoles in the interstitial tissue and many seminiferous tubules were severely damaged **[4].**

The histopathological examination of testicular tissues showed improvement of seminiferous tubules cells and showing the near normal structure of seminal vesicles in groups that administered with water melon and cantaloupe (seeds extract and juices). This protective effect could be a result of free radical scavenging activities and reduction of the oxidative stress on testis caused by the tested extracts that can counteract the lipid peroxidation and decrease apoptosis and DNA damage in the reproductive organs. So that, the present results suggested that watermelon and cantaloupe provide highly effective anti-oxidants and reversing the negative effect caused by MSG.

Resveratrol, one of cantaloupe's active components, is a free radical scavenger and enzyme regulator and therefore protects against tissue damage caused by oxidative stress. Additionally, one study showed that resveratrol can serve like the antioxidant enzymes SOD1 and GPx1. Resveratrol also seems to interact with many different proteins, including cyclooxygenases, ribonucleotide reductase, kinases and DNA polymerases **[68].** Histologically, a study showed that resveratrol treatment significantly protected testicular seminiferous tubules against toxicity and increased the progressive sperm motility. The protective effect of resveratrol treatment may be due to its protection of cellular membranes against oxidative damage, reduced oxidative stress and apoptotic cell death and protected spermatogenesis **[69].**

4. CONCLUSION

From the results of this study, we revealed that exposure to MSG (60mg/kg) for 6 weeks can adversely affect the reproductive capacity and induce male infertility as manifested by reduce semen parameters, increased DNA damage and oxidative stress in the testicular tissue and decrease the levels of sex hormones as well as alteration in the histopathological structures of testicular tissue. The biochemical and histopathological alterations observed in rats exposed to MSG were significantly improved after treatment with water melon and cantaloupe (seeds extract and juices).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between all authors. the two Authors read and approved the final manuscript.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

All authors hereby declare that "principles of laboratory animal care were followed.

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