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3 **Amelioration of monosodium glutamate- induced**
4 **testicular damage and infertility in male rats by**
5 **water melon and cantaloupe seeds extract and juices**
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8
9 **ABSTRACT**

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11 **Aims:** Monosodium glutamate (MSG) is extensively used as food additive and flavor enhancer, there is
12 a growing concern that this may affect the male reproductive system and fertility. The objective of this
13 study is to investigate the effect of MSG on fertility and testes of mature male rats and the ameliorative
14 role of water melon and cantaloupe (seeds extract and juices).
15

16 **Study design:** Thirty-six male Sprague - Dawely rats (150-180g) were randomly assigned into six
17 groups (n=6). Group (1): orally administered with distilled water. Group (2): orally administered with
18 60mg/kg of MSG. Groups (3 and 4): orally administered with 60mg/kg of MSG + 200mg/kg of water
19 melon seeds extract and juice respectively. Groups (5 and 6): orally administered with 60mg/kg of MSG
20 + 200mg/kg of cantaloupe seeds extract and juice respectively.
21

22 **Results:** Results showed that administration of MSG for 6 weeks caused *abnormalities of semen*
23 *characteristics, increased DNA damage and up-regulation of caspase3 expression in the testes tissue.*
24 *Also, the levels of plasma sex hormones were decreased and the oxidant-antioxidant status was*
25 *disturbed, moreover, MSG caused alteration in the histopathological structures of testicular tissue.*
26 *Administration of seeds extract or juices of water melon and cantaloupe almost corrected the*
27 *biochemical and histopathological alteration produced by MSG.*
28

29 **Conclusion:** this study concluded that water melon and cantaloupe seeds and juice extracts have an
30 ameliorative role against MSG-induced testicular damage and infertility in rats.
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32
33 *Keywords:* Monosodium glutamate, Testes, male infertility, watermelon, *Citrullus lanatus*, cantaloupe, *Cucumis Melo L.*,
34 antioxidant.
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38 **1. INTRODUCTION:**

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

47 brownish white or white crystals are sold as pure MSG [3]. It is present in a wide variety of processed foods including
48 prepared meals, flavored chips and snacks, marinated meats, flavored tuna, soups or sauces (canned, packed), bottled
49 soy or oriental sauces, fresh sausages, and stuffed or seasoned chicken, vegetarian burgers, luncheon chicken and
50 turkey and sausages. It may be present in packaged foods without appearing on the label [4].

51 Various studies have shown that Monosodium glutamate is neurotoxic, nephrotoxic, hepatotoxic, and gonadotoxic [5, 6
52 ,7]. These molecules can contribute to the oxidative stress. Moreover, MSG has a toxic effect on the testis by causing a
53 significant oligozoospermia and increases abnormal sperm morphology. It has been implicated in male infertility by
54 causing testicular hemorrhage, degeneration and alteration of sperm cell population and morphology [8].
55

56 Plant extracts have been used as medicines, nutrition, and other industrial purpose. The natural products today symbolize
57 safety in contrast to the synthetic drugs. A melon belongs to the family Cucurbitaceae with an edible fruit. Melons have
58 their origin in Africa and southwest Asia, but they later started appearing in Europe at the end of the Roman Empire [9].
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60 The Watermelon (*Citrullus lanatus*) is a member of the family Cucurbitaceae. The juice or pulp from watermelon is used
61 for human consumption, while rind and seeds are major solid wastes. The rind is utilized for products such as pickles and
62 preserves, as well as for extraction of pectin) [10]. Melon fruit contains large quantities of seeds. The kernels are
63 sometimes used as dressing for bread, cake, sweetmeats and snack foods, often in place of almonds and pistachio. The
64 seeds can be cooked and dried and served as snacks e.g. Egypt, Iran and might also be cooked, ground (West Africa)
65 and fermented for use as a flavor enhancer in gravies and soups [11]. Watermelon is one of such medicinal plant that has
66 attracted scientific interest due to its bioactivities. *C. lanatus* sp. is a natural source of antioxidants such as beta-carotene,
67 vitamin C, citrulline, B vitamins, especially B1 and B6, as well as minerals such as potassium and magnesium.
68 Watermelon juice with red flesh is an excellent source of lycopene, having about 40% higher lycopene content than raw
69 tomatoes [12]. The tissue protective effects of watermelon juice have been previously reported. The anti-inflammatory,
70 antioxidant, anti-ulcerogenic and anti-diabetic effects of watermelon have also been documented [13, 14]. The
71 constituents of watermelon juice are known for their free radical scavenging activities and antioxidant effects [15]. These
72 functional ingredients act as protection against chronic health problems like cancer and cardiovascular disorders [16].
73

74 Cantaloupe melon (*Cucumis melo* L.) also belongs to Cucurbitaceae family. This fruit is one of the most consumed crops
75 worldwide due to its sweetness, juicy taste, pleasing flavor, and it is known for nutritive and medicinal properties of pulp. It
76 is rich in important vitamins, such as riboflavin, thiamine and folic acid. It is also a good source of pro-vitamin A and
77 vitamin C [17]. It has been shown to possess useful medicinal properties such as analgesic, anti-inflammatory, anti-
78 oxidant, anti-ulcer, anti-cancer, anti-microbial, diuretic, anti-diabetic, and anti-fertility activity [18].
79

80 During fruit consumption and industrial processing, a large quantity of waste materials is produced, such as melon peels
81 and seeds. These by-products are still rich in phytochemicals, such as polyphenols, carotenoids, and other biologically
82 active components, which have a positive influence on health and preventing aging effects. Among all, polyphenol
83 compounds show antioxidant activity, delaying or inhibiting the oxidation of lipids and other molecules, so protecting cells
84 from damage by reactive oxygen species (ROS) [19].
85

86 The main objective of the present work is to study the protective effect of water melon and Cantaloupe melon juices and
87 aqueous seed extracts against testicular toxicity induced by MSG.
88

89 **2. MATERIAL AND METHODS:**

90 **2.1. Animals:**

92 Adult male albino rats (Sprague-Dawley strain) weighing 150-180 g were obtained from El -Salam Farm, Giza, Egypt. The
93 experiment was carried out in the Animal House of the Medical Research Center, Ain Shams University, Cairo, Egypt.
94 Thirty-six rats were individually housed in stainless steel cages with constant controlled environments of temperature
95 $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$, air humidity $55\% \pm 10\%$ and 12/12 hours light/dark cycle and offered the standard commercial pellet diet and
96 drinking water *ad libitum* for one week as adaptation period, then all rats were kept on commercial pellet diet and drinking
97 water *ad libitum* to the end of the experiment (6 weeks).

98 **2.2. Chemicals:**

99 Monosodium-glutamate ($\text{C}_5\text{H}_9\text{NO}_4 \cdot \text{Na}$) was purchased from Top Chem company, Cairo, Egypt.

100 **2.3. Plant materials:**

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

104 The healthy-looking seeds collected from watermelon and cantaloupes were oven-dried at 35°C, to a constant weight.
105 The dried seeds were reduced into fine powder using a laboratory grinding hand mill. The powder was soaked in water
106 for 48 hours at the ratio of 1g to 20ml of water. Mixture was stirred at 1-hour interval and kept overnight. Mixture was
107 separated by filtering it to get a clear solution. The extract was concentrated using a Rotary evaporator. The concentrated
108 water extracts of watermelon and cantaloupe seeds were stored in sealed bottles in refrigerator at 4°C until used [20].

109 **2.4. Experimental design:**

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

111 Group 1 (control group): Rats were received distilled water by gastric tube daily.

112 Group 2 (MSG): Rats were received 60 mg/kg b.wt of MSG by gastric tube daily.

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

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

116 Group 5 (CPS): Rats were received 60 mg/kg b.wt of MSG + 200 mg/kg b.wt of cantaloupe seeds extract by gastric tube
117 daily.

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

119 **2.5. Samples collection:**

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

127 **2.6. Semen Analysis:**

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

133 **2.7. Comet assay for determination of DNA damage in testes tissue:**

134 0.5 g of crushed samples were transferred to 1 ml ice-cold PBS., this suspension was stirred for 5 min then filtered. Cell
135 suspension was mixed with low-melting agarose (0.8% in PBS). 100 µl of this mixture was spread on pre-coated slides.
136 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
137 placed in electrophoresis chamber containing the same TBE buffer, but devoid of SDS. The extent of DNA migration for
138 each sample was determined by image capture and scoring of 50 cells at x400 magnification using Komet 5 image
139 analysis software developed by Kinetic Imaging, Ltd (Liverpool, UK). The comet tails lengths were measured from the
140 middle of the nucleus to the end of the tail with 40x increase for the count and measure the size of the comet. For
141 visualization of DNA damage, observations are made of EtBr-stained DNA using a 40x objective on a fluorescent
142 microscope according to [21].

143 **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 5000xg, 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 ELISA 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 to 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 \pm Standard deviation (S.D.), differences considered significant when $P \leq 0.05$ according to [25].

3. RESULTS AND DISCUSSION

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 ($P \leq 0.05$) 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 ($P \leq 0.05$) 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 ($P \leq 0.05$) 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 ($P \leq 0.05$) 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 ($\times 10^6$ sperm/ml)	Sperm motility (% of motile sperm)	Sperm morphology (% of abnormal sperm)	Sperm vitality (alive/dead %)
Control	94.833 \pm 10.00a	83.50 \pm 3.61a	10.66 \pm 2.50a	85.16 \pm 2.04a
MSG	60.11 \pm 10.60b	49.66 \pm 7.89b	40.16 \pm 3.71b	51.00 \pm 4.33b
WMS	87.68 \pm 6.83a, c	77.50 \pm 2.51c	21.83 \pm 1.94c	71.16 \pm 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)

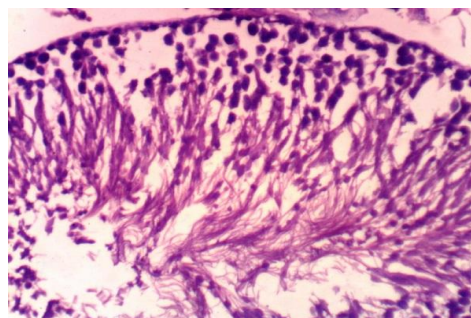
3.5. Microscopic examination of testes and seminal vesicles:

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 vesicles (Figure 2B).

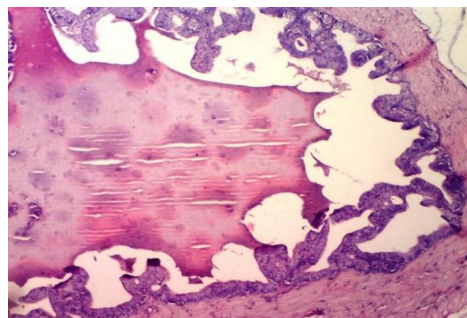
Testes of rats from WMS group showed no histopathological changes and complete spermatogenesis with sperm production (Figure 3 A), while the seminal vesicles revealed some hyperplasia of epithelial lining (Figure 3B). The testicular tissue of WMJ group revealed some degeneration of spermatogoneal cells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

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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).



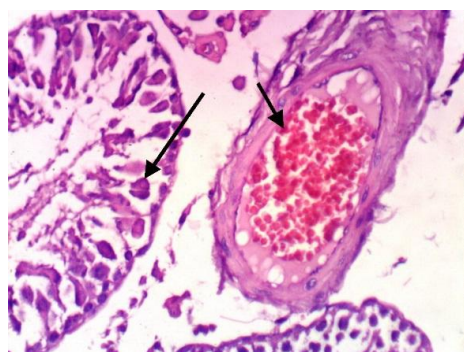
1A



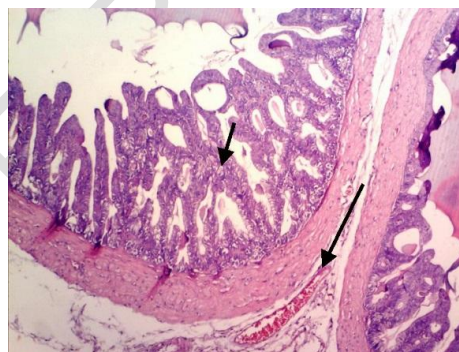
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Figure (1): (1A) - Testicular section of control rats showing normal histological structure. **(1B)**- Seminal vesicles of control rats revealed no histopathological alterations.

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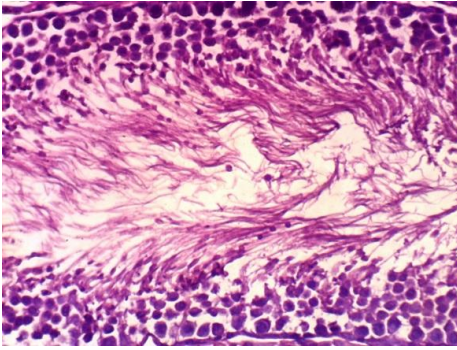
2A



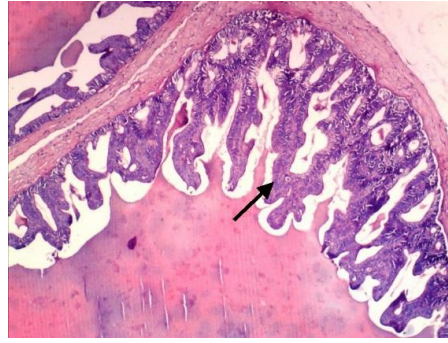
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Figure (2): (2A)- Testicular section of MSG rats showing congestion of interstitial blood vessel and degeneration of spermatogoneal cells lining seminiferous tubules. **(2B)**- Seminal vesicles of MSG rats showing hyperplasia and vacuolation of epithelial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

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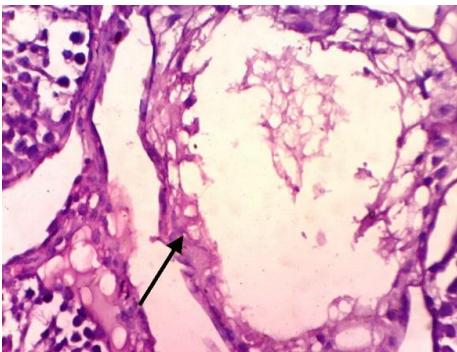
3A



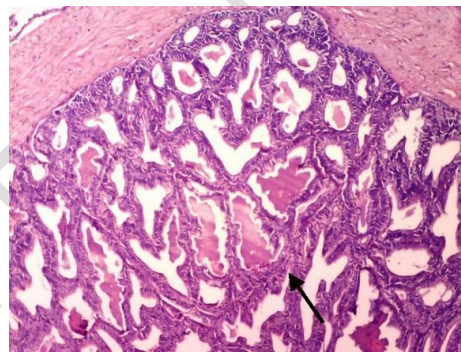
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Figure (3): (3A)- Testicular section of WMS rats showing no histopathological changes and complete spermatogenesis with sperm production. **(3B)-** seminal vesicles of WMS rats showing some hyperplasia of epithelial lining

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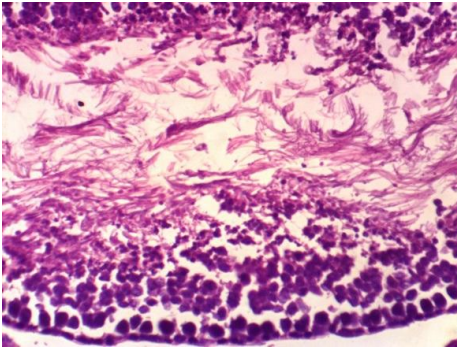
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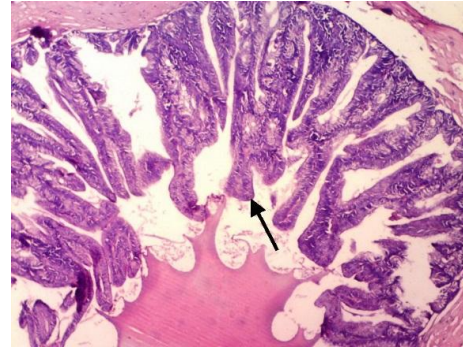
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Figure (4): (4A)- Testicular section of WMJ rats showing some degeneration of spermatogoneal cells lining seminiferous tubules. **(4B)-** seminal vesicles of WMJ rats showing few hyperplasia of epithelial lining

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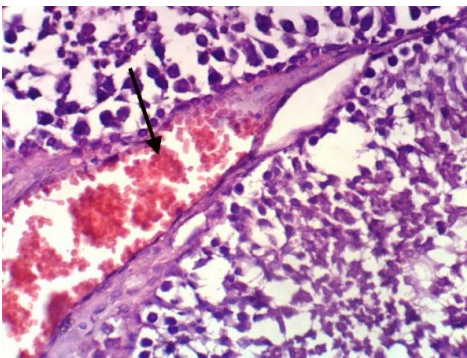
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Figure (5): (5A)- Testicular section of CPS rats showing no histopathological changes and complete spermatogenesis with sperm production. **(5B)-** seminal vesicles of CPS rats showing few hyperplasia of epithelial lining

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

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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].

283 Some mechanisms by which MSG inhibited the spermatogenesis are explained in the previous studies, **Takarada et al.,**
284 **(2004)** proved the presence of functional glutamate transporters and receptors in testes of rat, so that, testes are
285 considered to be target organ for MSG [32]. **Giovabattisa et al., (2003)** stipulates that MSG have neurotoxin effects on
286 the function of hypothalamus-pituitary-gonadal system and this affect the male reproduction. The ability of MSG to damage
287 nerve cells of the hypothalamus is a central cause of alteration in the neural control of reproductive hormone secretion via
288 the hypothalamic-pituitary-gonadal regulatory axis [33]. These alterations in reproductive hormone secretion may
289 adversely affect the reproductive capacity of the affected animals [29]. Another mechanism reported that exposure to
290 MSG resulted in a decrease in the testicular Ascorbic acid level that could lead to oxidative damage of rat testes [7].

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292 DNA damage in the testes tissue was significantly observed in this study as measured by comet assay. The average of
293 tail DNA, tail length and tail moment were found to be increased in testicular tissues of rats treated by MSG. DNA damage
294 measured using the comet assay in human spermatozoa has been shown to be associated with infertility [34].MSG has a
295 toxic effect on many body organs by altering ionic permeability of neural membrane and induces persistent depolarization
296 [35].

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

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

313
314 Testes are an important organ responsible for the production of sperms and testosterone hormone, which is necessary for
315 maintenance of secondary sexual characters and spermatogenesis [41]. Gonadotropins (FSH, LH) and testosterone are
316 the prime regulators of germ cell development. LH stimulates the production of testosterone in Leydig cells, which act on
317 the Sertoli and peritubular cells of the seminiferous tubules and stimulates spermatogenesis [42]. So, FSH, LH and
318 testosterone evaluation are useful in the management of male infertility [43].

319
320 MSG administration caused reduction in LH and testosterone levels. **Sakr and Badawy, (2013)** concluded that daily
321 administration with MSG to male rats for 4 weeks significantly reduced the serum levels of testosterone and LH [44].

322
323 **Franc et al., (2006)** reported that the central nervous system of MSG-treated rats showed neurogenic functional changes
324 in the hypothalamus that induced a reduction in levels of LH and testosterone [45]. **Boodnard et al. (2001)** explained that
325 the low serum testosterone and LH levels associated with MSG may be due to destruction of neurons in the
326 hypothalamus [46]. This destruction can result in disturbance of the hypothalamic-pituitary-testes axis that regulate the
327 steroidogenesis of testicular Leydig cells leading to decrease in serum testosterone level. Moreover, MSG lowered serum
328 cholesterol level, which is a precursor of steroid hormones including testosterone hormone leading to lowering its level
329 [47]. This may explain the decrease of plasma testosterone and LH levels recorded in the present work.

330
331 Also, oral administration of MSG caused increase in lipid peroxidation markers as MDA and decrease in free radical
332 scavenging enzymes such as reduced glutathione (GSH). Lipid peroxidation is one of the main manifestations of oxidative
333 damage and has been found to play an important role in the toxicity of many xenobiotic. It was evaluated by assessment
334 of TBARS (MDA). Free radicals are known to attack the highly unsaturated fatty acids of the cell membrane and induce
335 lipid peroxidation which considered a key process in many pathological events [48].

336
337 Reduced glutathione (GSH) is a potent endogenous antioxidant that helps protecting the body cells from a number of
338 noxious stimuli including reactive oxygen species (ROS) [49]. Reduced levels of GSH in this study confirm an increased
339 susceptibility to oxidative damage and this observation is in agreement with the reports that inverse relationship exists
340 between lipid peroxides and glutathione status. Glutathione depletion of 20% to 30% can impair the cell defense against

341 the toxic action of xenobiotics and may lead to cell injury/death via damage to lipids, proteins and DNA. Therefore, it may
342 cause loss of enzymatic activity and structural integrity of enzymes and activate inflammatory processes [50,51].
343

344 It was reported that the toxic effects of MSG lead to alterations in the structural integrity of mitochondrial inner membrane,
345 resulting in the depletion of mitochondrial GSH levels and increased formation of hydrogen peroxide by the mitochondrial
346 electron transport chain[51].We suggested that the major reason for damage of testicular tissues is the increasing level of
347 lipid peroxidation and decrease efficiency of the antioxidant system. The increased lipid peroxidation caused oxidative
348 damage to sperms DNA, impair motility and have a significant effect on the development of spermatozoa.
349

350 In our study co-administration of water melon and cantaloupe (seeds extract and juices) to MSG-treated rats improved
351 semen quality and quantity, ameliorated the testicular damage of DNA and apoptosis process in testicular tissue,
352 increased the plasma levels of sex hormones (testosterone and LH) and there was also a significant decrease in lipid
353 peroxidation and an increase in the content of GSH
354

355 Watermelon and cantaloupe juices and seeds are rich sources of phenolics, α - tocopherol, carotenoids and vitamin C.
356 **Watermelon (*Citrullus lanatus*)** is very rich in phytonutrients such as lycopene a forerunner of β -carotene and a
357 carotenoid which have antioxidant capacity in scavenging ROS [52]. It was reported that high consumption of fruits and
358 vegetables containing lycopene is associated with reduced incidence of some types of prostate cancer, furthermore,
359 provoke sexual and reproductive system [53]. The mechanisms by which watermelon seeds extract protect against
360 experimentally induced testicular damage may be due to rich source of vitamin C, thiamine, flavonoids and a high level of
361 polyphenolic compounds present in the plant.
362

363 The protective effect of water melon seeds extract against MSG-induced testicular injury in male rats, reported in this
364 study agree with that reported by [54], who concluded that, the extract of water melon seeds has ameliorative potentials
365 on male reproductive system by increased sperm motility, well defined cellularity of the testis, increased sperm viability,
366 decreased sperm morphological alterations, increased sperm count and increased testosterone level. Furthermore, the
367 results of **Khaki et al., (2013)** showed increase in sperm viability, motility and population of male rats received water
368 melon seeds extract for 4 weeks so they concluded that it has a positive effect on male infertility [55].
369

370 **Cantaloupe (*Cucumis melo L.*)** is one of the most consumed fresh fruits worldwide and its residue, peel and seeds, is
371 commonly discarded, the plant is rich in beneficial compounds such as resveratrol, lycopene and astaxanthin, and
372 phenolic acids [56,57]. The presence of phenolic compounds possibly explains the antioxidant potential found in both
373 melon juice and seed extract [58].The phytochemical study of *Cucumis melo* seeds extract made by **Arora et al.,(2011)**
374 showed the presence of flavonoids, terpenoids, alkaloids and phenolic compounds, these phyto compounds are
375 responsible for the antioxidant and anti-inflammatory effects of cantaloupe, thus its seeds can be used to treat diseases
376 caused by free radicals[59]. Furthermore, this paper investigates for the first time the ameliorative effects of cantaloupe
377 (seeds extract and juices) against MSG -induced infertility in male rats. We suggested that the high content of antioxidant
378 and phyto compounds are responsible for this effect.
379

380 The ability of aqueous extract of watermelon seeds and juice to decrease MDA level may be due to its metal chelating
381 capacity and the presence of lycopene in its phytochemical constituent. Melon is reported to have high lycopene content,
382 a lipophilic antioxidant that is present in high concentration in the testis and in the seminal plasma. Its lipophilic nature
383 enables it to accumulate in cell membranes and lipoproteins, thus exerting a more noticeable effect on components of
384 such a cell. It also traps free radicals and halts the propagative chain reactions, reducing the ROS burden and alleviating
385 oxidative stress, thus preventing oxidative damage to lipids, proteins and DNA [60]. Lycopene utilizes redox defense
386 mechanism to fight against free radicals that could cause infertility. Testes is believed to be an organ that store lycopene
387 in human [61]. Lycopene strongly inhibits the induction of oxidative stress by chain-breaking, trapping free radical and to
388 lesser extent by interacting with ROS or chelating metal ions. Similarly, the impacts of lycopene on GSH might be
389 returned to inhibition of GSH oxidation. Also, high percent of conjugated double bonds on lycopene help in quenching free
390 radical anions render it a potent free radical scavenger [62].
391

392 Moreover, Saponin that was found to be present in the seed extracts functions majorly at stimulating an increase in the
393 body's natural endogenous testosterone levels which helps to maintain testosterone levels [54]. Also, Astaxanthin, a very
394 potent antioxidant was reported to have positive effects on the reproductive system and particularly on infertility. the
395 Astaxanthin has positive effects on sperm parameters and fertility by increasing inhibin B secretion by Sertoli cells.
396 Astaxanthin has not only improved sperm morphology but also significantly increased the number and motility of
397 spermatozoa [63].
398

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

410
411 On the other hand, vitamin C a low molecular weight compound is a potent antioxidant that is capable of protecting the
412 testis against oxidative stress due to increased generation of free radicals such as H_2O_2 . The beneficial effects of vitamin
413 C are attributed mainly to its antioxidant properties [64]. The constituents of watermelon juice are known for their free
414 radical scavenging activities and antioxidant effects which illustrate their ameliorative effect against MSG presented in this
415 study. Watermelon contains high amount of Vitamin C, it has been reported that vitamin C protects human spermatozoa
416 against endogenous oxidative damage by neutralizing hydroxyl, superoxide and hydrogen peroxide radicals and
417 preventing sperm agglutination. Therefore, it is possible that the Vitamin C content of juices helped to ameliorate the
418 production of peroxidation thus leading to improvement in morphology and viability of spermatozoa of treated rats. MSG is
419 known to adversely affect the production of testosterone by disrupting the hypothalamic-pituitary-testicular axis through
420 oxidative stress and inducing cellular toxicity [65].

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

430
431 The histopathological examination of testicular tissues showed improvement of seminiferous tubules cells and showing
432 the near normal structure of seminal vesicles in groups that administered with water melon and cantaloupe (seeds extract
433 and juices). This protective effect could be a result of free radical scavenging activities and reduction of the oxidative
434 stress on testis caused by the tested extracts that can counteract the lipid peroxidation and decrease apoptosis and DNA
435 damage in the reproductive organs. So that, the present results suggested that watermelon and cantaloupe provide highly
436 effective anti-oxidants and reversing the negative effect caused by MSG.

437
438 Resveratrol, one of cantaloupe's active components, is a free radical scavenger and enzyme regulator and therefore
439 protects against tissue damage caused by oxidative stress. Additionally, one study showed that resveratrol can serve like
440 the antioxidant enzymes SOD1 and GPx1. Resveratrol also seems to interact with many different proteins, including
441 cyclooxygenases, ribonucleotide reductase, kinases and DNA polymerases [68]. Histologically, a study showed that
442 resveratrol treatment significantly protected testicular seminiferous tubules against toxicity and increased the progressive
443 sperm motility. The protective effect of resveratrol treatment may be due to its protection of cellular membranes against
444 oxidative damage, reduced oxidative stress and apoptotic cell death and protected spermatogenesis [69].

445 **4. CONCLUSION**

446
447 From the results of this study, we revealed that exposure to MSG (60mg/kg) for 6 weeks can adversely affect the
448 reproductive capacity and induce male infertility as manifested by reduce semen parameters, increased DNA damage and
449 oxidative stress in the testicular tissue and decrease the levels of sex hormones as well as alteration in the
450 histopathological structures of testicular tissue. The biochemical and histopathological alterations observed in rats
451 exposed to MSG were significantly improved after treatment with water melon and cantaloupe (seeds extract and juices).
452
453
454

COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between all authors. the tow 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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