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Monosodium Glutamate Induce Toxicity on Male Reproductive System: A Review

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Abstract: **Reproductive alterations pose a significant concern today, with various factors contributing to this issue, including genetic factors, reproductive system disorders, therapeutic drugs, lifestyle changes, and food additives. Food additives are substances utilized to enhance the taste of food and are commonly employed in various culinary practices. One such widely used food additive is monosodium glutamate (MSG), also known as Ajinomoto. Extensive scientific research has been conducted on MSG due to its widespread use, leading to the discovery that it can have adverse effects on the male reproductive system. These effects include abnormalities in sperm, reduced sperm count, and alterations in the anatomy of male reproductive organs.**

Index Terms: **Monosodium glutamate, testes, epididymis, sperm abnormalities, hormones**

I. Introduction

Food additives are substances added to basic food items to enhance various aspects such as taste, flavor, color, texture, nutritional value, and preservation (Imane *et al*., 2011). These additives can be either natural or industrial in origin (Harris, 1986). Monosodium glutamate (MSG) is a subset of glutamate, a non-essential amino acid found in several foods such as beef, milk, tuna, and vegetables, and it plays a vital role in human metabolism (Bera *et al*., 2017). MSG is widely used as a food additive and can be found in various ingredients and processed foods available in grocery stores. It imparts a distinct aroma to processed foods known as umami, a savory taste sensation (Xiong *et al*., 2009). MSG is often described by the Japanese as umami, referring to a meaty taste found in certain fish and broths (Schiffman, 2000). Due to changing lifestyles and increased consumption of processed foods, the intake of MSG has been on the rise. Based on official data from the European Food Safety Authority (EFSA), the "Acceptable Daily Intake" (ADI) for MSG is 30 mg per kilogram of body weight per day. In European countries and the USA, the typical daily intake of MSG ranges from 0.3 to 1.0 grams, while in Asian countries, it can be higher at 1.2 to 1.7 grams. Studies have estimated that Asians consume MSG at levels 10 to 20 times higher than the European and American average daily intake, ranging from 1200 to 3000 mg per day (Brosnan *et al*., 2014). The average daily intake of MSG from processed foods is reported to be approximately 1 gram in some European countries, 4 grams in Asia, and 10 grams in Germany (Park *et al*., 2014). Previous studies on MSG toxicity primarily focused on high doses administered to rats, ranging from 2000 to 8000 mg/kg body weight, which is unlikely to be consumed by humans at equivalent doses (Shin *et al*., 2010). However, in street food establishments or hotels, the precise amount of MSG used is often not measured.

The risks associated with food additives were globally assessed in the mid-twentieth century by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (Heinemeyer, 2019). Given the widespread use and popularity of MSG in enhancing food taste, researchers have investigated its potential effects on human health. Studies conducted since the 1960s have indicated possible dangers associated with MSG, although varying observations have emerged over time. Experimental animals, especially neonatal mice, have shown adverse effects, as MSG at higher doses can act as a neurotoxic substance, affecting the hypothalamic-pituitary-

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adrenal axis and causing damage to hypothalamic nuclei neurons (Pizzi *et al*., 1977; Garattini, 2000). Initial studies on rats' reproductive organs indicated that MSG administration during the neonatal period (Days 6-10 or 1-10) affects the hypothalamic center controlling pituitary follicle- stimulating hormone (FSH) and luteinizing hormone (LH) release (Lamperti and Blaha, 1976). Chronic administration of MSG in Wistar rats has been found to induce significant oligozoospermia (Low sperm count) and increase abnormal sperm morphology in the testes (Onakewhor *et al*., 1998). MSG toxicity in rats has also been observed to cause dose-dependent effects on testicular and epididymal weight, sperm motility, sperm count, and abnormalities in sperm head morphology (Ekaluo *et al*., 2013). Studies on male mice have shown that MSG can cause reproductive toxicity by damaging gonadotropin-releasing hormone (GnRH) neurons, and this reproductive damage does not naturally recover over time (Wang *et al*., 2021). The high presence of glutamate receptors in reproductive organs and sperm makes the reproductive system vulnerable to excitatory damage from excessive glutamate in the body. Glutamate toxicity can also directly affect the hypothalamic-pituitary-gonadal axis, leading to imbalances in reproductive homeostasis (Igwebuike *et al*., 2010). MSG consumption has been found to severely affect testicular tissues and spermatogenesis, leading to decreased testicular weight and diameter, reduced germinal epithelium height, decreased sperm count, and increased abnormalities in sperm morphology (Das and Ghosh, 2010; Nosseir *et al*., 2012). Additionally, daily MSG consumption has been associated with deteriorated semen quality, decreased testosterone levels, body weight, and relative testes weight (Khaled *et al*., 2016). This comprehensive review aims to provide an overview of the potential risks associated with MSG consumption based on recent preclinical and clinical research findings regarding its toxic effects.

II. Discovery

In 1866, German chemist Karl Heinrich Ritthausen discovered glutamic acid while working with wheat gluten. In 1908, Professor Ikeda identified the savory taste of glutamic acid (glutamate), a nonessential amino acid. Combining glutamate with sodium resulted in the substance known as monosodium glutamate (MSG). Ikeda recognized that sodium glutamate had the most pleasant taste and best solubility among the salts he studied, such as potassium glutamate, magnesium, and calcium. He also observed its easy crystallization (Ikeda, 1908). In the same year, Kikunae Ikeda isolated glutamic acid as a flavoring substance from a type of seaweed called Laminaria japonica (kombu) through crystallization and aqueous extraction. He described its taste as umami (Lindemann *et al*., 2002). In 1909, the Suzuki Brothers produced MSG, naming it "Aji-no-moto," which translates to "essence of taste" (Chiaki, 2009).

III. Structure and properties

Monosodium glutamate (MSG) is a white or off-white crystalline powder with a slight peptone-like odor (NTP, 1992). It is a soluble compound with a molecular weight of 187.13 and is commonly available in the form of a white crystalline powder. MSG does not exhibit hygroscopic properties and remains stable in quality and appearance during extended storage at room temperature. It is also resistant to decomposition under normal food processing or cooking conditions, except in acidic environments with pH levels of 2.2-2.4 and at high temperatures. In such conditions, MSG can undergo partial dehydration and convert into 5-pyrrolidone-2-carboxylate. Additionally, at very high temperatures and alkaline conditions, glutamate may racemize to D, L glutamate. Like other amino acids, MSG can participate in Maillard-type reactions when in the presence of reducing sugars. The unique taste imparted by MSG is a result of its taste-active chemical properties. The taste perception is dependent on the stereochemical structure, with the D-isomer of MSG not contributing to any distinct taste (Kuninaka, 1960). The ideal palatability concentration for MSG is between 0.2% to 0.8%, and its use tends to be self-limiting as excessive amounts can diminish palatability. The largest palatable dose for humans is approximately 60 mg/kg body weight (Walker and Lupien, 2000).

IV. Uses of MSG

A. Food additive: MSG is a food additive that is utilized to enhance the taste and flavor of food.

B. Staining agent: MSG has excellent bleaching properties, and both commercial launderers and private persons frequently use it in Nigeria to remove stains from clothing and other textile fabrics (Rogers and Blundell 1990).

V. Effects of MSG

A. Morphological and Anatomical study of reproductive organ

Multiple studies have documented the morphological and anatomical effects of MSG on reproductive organs. For instance, an experimental study conducted on male hamsters revealed that administration of 4 or 8 mg MSG/gm from Days 1-5 resulted in significantly lower weights of the testes, adrenal glands, and pituitary glands, while seminal vesicle weights remained like those of the control groups. When the male hamsters were given 4 or 8 mg MSG/gm on Days 6-10 or 1-10, all organ weights were significantly lower compared to the control values, and the testes in the groups receiving 8 mg/gm MSG appeared atrophic (Lamperti and Blaha, 1976). Another study by Kadir *et al*., (2011) observed that animals receiving the highest dose of MSG exhibited increased aggression. Although animals in the treated groups consumed more food and drink water, and did not showed in increased body weight. Animals in the treatment groups exhibited slower growth rates, with the group

receiving the highest MSG concentration showing the slowest growth rate. According to Nossier *et al*., 2012 showed that all animals in the treated groups had smaller testes compared to the age- matched control groups. MSG administration induced toxicity, leading to reduced weights of the testes and epididymis in rats (Ekaluo *et al*., 2013). Additionally, MSG-treated animals exhibited significantly smaller diameters of seminiferous tubules and a decrease in germ cell height (Sakr and Badawy, 2013). According to Alalwani, (2013) rats treated with MSG observed severe diarrhea, frequent urination with an unpleasant odor, testicular hemorrhage during anatomy, increased appetite, and weak limb movement. In male rats, MSG induction resulted in smaller epididymis, vas deferens, and seminal vesicles. Iamsaard *et al*., (2014) and also led to a significant decrease in testicular weight (Mohamed *et al*., 2017). Similarly, a study conducted on mice revealed that at 60 days of age, the group exposed to monosodium glutamate exhibited significant differences, including dull hair, a short and fat body composition, thick subcutaneous fat, a short penis, testis dysplasia, and the inability of the testis to descend into the scrotum. These conditions persisted at 90 days of age (Wang *et al*., 2021). These findings indicate that MSG exposure can have detrimental effects on morphological and anatomical changes, potentially leading to various biological dysfunctions.

B. Weight Response

MSG has been associated with increased food consumption, which can contribute to obesity. In a study by Ashoush (2007), rats treated with MSG showed a significant increase in final body weight, potentially due to a hypothalamic lesion that impairs sympathetic transmission in the adrenal medulla, leading to reduced catecholamine synthesis and secretion. Kumar *et al*., (2008) found that MSG exposure reduced sperm count, testicular weight, sperm abnormalities, and ascorbic acid levels in the testis, with a close correlation observed between decreased ascorbic acid concentration and decreased sperm count and increased abnormalities. According to Fernandes *et al*., (2012) observed diminished body weight and naso-anal length in all rats treated with MSG, and male obese rats showed significant reductions in absolute and relative weights of the testis, epididymis, prostate, and seminal vesicle. In other studies, on reproduction by Sakr and Badawy (2013) reported significantly lower testicular weights in MSG-treated rats after four weeks of treatment, Ekaluo *et al*., (2013) found significantly reduced the weights of testes and epididymis and Alalwani (2013) also reported changes in body weights and testis tissue. These studies suggesting that MSG treatment may contribute to infertility in rats. Similarly, Abd-El-Aziz and colleagues (2014) conducted a study demonstrating that extended exposure to MSG in adult male rats' results in an initial rise in weight gain, succeeded by eventual suppression, irrespective of their food intake. The researchers attributed this phenomenon to the development of gastric mucosal damage. This suggests that the prolonged consumption of MSG might lead to gastric impairment, subsequently causing a reduction in body weight. Khaled *et al*., (2016) initially observed gaining weight in MSG treated rats but after some time rats showing lower body weight, reduced feed intake, and decreased testicular weight. Some similar reports were also studied by Mohamed *et al*., (2017) Jubaidi *et al*., (2018) Kianifard *et al*., (2020). Numerous studies have indicated that MSG can increase food intake due to its potential to enhance saliva secretion and alter metabolism. However, further research is needed to investigate the effects of MSG on metabolism, appetite, and long- term exposure. Large-scale clinical studies with a significant number of participants are necessary to determine the effects of prolonged MSG exposure on food consumption, body weight, and body mass index (BMI).

C. Histomorphological Alteration

1) Testes

MSG administration has been associated with histomorphological changes in various reproductive organs. Lamperti and Blaha (1976) conducted a study on hamsters and found that treating them with 8 mg MSG/gm from Days 6 to 10 after birth resulted in shrinking of the testicular tubules and inhibited spermatogenesis. Spermatids and spermatozoa were absent in these tubules. Das and Ghosh (2010) reported that MSG- induced histological changes affected both the germinal epithelium and Leydig cells in the testes. There was a decrease in spermatogenic cells in many tubules, along with an increase in the pachytene stage of primary spermatocytes. Leydig cells exhibited growth. According to Igwebuike *et al*., (2011) examined the seminiferous tubule of male rats given MSG 4 mg/g body weight found no apparent pathological lesions. The histological studied expanded by Kadir *et al*., (2011) showed different histological changes in the testes, the sperm cell population was lower, and the seminiferous tubules showed varying degrees of disorganization and a less convoluted structure. Nosseir (2012) revealed that the testes of MSG-treated rats showed histological changes, variable degrees of atrophy in the seminiferous tubules, disorganization of the germinal epithelium, loss of spermatogenic cells (especially spermatocytes and spermatids), and exfoliation of germ cells. The seminiferous tubule lumina exhibited severe atrophy due to epithelial loss, with only Sertoli cells and spermatogonia remaining. Spermatogenic cells displayed signs of degeneration and necrosis, with pale or vacuolated cytoplasm and various chromatin abnormalities. Vacuolations of different sizes were also observed in the tubule lumina. The number of Leydig cells was significantly reduced. Iamsaard *et al*., (2014) compared the histology of rat testes after MSG administration at different doses. They found no significant histological changes in the testes of rats given a dose of 0.25 gm/kg body weight of MSG.

However, mild sloughing of spermatogenic cells, vacuolization, and shrinkage of interstitial tissues were observed in rats given higher doses of MSG. In another study by Alalwani (2013), rats injected with MSG exhibited disruption of spermatogenic cells in the seminiferous tubules, an irregular basement membrane, necrosis of Leydig cells, and loss of interstitial connective tissue cells. Spermatogenic arrest, indicated by the absence of sperm formation and presence of primary spermatogonia, (Hamza and Harbi, 2014). Theses MSG treated studies are extended by many researchers the presence of heavily pigmented nuclei in Sertoli cells, malformed germ cells with pyknotic nuclei, and the presence of vacuoles between germ cells (Mohamed *et al*., 2017), a decrease in sperm concentration in the epididymis lumen of the prostate gland and observed folding of the basal membrane (Abu Hanipah *et al*., 2018), congested interstitial blood arteries and deteriorating spermatogonial cells (El-Masry and El-sayed 2019), deformations in seminiferous tubules, thinning of the epithelial layer, and loss of spermatocytes (Jubaidi *et al*., 2019). histological alterations in the testes (El Kotb *et al*., 2020). Some recent studies are also proved the destructive effect of MSG by Kianifard *et al*., (2020) atrophy, uneven epithelium, loss of germ cells, and arterial hyperemia in the seminiferous tubules and Abdul Hamid *et al*., (2021) irregular, congested blood vessels, disorganized testicular structure, degenerated interstitial tissue, and damage to the seminiferous epithelium. They also noted a decrease in the layers of spermatogenic cells and the presence of pyknotic nuclei and sloughed cells in the tubule lumina. Al Husseini *et al*., (2022) found congestion, absence of sperm, and sloughing of the epithelial layer in the treated groups.

2) Epididymis

There are very few reports available on histological examination of the ductus epididymis in rats treated with MSG revealed the presence of vacuolated cells (Sakr and Badawy, 2013). In a study conducted by Hanipah *et al*., in 2018, it was reported that the epididymis exhibited a decrease in the mass of spermatozoa within the lumen. Additionally, the 21characterized by irregular nuclei. The mass of spermatozoa was significantly reduced. Another research study documented that male rat treated with MSG exhibited congestion and degeneration of columnar epithelial cells and their stereocilia in the epididymal tissue. Furthermore, the epididymal lumen was devoid of sperm (Al Husseini *et al*., 2022).

3) Prostate Gland

A study on MSG was conducted by Jubaidi *et al*., (2019) observed the prostate gland of rats exhibited prostate lumen atrophy and prostate epithelium appeared less wrinkled and thinner.

4) Seminal Vesicle

The seminal vesicles of rats treated with MSG exhibited decrease in mucosal folding. The epithelial lining of the rat seminal vesicle showed irregular and disorganized cell structural patterns. In comparison to the control groups, the epithelium lining displayed uneven and irregular cell structural configurations (Jubaidi *et al*., 2019). Furthermore, El- Masry and El-sayed (2019) reported exhibited blood vessel congestion, hyperplasia, and vacuolation in the serosa of the seminal vesicles.

These findings indicate that MSG supplementation has detrimental effects on histomorphological changes in the male reproductive organs. The histological structure is significantly affected by MSG. Considering the adverse effects and the importance of these findings, it is crucial to confirm these observations through clinical research.

D. Sperm Analysis

While explaining sperm abnormality after administration of MSG, Kumar *et al*., (2008) asserted significant increase in incidence of abnormal tails, a considerable decline in the number of normal sperm, and an increase in sperm abnormalities. In another study, it was reported that the adult male rat's cauda of epididymal sperm reserves reveals that the value obtained from the three MSG-treated groups was considerably lower (Igwebuike *et al*., 2011). Sperms which had an excellent forward directional movement, progressivity was reduced uniformly across all MSG treated groups. Highest dose of MSG had the largest percentage of atypical morphology, various abnormal head shapes (curved, rounded) and tail lengths (short, long, double). Statistically significant percentages of sperm cells with aberrant shapes were present in other MSG treated groups as well (Kadir *et al*., 2011), and showed significantly different sperm motility, sperm count, and sperm head abnormalities (Ekaluo *et al*., 2013).

According to Iamsaard *et al*., (2014) the endogenous acrosome reaction is represented by the concentration and proportions of sperm in the epididymis, the epididymal sperm concentration was considerably lower in the MSG group that received 6 gm/kg of body weight on days 14, 28, and 42 of the MSG, the mean cauda epididymal sperm reserves (CESR) of all the treated groups were considerably lower. The finding of Ochiogu *et al*., (2015) revealed that the groups that received 1.0 gm/kg BW of MSG subcutaneously and the group that received 1.0 g/kg BW of MSG orally had the lowest mean CESR on days 14 and 28, respectively. Other researchers' findings showed that MSG-treated male rabbits had significantly lower sperm motility, total motile sperm, total function sperm fraction, and initial fructose levels. on the other hand, a substantial rise in the parameters of dead sperm and abnormal sperm was seen in the rabbits (Khaled *et al*., 2016). Radhiah Najm Abd, (2017) observed that MSG influenced sperm abnormalities in male mice, according to the findings. When mice were given MSG for 7, 14, and 21 days, their normal sperm count decreased

significantly than in the groups that received MSG orally for 1, 2, and 3 weeks, respectively. However, sperm abnormalities come in a variety of shapes, including headless, tailless, hookless, and abnormal sperm heads. Significant reductions in sperm motility, sperm percentage, and sperm abnormality were brought on by MSG (El-sawy *et al*., 2018). Treatment with MSG at 120 mg/kg body weight significantly decreased the epididymal sperm count, motility, and viability as well as increased the proportion of sperm with aberrant morphology (Jubaidi *et al*., 2018). A rat given MSG demonstrates defective sperm morphology features were divided into three categories: tail, neck, middle piece, and head defects. The results were then expressed as abnormal sperm (El-Masry and El- sayed, 2019). All sperm analysis indices were non-significantly decreased in the MSG-receiving groups (Kianifard *et al*., 2020).

Although MSG is regarded to be a probable triggering agent for sperm abnormalities such as reduced sperm count, deformities of sperm shape, and so on, studies demonstrate that MSG has a greater impact on reproductive function.

E. Hormones Study

Several studies have reported on hormone level alterations following MSG administration. Igwebuike *et al*., (2011) found lower mean serum testosterone levels in both young and adult rats that received low, medium, and high doses of MSG. The similar results were reported by Fernandes *et al*., (2012) diminished plasma testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Sakr and Badawy (2013) reported lower testosterone and LH levels. Some researchers were extended this studied and analyze the different hormones level such as Iamsaard *et al*., (2014) found that rats given higher doses of MSG (3 gm/kg and 6 gm/kg body weight) had significantly lower plasma testosterone levels, whereas rats given a lower dose (0.25 gm/kg body weight) had normal testosterone levels. Decreases in blood levels of GnRH, LH, testosterone, and thyroid (Ichimoku *et al*. 2014), decline in level of gonadotropin-releasing hormone (GnRH), Testosterone and LH (Ochiogu *et al*., 2015), significant decreases in serum LH, testosterone, and cholesterol levels, as well as serum ALT activity, in male rabbits (Okoye *et al*., 2016), lower blood testosterone levels (Khaled *et al*., 2016), decrease in serum testosterone and LH levels (Mohamed *et al*., 2017). Jubaidi *et al*., (2019) observed a decrease in LH levels in rats treated with MSG at a dosage of 120 mg/kg body weight, while FSH and testosterone levels did not change. El-Masry and Elsayed (2019) found a significant drop in plasma levels of LH and testosterone in rats orally treated with MSG for six weeks, lower blood testosterone levels (Kianifard *et al*., 2020), lower blood testosterone and serum LH (Mohamed El Kotb *et al*., 2020), decrease in FSH, LH, and thyroid hormone (Wang *et al*., 2021), in the same year Abdul Hamid *et al*., (2021) reported lower serum testosterone levels in rats.

Taken together, these studies indicate that MSG has a negative impact on fertility due to hormonal imbalance. However, it is important to consider the duration and routes of administration used in these studies to assess the potential threat to human health.

F. Enzyme Test

In 2014, Hamza and Herbi conducted a study in which rats were administered MSG at three distinct dosages (high, medium, and low). They found the activities of catalase (CAT), superoxide dismutase (SOD), and lactoperoxidase (LPO) were significantly reduced. Some other researchers also reported decline in SOD activity El-sawy *et al*., (2018) and Abdul Hamid *et al*., (2021).

Overall, these findings indicate that MSG ingestion leads to changes in enzyme levels, resulting in a reduction in the body's antioxidant defense against oxidative stress. However, it is important to note that this research provides limited insights into the overall outcomes of MSG consumption on enzyme activity.

G. Immunohistochemical alteration

In a study by Mohamed El Kotb *et al*., (2020), it was observed that the control group showed positive proliferating cell nuclear antigen (PCNA) immunoreactivity in the nuclei of the entire population of germ cells (deep brown nuclear response). However, in the MSG group, only a few germ cells, specifically spermatogonia, exhibited positive PCNA antibody staining. There was a significant decrease in PCNA reactivity observed in some karyolytic cells. In the immunohistochemical study conducted by Al Husseini *et al*., (2022), male rats fed MSG for 28 days were examined for nuclear factor (NF)-κB immunoreactivity in their testicles and epididymis. In the control group, no immunological reactivity of NF-κB was detected in the testis and epididymis sections. However, in Group A (MSG-treated group with a lower dose), there was mild immune reactivity of NF-κB protein observed in Leydig cells, while robust immune responses were seen in the germinal epithelial layer of seminiferous tubules. In Group B (MSG-treated group with 120 mg/kg dosage), the NF-κB protein showed immunoreactivity in the interstitial space, germinal layer of seminiferous tubules (including Leydig cells), and mild immune staining in epididymis tissues.

These immunohistochemical studies indicate that the use of MSG as a food additive can induce an inflammatory response in the male reproductive organs, which may affect male fertility. This was evidenced by increased levels of NF-κB in the treated testis and epididymis tissues, which is a key regulator of inflammatory responses.

H. Monosodium Glutamate (MSG) and its Role in Triggering Reproductive Dysfunction

In this review paper several studies have reported that the MSG (monosodium glutamate) can cause various problems such as morphological changes, weight response, histological alterations, sperm abnormality, hormonal imbalance, enzyme activity and immunohistochemical alterations in rats, mice, hamster and rabbit these findings are outlined in Table 1, 2, 3 and 4 respectively.

Table No 1: Overview of preclinical research examining the potential Reproductive effects of monosodium glutamate (MSG) on Rats.

Model organism	**Dosage**	**Duration**	**Inference**	**Reference**
Male Wistar rat	1gm/kg BW	8 days	Alteration in hormone level	Yonetani and Matsuzawa, 1977
Male albino Wistar Norwegian brown hybrid rats	4mg/gm BW	10 days	Oxidative and genotoxicity	Farombi and Onyema, 2006
Male Wistar rat	4gm/kg BW	15 and 30 days	Toxic effect on reproductive system	Kumar *et al*., 2008
Adult Wistar rat	250gm,500gm,1gm and 2gm/ kg BW	14 days	Aggressive behaviour	Kadir *et al*., 2011
Male Sprague-Dawley rats	1, 2, and 4mg/kg BW	Every 48 hours for 6 weeks	Disrupt hypothalamic-pituitary-testes regulatory axis	Igwebuik *et al*., 2011
Male Wistar rats	4mg/kg BW	120 days	Lowers sperm production	Fernandes *et al.*, 2012
Male albino rat	4ml/kg BW	14 days	Histological alteration	Nosseir *et al.*, 2012
Male albino rat	2mg/kg BW	65 days	Sperm toxicity and abnormality	Ekaluo *et al*., 2013
Male Wistar rat	30 and 60mg/kg BW	2 months	Deleterious effect on testes	Alalwani, 2013
Sprague-dawley male rats	0.25, 3 or 6 gm/kg BW	30 days	Sensitivity of male rat reproductive organ	Iamsaard *et al*., 2013
Male Sprague-Dawley Rats	4mg/kg BW	4weeks	Reproductive toxicity	Sakr and Badawy, 2013
Male Wistar rat	6, 17.5 and 60 mg/kg BW	30 days	Testicular toxicity	Hamza and Al-Harbi, 2014
Adult male Sprague-Dawley rats	395 mg/ kg bw	3 and 6 weeks	Histological alterations	Abd El-Aziz *et al.*, 2014
Male albino rat	0.25, 0.5 and 1gm/kg BW	Every 48 hours for 6 weeks	Hormonal and histomorphology disfunction	Ochiogu *et al*., 2015
Male albino rat	4g/kg BW	6 Weeks	Adverse effect on reproduction	Mohamed *et al*., 2017
Male Wistar rat	2gm/kg BW	4 Weeks	Testicular disfunction	El-Sawy *et al*., 2018
Male Sprague-Dawley Rats	60 and 120 mg/kg BW	28 days	Oxidative stress in accessary reproductive organ	Abu Hanipah *et al*., 2018
Male albino rat	0.83, 1.66 and 15-18g/kg BW	30 days	Affects cognitive function	Moneim *et al*., 2018
Male Sprague-Dawley Rats	60 and 120mg/kg BW	28 days	Reproductive system damage	Jubaidi *et al*., 2019
Male Sprague-Dawley Rats	60mg/kg BW	6 Weeks	Male infertility	El-Masry and El-Sayed, 2019
Male Wistar rat	2 and 4 g/kg BW	28 days	Testicular structural and functional alteration	Kianifard *et al*., 2020
Male Wistar albino rat	2mg/gm BW	Three weeks	Testicular toxicity	El Kotb *et al*., 2020
Male albino rat	15mg/kg BW	30 days	Toxicity in the rat testes	Abdul Hamid *et al*., 2021
Male Wistar rat	60 and 120mg/kg BW	28 days	Inflammatory response in reproductive organ	Al-Al Husseini *et al*., 2022

Table 2: Overview of preclinical research examining the potential Reproductive effects of monosodium glutamate (MSG) on Mice.

Model organism	**Dosage**	**Duration**	**Inference**	**Reference**
Swiss albino mice	2mg/gm BW	day 2, 4, 6, 8 and 10 of postnatal life	Effect on spermatogenesis	Das and Ghosh, 2010

Male mice	4mg/g m BW	7, 14 and 21 days	Sperm abnormalities	Radhia h Najm Abd, 2017
Neonata l Male and Female Kunming mice	4mg/g m BW	60 and 90 days	Damaging GnRH Neuron	Wang *et al*., 2021

Table 3: Overview of preclinical research examining the potential Reproductive effects of monosodium glutamate (MSG) on Hamster.

Model organism	**Dosage**	**Duration**	**Inference**	**Reference**
Female/ Male golden hamster	4 and 8 mg/kg BW	60 days	Lowers organ weight	Lamperti and Blaha, 1976

Table 4: Overview of preclinical research examining the potential Reproductive effects of monosodium glutamate (MSG) on Rabbit.

Model organism	**Dosage**	**Duration**	**Inference**	**Reference**
Male Rabbit	0.25, 0.5 and 1 g/kg	14, 28 and 56	Significant lower in hormone level	Okoye *et al*., 2016
Male Rabbit	8mg/kg BW	12 weeks	Reproductive toxicity	Khaled *et al*., 2016

I. Mechanism of MSG in Animal

The impact of MSG on male reproductive organs, structure and function might stem from its varied effects on cells. This can lead to changes in sperm production, oxidative harm, histological modifications, and hormonal imbalances. These factors could ultimately lead to reproductive issues in males, as depicted in Figure 1.

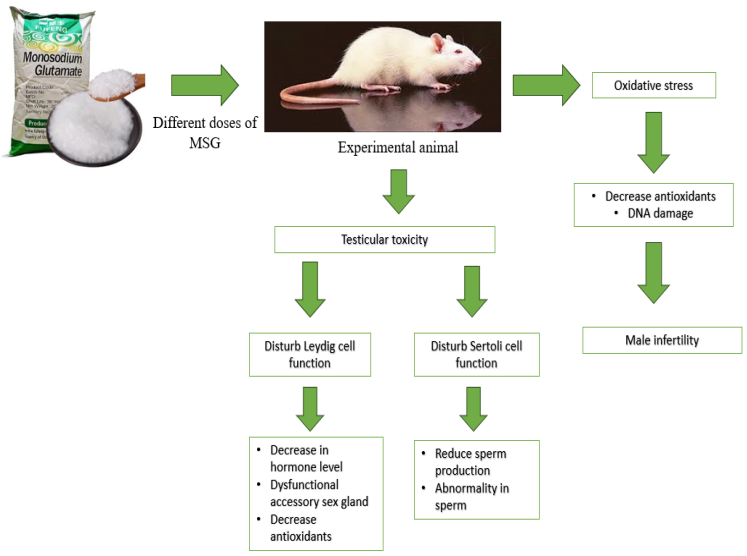

Fig.1 Mechanism of MSG in Animal

Conclusion

The above review brings us to the conclusion that the MSG effects encompass morphological changes, sperm abnormalities, histological alterations, and weight gain. Researchers have also underscored the detrimental impact of MSG on the overall physiological systems of both humans and animals. Consequently, it is crucial to acknowledge that the consumption of MSG may yield negative effects when exceeding certain limits. Subsequent research is imperative to ascertain the optimal and safe quantity of MSG that can be consumed.

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