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Review

Targeting On The Regulation On Testicular Spermatogenic Activity Against Monosodium Glutamate Adverse Effects

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Abstract

Monosodium glutamate (MSG) is a well-known food additive that has been shown to be effective in causing male reproductive abnormalities. This common flavor enhancer is used extensively in many diets to improve flavor. There are various mechanisms through which it can cause reproductive dysfunctions. These include spermatogenic alteration, which can lead to abnormalities such as low sperm count, high sperm count, reduced live sperm and decreased sperm pH; oxidative damage, which can involve increased lipid peroxidation and decreased antioxidant enzyme activities; histological alteration, which can involve blood clots, distorted germ cells, and Sertoli cells; and gonadotropin imbalance, which can involve decreased levels of follicle-stimulating hormone, testosterone and luteinizing hormone. The different known pathways through which MSG may cause reproductive dysfunction are therefore covered in this review along with mitigation techniques for its harmful consequences.

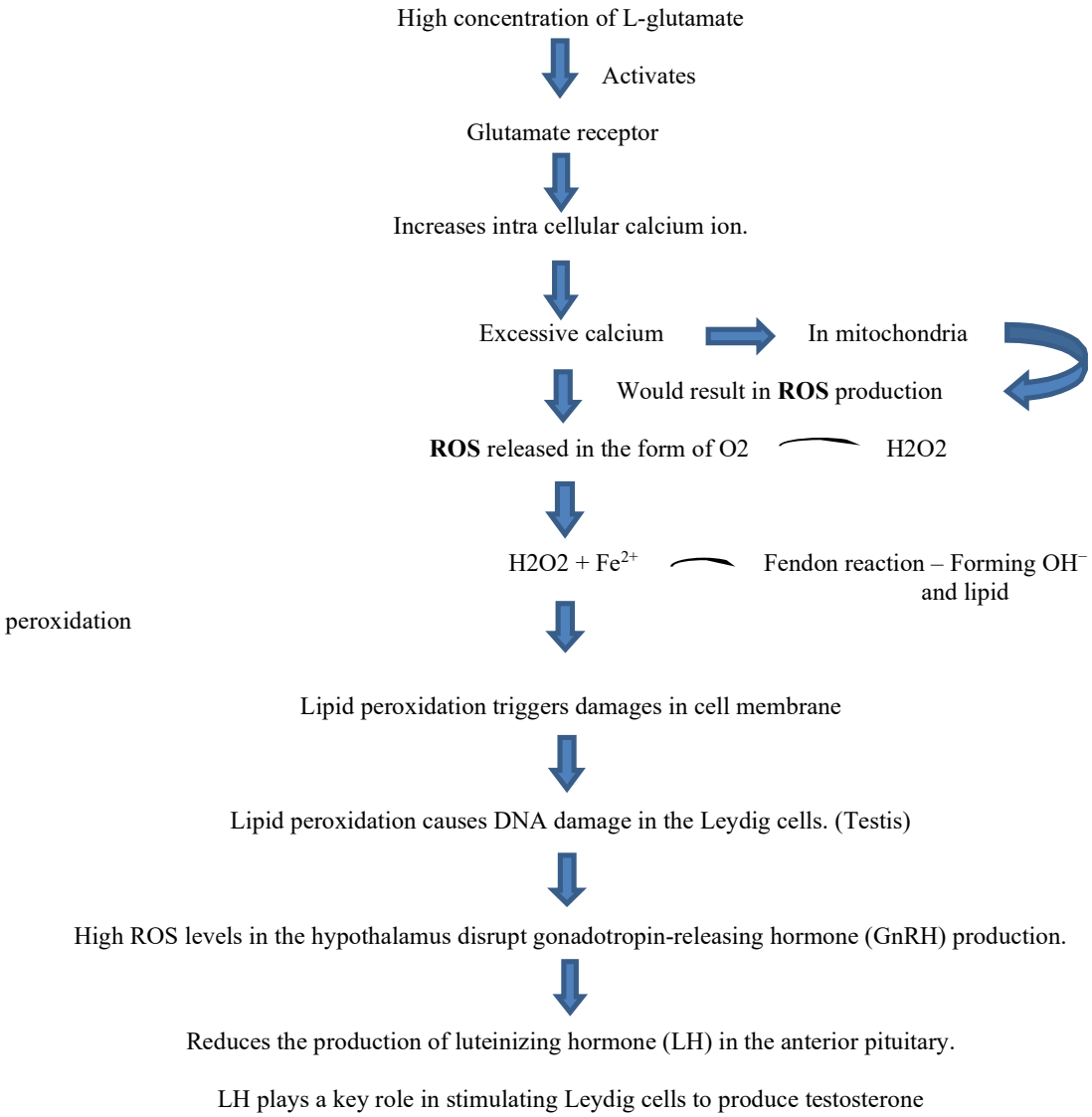
Keywords: Monosodium glutamate, spermatogenic, Infertility, sperm quality, testosterone.

INTRODUCTION

One year of regular, unprotected sexual activity without conception is considered infertile. Based on analysis, the reason of infertility in about 50% of affected couples is related to or caused by male factors[1]. Infertility sufferers manage this condition individual often both modern medicine and traditional therapies derived from natural botanicals [2,3]. Since roughly 25% of current medications are derived from plant. Based, the use of

medicinal plants in the treatment of illnesses and dysfunctions dates back several millennia and has greatly influenced the creation of medicines. Furthermore, up to 60% of people use herbal medications for medical purposes worldwide[4,5]. Today, many of the extracts, fractions or molecules that have been extracted from these plants are widely utilized to treat or cure many aspects of male infertility, including loss of orgasm, sperm abnormalities, erectile dysfunction, sexual asthenia, libido absence and relaxation and ejaculatory dysfunctions. Male infertility has a variety of causes but psychogenic and endocrine diseases, vascular injuries and drug usage are among the symptoms that infertile individuals experience[6]. Numerous in vitro, in vivo and clinical investigations have demonstrated the practical application of plants in enhancing male fertility metrics. The use of medicinal plants to treat male infertility symptoms such as libido problems, erectile dysfunction, ejaculatory disorders and sperm abnormalities, was the main emphasis of this review, along with the efficacy of phytomedicines as a therapeutic approach. Data from a few chosen papers was categorized based on the intended impact of a plant extract on male reproductive function as well as the subject (human, rodent) that the extract was tested on to determine its possible activity[7].

CAUSTIVE AGENT: MONOSODIUM GLUTAMATE[8]

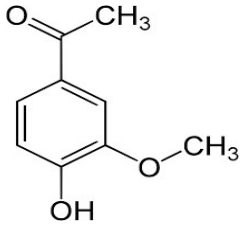


MEDICINAL HERBS

Currently the medicinal plants and herbs are being used in extracts forms for their spermatogenic activity, various clinical studies confirmed that medicinal plant extracts shows Testicular spermatogenic activity and Targeting on the regulation on Testicular spermatogenis.

APOCYNIN, PROPOLIS EXTRACT, MARSELIA CRENATA, HIBISCUS SUBDARIFFA, CYDONIA OBLONGA, MORINGA OLEIFERA, ZINGER EXTRACT, NIGELLA SATIVA L., TEMULAWAK, DAYAK ONION.

APOCYNIN
BIOLOGICAL SOURCE: *Picrorhiza kurroa* and *Apocynum cannabinum*
FAMILY: Scrophulariaceae
USES: Atherosclerosis, Antioxidant



It is well known that apocynin (APO), which is isolated from the roots of the plant Apocynum cannabinum, effectively inhibits NOX [9]. Numerous experimental investigations have proven that APO has an anti-inflammatory effect [10]. The movement of cytosolic elements to the cell membrane causes NOX activation [11,12]. By affecting NOX activity in live human neutrophils, APO selectively inhibits the generation of ROS. APO, however, has little effect on other intracellular killing processes such as phagocytosis[13,14]. Diverse cells express diverse types of NOX and they each have a distinct physiological purpose. Eosinophils, macrophages and neutrophils all contain the NOX-2 isoform[15].

The Acibadem Mehmet Ali Aydinlar University Experimental Animals Ethics Committee accepted this experimental investigation (ACU-HADYEK, Approval number: HDK- 2020/39). Eight-week-old male Sprague Dawley albino rats (n = 32) were housed in cages with a standard light/dark cycle (12:12 h) at a temperature of 22 ± 2 °C. During the 28-day trial period, rats were fed ad libitum with regular animal feed. The rules and requirements of ARRIVE (Animal Research: Reporting of in Vivo Experiments) were followed in the conduct of this study.[16]

Assessment of Testicular MDA, GSH, and SOD Levels; Measurement of Serum Testosterone, FSH and LH Concentrations; Sperm Count, Motility and Morphology. MSG led to a reduction in cell proliferation an increase in oxidative stress, apoptosis and a deterioration of testis morphology including the blood-testis barrier. In the MSG + APO group, apocynin administration corrected all of the declining morphological and biochemical markers. By preserving the integrity of the blood-testis barrier and promoting balanced hormone and oxidant/antioxidant levels, apocynin is thought to prevent testicular degeneration.[17]

PROPOLIS EXRACT
BEE GLOW
BIOLOGICAL NAME: *Apis mellifera*
FAMILY: Apidae
USES: Antibacterial, antifungal, antioxidant, anti-inflammatory

Monosodium glutamate (MSG) is a common flavor enhancer found in a variety of food products. It is the sodium salt of naturally occurring (non-essential) L-form of glutamic acid. Resinous materials that honeybees gather from a variety of plant sources are known by the generic name propolis sometimes known as "bee glue." The purpose of the current study was to look into propolis's potential therapeutic and preventive benefits against MSG on rat testes. As a result, fifty male albino rats in all were split up into five groups. The second group received propolis orally once a day for eight weeks at a dose of 200 mg/kg/b. w., whereas the first group functioned as the control. For eight weeks the third group was given MSG at a dose of 1 g/kg b.w. The protecting group or fourth

group was for four was given exclusively in the first instance and for the next four weeks propolis and MSG were combined. The fifth group (the therapeutic group) received propolis in addition to MSG for four weeks after receiving MSG alone for four weeks. Testes tissues were removed for histological analysis after four and eight weeks. Studies on histopathology revealed harmful changes in the tissues of the testes. Seminiferous tubules experienced atrophic alterations, spermatogenic process impairment, thicker intertubular space, necrosis of primary spermatocytes exhibiting karyolysis of their nuclei and severe oedematous fluid infiltration due to MSG. The protective group's propolis extract significantly improved the histopathological analysis. Extract from propolis in the therapeutic group.[18]

MARSELIA CRENATA
A SPECIES OF FERN
Clover fern family
BIOLOGICAL SOURCE: *Marsilea crenata*
FAMILY: Marsileaceae
USES: Diuretic, anti-inflammatory, depurative properties


An aquatic plant called Marsilea crenata has a high quantity of antioxidants and may be able to stop free radical-induced cell damage. In this study, adult male rats were given monosodium glutamate (MSG) to promote luteinizing hormone (LH), testosterone levels, sperm quality and testis histology. The purpose of the M. crenata ethanol extract was to examine these effects.48 male rats were randomly assigned to one of eight groups (n = 6); these groups included the control group; the MSG group (dosed at 4 mg/g b.w.) for 30 days; the MS1, MS2, and MS3 groups (dosed at 4 mg/g b.w. MSG and M. crenata ethanol extract at doses of 0.216, 0.432, and 0.648 mg/g b.w., respectively for 30 days); and the S1, S2, and S3 groups (dosed at 0.216, 0.432, and 0.648 mg/g b.w., respectively for 30 days). Days 0 and 30 saw the collection of the blood sample in order to measure the levels of testosterone and LH. On day 30, the mice were dissected and the testes were separated for analysis using malondialdehyde (MDA), histology (spermatogenic cell count) and morphometric techniques. Additionally, semen was taken in order to measure the sperm quality parameter. Following the injection of M. crenata at all doses there was a significant ($p<0.05$) increase in the levels of testosterone and LH. Increases in spermatogonia, spermatocytes, spermatids and Leydig cells were observed in the rat testis treated with MSG after a greater dose of M. crenata ethanol extract was administered. Additionally there was a notable drop in MDA levels and an increase in seminiferous tubular diameter and germinal epithelium thickness. The number of testis morphometric, spermatogenic, and Leydig cells as well as the levels of LH and testosterone can all be enhanced by the ethanol extract of M. crenata.[19]

HIBISCUS SUBDARIFFA
BIOLOGICAL NAME: *Hibiscus rosasinensis*
FAMILY: Malvaceae
USES: Anti-hypertensive, anti-inflammatory, antimicrobial.


Male reproductive dysfunction is brought on by monosodium glutamate (MSG), a popular flavor

enhancer and feed additive. Nonetheless the efficacy of Roselle tea, a popular Hibiscus sabdariffa (HS) beverage on male fertility remains debatable. Thus, the goal of the current investigation was to determine whether aqueous HS extract (HSE) had a negative effect on the testicle or whether it could have a positive effect. This included looking at several stress markers, biochemical expressions and immunohistochemistry expressions in rats that were given MSG. The animals were split up into four groups and given gavages of distilled water, HSE, MSG and HSE + MSG in that order. Blood samples were taken for hormonal examination six weeks after the experiment started. Furthermore, testicular specimens were removed and processed for histological analysis, immunohistochemical assessment of Bax and PCNA positive spermatogenic cells and detection of oxidative/antioxidant parameters. [20]

Testing was done on the HSE's antioxidant capacity in addition to preliminary phytochemical analysis. According to our findings, the phytochemical components of HSE have a potent inhibitory effect on the DPPH radical. Comparing the MSG group to the control and HSE groups, the MSG group showed a substantial drop in testosterone, LH, FSH, and antioxidant markers with higher MDA. Along with increased Bax and decreased PCNA positive cells, the MSG group also showed alterations to the testicular histoarchitecture. In the meantime, the HSE demonstrated a strong protective effect against MSG-induced oxidative stress and testicular injury. Overall, our results show that HSE can lessen the toxicity of MSG-induced testicular in adult rats by stimulating cell proliferation, reducing oxidative stress, and reducing cellular apoptosis. [21]

CYDONIA OBLONGA
BIOLOGICAL NAME: *Cydonia oblonga* Miller
FAMILY: Rosaceae
USES: Anti diabetic, anti-cancer, hepatitis, respiratory and urinary infections.

This study aimed to assess the preventive effects of quince leaf extract a natural antioxidant on the reproductive dysfunction caused by monosodium glutamate (MSG) in rats starting from the cytotoxic effects of MSG. A dose of 500 mg/kg of quince leaf extract and two doses of 30 and 60 mg/kg of monosodium glutamate were administered. Testicular and body weight measurements as well as hormonal and epididymal sperm analysis were done at the conclusion of the study. Following the ingestion of monosodium glutamate, levels of testosterone and follicle stimulating hormone (FSH) were decreased. There were no appreciable variations in the luteinizing hormone (LH) levels. Levels of testosterone and follicle stimulating hormone improved after quince leaf extract treatment. Following the administration of monosodium glutamate and treatment with quince leaf extract the population of epididymal sperm was decreased. After being treated with quince leaf extract the elevated sperm motility rate caused by monosodium glutamate was decreased. When monosodium glutamate and quince leaf extract were administered together the result was a greater increase in body weight. The functional changes in the reproductive system caused by monosodium glutamate can be lessened by the quince leaf extract. [21]

MORINGA OLEIFERA
BIOLOGICAL NAME: *Moringa Oleifera*
FAMILY: Moringaceae
USES: Anti-inflammatory, anticancer, antioxidant, hepatoprotective, anti-ulcer, cardiovascular, anti-obesity, antiepileptic, antiasthmatic, ant diabetic, anti-urolithiatic.

Men who use MSG excessively in their daily lives may become infertile. MSG exposure has the potential to induce oxidative stress in cells which in turn sets off the production of free radicals. Antioxidants can help fend off free radicals. Using male mice as the experimental subject this study used a post-test only control group design in a laboratory setting. The One Way ANOVA test was utilized in the statistical analysis. Five male mice were used in this study; they were divided into four groups and one control group. The motility group of spermatozoa with active movement ($p < 0.001$) and the motility group of spermatozoa with weak movement ($p = 0.036$) showed significant differences in ≥ 2 treatment groups, according to the results of the One Way ANOVA test. The two groups displayed notable variations. The motility group with active movement underwent a Post hoc LSD test which revealed significant differences between the treatment group (600 mg/kgW; $p < 0.001$) and the control group (MGS treatment; $p < 0.001$) as well as between the treatment group and the control group. At doses of 300 mg/kgW and 600 mg/kgW an extract from moringa leaves can increase the motility of spermatozoa exposed to monosodium glutamate. [22]

ZINGER EXTRACT
BIOLOGICAL NAME: *Zingiber officinale*
FAMILY: Zingiberaceae
USES: Antioxidant, anticancer, anti-inflammatory, anti-apoptotic, anti-hyperlipidemia and anti- emetic properties.

The purpose of the study is to look into the potential protective effects of ethanolic ginger extract against male rat reproductive problems caused by monosodium glutamate (MSG). Four experimental groups consisting of 48 male albino rats were created: the normal control group the ginger extract group, the MSG only group and the MSG + ginger extract group. For four weeks, all experimental regimens were administered orally. After two and four weeks from the commencement of the experiment dissection was completed. Weight measurements for the body and testicles, aberrant sperm, and biochemical analyses were noted. Furthermore, testis tissue was subjected to molecular, histological and immunohistochemical procedures. The current data indicates that following MSG treatment, there was a substantial decrease in serum testosterone levels, serum luteinizing hormone (LH), serum FSH and anomalies related to sperm. There was also a significant increase in body weight and serum total cholesterol. When comparing the MSG group to the normal control there was an overexpression of the Bax protein and a down regulation of the B-cell lymphoma-2 (BCL-2) protein. In addition, testicular changes were identified in the group receiving only MSG treatment, as were increased caspase-3 and decreased BCl-2 positive cells in testis tissue. When ethanolic ginger extract was administered, the effects were lessened as opposed to the changes in the testicles caused by monosodium glutamate. [22]

NIGELLA SATIVA L
BIOLOGICAL NAME: *Nigella sativa L.*
FAMILY: Ranunculaceae
USES: Antihypercholesterolemic, anticancer, antibacterial, ant diabetic, anti-inflammatory.

One of the most prevalent dietary additives that may lead to male infertility is monosodium glutamate (MSG). On the other hand, Nigella sativa L. seeds (NSS) might offer an answer. The purpose of this study was to look into possible effects of NSS on rats that were fed MSG. In order to accomplish this goal, adult male albino rats were divided into three groups at random and kept in each group for 21 days: the control group did not receive any treatment; the MSG group was fed 30 g/kg of MSG; and the MSG+NSS group was fed 30 g/kg of both MSG and NSS. Testicular histomorphometry revealed that MSG caused atrophic seminiferous tubules with lining cell degeneration, damaged Leydig cells and a reduction in the number of germ cells. The irregularly interrupted basement membranes were identified by the Periodic Acid Schiff stain. In testicular cells the immunoexpressions of glutathione reductase, superoxide dismutase 2 (SOD2), and caspase-3 increased. [24]

In rats exposed to MSG, luteinizing hormone levels increased considerably and testosterone levels declined significantly; NSS restored the normalcy of this hormonal profile. Additionally, exposure to MSG resulted in significantly higher levels of glutathione-S- transferase, lipid peroxides (LPO) and total antioxidant capacity (TAC), while significantly lower levels of nitric oxide and SOD2. By rebalancing LPO and TAC, NSS was able to lessen the architectural disruptions. Through its cytoprotective and antioxidant properties, NSS lessened the testicular damage caused by MSG. [24]

TEMULAWAK
BIOLOGICAL NAME: Curcuma xanthorrhiza
FAMILY: Zingiberaceae
USES: Appetite stimulant, anti-inflammatory, anti-cancer, antibacterial.

The objective of the current investigation was to examine the protective impact of the temulawak (*Curcuma xanthorriza*) rhizome aqueous extract on the sperm quality of mice that had been treated with monosodium glutamate (MSG). 30 male mice, weighing 25– 30 g and 2.5–3 months old were used in this study. The mice were then randomly assigned to five groups: K– which received only aquadest and were healthy; K+, which received 4 mg/kg BW MSG; MT1, MT2, and MT3, which were MSG–induced male mice given oral treatment with 0.2, 0.4, and 0.6 mg/g BW temulawak (C. xanthorriza) rhizome extract for 14 days, respectively. After the course of treatment the cauda epididymis was separated and all of the mice were slaughtered. [25]

The quality of the collected semen was examined, including spermatozoa abnormalities, concentration, motility, and viability. Of the mice stimulated with MSG the MT2 group showed the highest sperm motility

(79.16±4.45%). Additionally, the MT2 group had the highest sperm viability (77.83±2.75%), followed by the MT1 and MT3 groups (70.19±5.93 and 72.41±5.53%, respectively). The MSG-induced mice's sperm concentration was shown to rise ($p<0.05$) by 14.03x106 and 14.46x106 cells/ml, respectively, in the MT2 and MT3 groups. On the other hand, sperm abnormalities in MSG-induced mice tend to decline by 38.10% (MT1), 36.32% (MT2) and 36.04% (MT3) in all treatment groups. In conclusion, 0.4 mg/g BW aqueous extract of C. xanthorriza rhizome could be administered to mice that were induced with MSG to change the sperm abnormalities and increase sperm motility, viability and concentration.[25]

DAYAK ONION
BIOLOGICAL NAME: Eleutherine palmifolia L.
FAMILY: Iridaceae
USES: Anti-oxidant, antitumor, antimetastatic effect, antibacterial, antiviral, anti-inflammatory.

The purpose of this study was to determine whether ethanol extract from Dayak onions (Eleutherine palmifolia) could protect mice (Mus musculus) against monosodium glutamate (MSG) by reducing the number of Leydig cells and the diameter of seminiferous tubules. Twenty-five mice in all were split up into five groups. Group C-was only given 0.5% CMC-Na. 0.5% CMC-Na and 4 mg/gBW/day of MSG were administered to Group C+. Dayak onion (Eleutherine palmifolia) ethanol extract was given to groups T1, T2, and T3 at doses of 30, 60, and 120 mg/kgBW/day, respectively, in addition to 4 mg/gBW/day of MSG. For 52 days, all therapies were given orally.[26]

The findings showed that exposure to MSG significantly reduced the diameter of seminiferous tubules and the number of Leydig cells in the C+ group as compared to the C- group ($p < 0.05$). When Dayak onion (Eleutherine palmifolia) ethanol extract was administered at doses of 30, 60 and 120 mg (T3) per kg BW, the outcomes were comparable ($p>0.05$) to those of the C-group. In summary, the administration of ethanol extract from dayak onions (Eleutherine palmifolia) reduces the negative effects of MSG on the quantity of Leydig cells and the diameter of seminiferous tubules in mice (Mus musculus) used as a model. According to this study, Dayak onions (Eleutherine palmifolia) are useful for maintaining reproductive health. [26]

CONCLUSION

Various mechanisms, such as oxidative damage, histomorphological changes, hormonal dysfunction and lower sperm quality may cause male reproductive harm when exposed to MSG. A more thorough mechanism for MSG-induced reproductive dysfunctions should be the main goal of future research in order to develop an improved treatment plan for the problem. It is also recommended to conduct human clinical trials to assess the harmful effects of MSG on the male reproductive system. The LH, testosterone, sperm quality, quantity of testis morphometric, Spermatogenic and Leydig cells in male MSG-treated subjects can all be enhanced by these medicinal herbs.

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