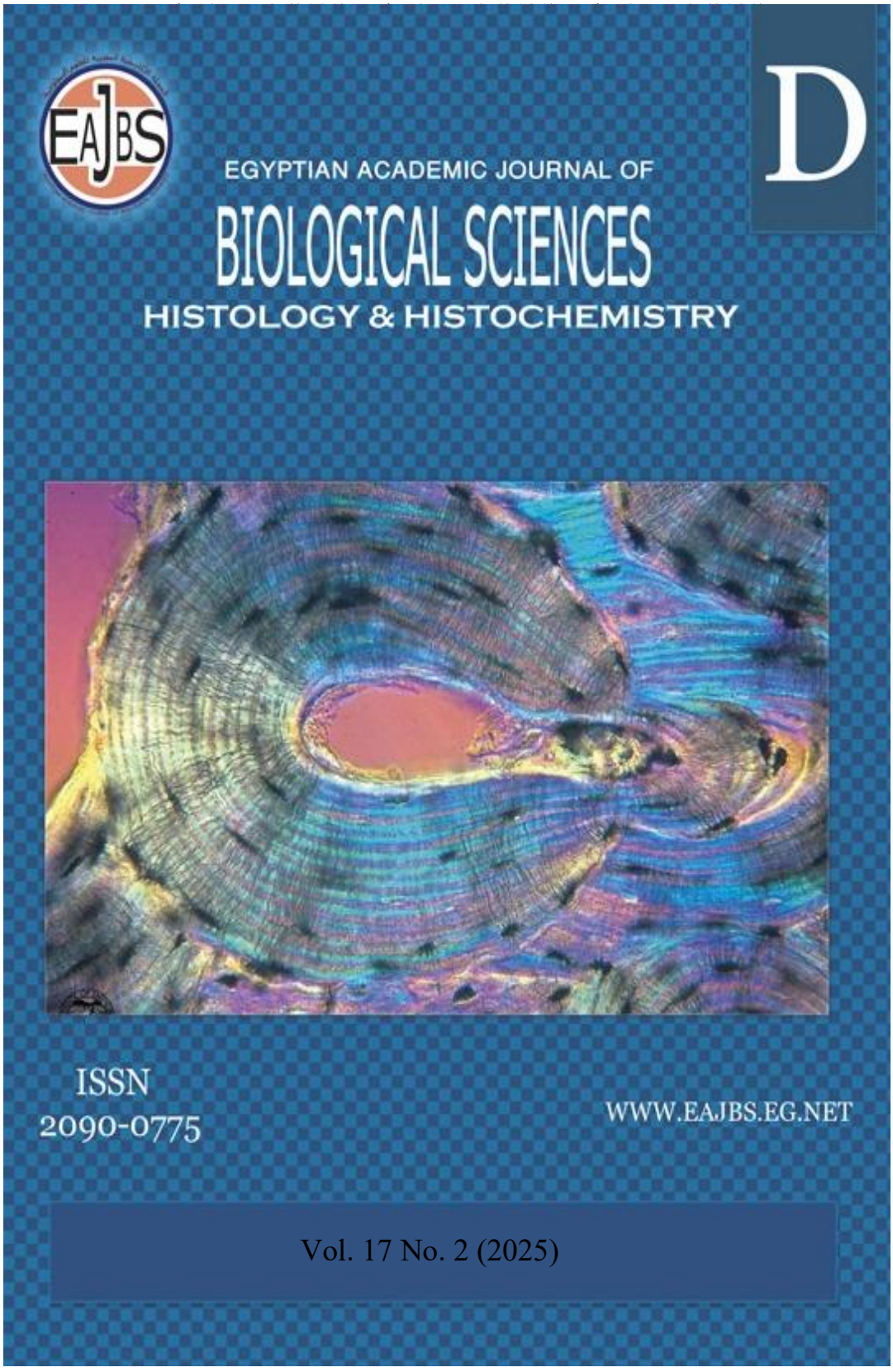

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Pomegranate Juice Mitigates Morphology, Fetal Heart and Kidney Inflammation Induced by Monosodium Glutamate Through Decreasing TNF-α and IL-6 Levels

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ABSTRACT

Background: Monosodium glutamate (MSG), a prevalent flavor enhancer in the food production business, faces opposition due to its detrimental effects on organs and its potential to induce developmental inflammatory damage in fetuses. This study aims to evaluate the impact of maternal intake of MSG on the structural and functional development of the fetus's heart and kidneys, specifically examining the expression of the inflammatory genes tumor necrosis factor-alpha and interleukin-6. Additionally, it seeks to determine whether the effects might be alleviated by the ingestion of pomegranate juice, recognized for its antioxidant attributes. **Methods:** Forty-two pregnant females were randomly assigned to six groups (n=7): the control group "C" received distilled water; "G1" received 10 ml (Pg. J) /kg body weight; "G2" received 0.55 g MSG /kg body weight; "G3" received 0.55 g MSG /kg body weight in conjunction with 10 ml (Pg. J) /kg body weight; "G4" received 1.6 g MSG /kg body weight; and "G5" received 1.6 g MSG /kg body weight along with 10 ml (Pg. J) /kg body weight. All groups received oral administration daily from the first to the twentieth day of gestation. **Results:** Exposure to MSG significantly diminishes maternal body and uterine weight, as well as fetal body weight, while elevating fetal mortality rates. The alterations were more significant at elevated dosages of (MSG). Histological analysis of the embryonic heart and renal tissues demonstrated alterations in both the cardiac and renal structures. Significant elevation of tumor necrosis factor-alpha and interleukin-6 was detected at the mRNA level in MSG-treated groups. The unfavorable effects were mitigated by the co-administration of pomegranate juice, which significantly enhanced tissue structure and inflammatory gene expression. **Conclusion:** MSG exposure during pregnancy impairs fetal development, while pomegranate juice exerts protective effects. These findings highlight the need to limit MSG intake and promote antioxidant-rich diets during pregnancy.

INTRODUCTION

Contemporary lifestyle alterations have led to heightened intake of processed foods; a behavior associated with numerous detrimental impacts on human health. This phenomenon can be ascribed to the overutilization of flavor enhancers, including monosodium glutamate (MSG) (Abdou *et al*., 2025). MSG is a food additive that functions as an effective flavor and taste enhancer, utilized in cooking to augment palatability, particularly in children's food (Hossain *et al*., 2020).

MSG enhances the distinctive flavor known as umami by possessing chemical qualities that stimulate the tongue's taste buds (Yamamoto & Inui-Yamamoto, 2023). The use of the prevalent food additive MSG in pre-prepared fast food improves meal palatability but markedly influences the appetite center, leading to obesity and many detrimental effects on humans and experimental animals (Das *et al*., 2022).

In recent years, the safety profile of MSG has been debated, as several reports link its consumption in food to adverse health reactions (Airaodion *et al*., 2019). Numerous individuals report experiencing headaches, nausea, or flushing after MSG intake, while others associate it with palpitations, chest discomfort, and fatigue (Bera *et al*., 2017). MSG exerts harmful effects on multiple organs, notably the kidneys, liver, and central nervous system, uterus, thyroid, spleen, thymus, and testes, and exhibits genotoxic effects (Rosa *et al.*, 2018). Morphological, osteological, and histological alterations are observed in 20-day-old fetuses subjected to maternal MSG treatment (Shawky *et al*., 2024).

MSG is believed to enhance the creation of free radicals in the body, resulting in a reduction in the body's antioxidant synthesis. This leads to oxidative damage across the body (Banerjee *et al*., 2021a and Banerjee *et al*., 2021b). The induction pattern of oxidative stress and modification of glucose metabolic enzymes in the animals indicated that MSG-induced oxidative stress in the renal tissues of rats may be attributed to elevated tissue glucose levels due to increased renal gluconeogenesis (Onyema *et al*., 2012). MSG significantly impacts liver and kidney cells. Research involving animals suggests that renal failure was induced by the administration of MSG due to its impact on the kidney's oxidative system (Othman & Bin-Jumah, 2019).

Certain investigations indicated a tendency suggesting an adverse correlation between glutamate consumption and blood pressure, mortality risk, and stroke mortality, but typical MSG intake does not appear to correlate with clinically significant weight gain (Loï & Cynober, 2022). Lipid peroxidation in the myocardium induces oxidative modifications of lipids and proteins, potentially resulting in arrhythmias, diminished contractility, infarction, cardiac failure, or sudden death (Banerjee *et al*., 2021b). Elevated lipid peroxidation in cardiac tissue may result from an accumulation of lipid substrates within the heart, providing a larger target for free radical oxidation (Banerjee *et al*., 2020). MSG significantly contributes to inflammation by elevating the levels of TNF-α and IL-6, which are pro-inflammatory indicators (Atteia *et al*., 2024).

Pomegranate (Pg) has historically been valued in traditional medicine, where it was administered as a natural remedy for diverse health problems, including gastrointestinal disturbances (such as diarrhea, dysentery, and ulcers), metabolic imbalances like acidosis, febrile conditions, hemorrhage, microbial and parasitic infections, as well as various respiratory ailments (Larrosa *et al*., 2010, and Mansouri *et al*., 2016). The beneficial effects of Pg are attributed to its broad array of phytochemicals, including tannins, alkaloids, and natural colors (Zarei *et al*., 2011). All Pg flavonoids exhibit antioxidant properties, thereby inhibiting inflammatory indicators, including tumor necrosis factor-alpha (TNF-α) (Zarfeshany *et al*., 2014).

Pg is abundant in antioxidant compounds, which may be advocated as a preventative element of a nutritious diet against the detrimental effects of stressors such as MSG (Martínez Soto *et al*., 2016 and Peña *et al*., 2018). Research demonstrated that Pg fruit may be utilized in the treatment of human prostate cancer due to its ability to suppress cell proliferation and induce

apoptosis (Deng *et al*., 2017). Pomegranate juice may possess antioxidant and anti-inflammatory properties by augmenting overall antioxidant capacity and reducing malondialdehyde (MDA) and interleukin-6 gene (IL-6) levels (Barati Boldaji *et al*., 2020). Tumor necrosis factor-alpha (TNF-α) is a multifunctional cytokine that influences various cell types and serves as a key mediator of inflammatory processes and is implicated in the pathophysiology of some inflammatory and autoimmune illnesses (Jang *et al*., 2021). Furthermore, TNF-α facilitates tissue repair along with regenerative and proliferative mechanisms (Moatti & Cohen, 2021). TNF and IL-6 are pivotal cytokines involved in inflammation, immunity, hematopoiesis, and tissue metabolism (Hunter & Jones, 2015; Hasegawa *et al*., 2016; and Jang *et al*., 2021). Their dysregulation is strongly linked to autoimmune disorders and persistent inflammatory conditions, aging, and cancer progression, mainly through the STAT3 signalling pathway (Jones & Jenkins, 2018; Johnson *et al*., 2018; Gyamfi *et al*., 2018; Masjedi *et al*., 2018; Rébé & Ghiringhelli, 2019).

MATERIALS AND METHODS

Fresh pomegranate (*Punica granatum L*) fruits were washed, crushed, and squeezed. The juice was filtered, pasteurized, and stored at -18°C.

Monosodium glutamate (MSG; $C_5H_8NNaO_4$; molecular weight = 187.13 g/mol; purity = 99%; catalog no. S209112) was obtained from Sigma Pharmaceuticals Manufacturing in Egypt. The median lethal dose (LD_{50}) of MSG in rats is 15–18 g/kg b.w. (Abdel Moneim *et al.,* 2018). The amounts of MSG dissolved in distilled water utilized in this investigation were 0.55 and 1.6 g MSG/kg b.w., which equals 1/30 and 1/10 of LD_{50}, respectively (Kandeel *et al*., 2019).

Experimental Design:

Pure-strain virgin male and female albino rats were obtained from the Faculty of Veterinary Medicine, Benha University (Benha, Egypt) (*Rattus norvegicus domestica*, weight: 200 ± 20 g, ages: 8-12 weeks). The rats were acclimatized in a sterile laboratory environment within air-conditioned cages, featuring a 12-hour light/dark cycle, a controlled temperature of 25°C, and unrestricted access to food and water. Following a week of acclimatization to the laboratory setting, male and female rats were paired in a 1:3 ratio. The occurrence of a vaginal plug signified day "1" of gestation. Benha University's local ethics committee issued guidelines for the use of animals in investigations (ZD/FSc/BU IACUC/2023-19b) with permit numbers (BUFS-REC-2024-260 Zoo).

Gestating rats were distributed into six groups, with 7 animals assigned to each group **(**Fig. 1**) a**nd all groups are treated on the 1^{st} -20^{th} days of pregnancy as follows:

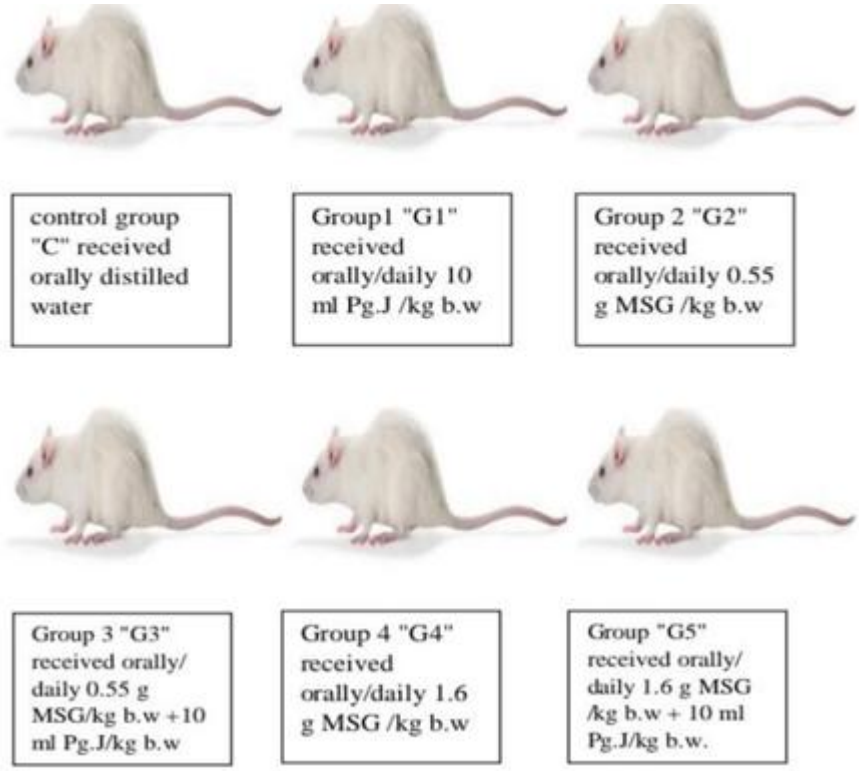

Fig.1: Experimental design.

On the 20th day of gestation, the pregnant rats were weighed, and cesarean sections were performed to extract the uterus, with the uterine weight also documented. The quantity of fetal swellings, survival rates, mortality rates, and fetal body weight were assessed in each horn. A dorsal midline incision was performed to access the unborn kidneys and cardiac structures for their expeditious removal. The collected tissue specimens were preserved in 10% neutral buffered formalin. Sections (5 µm) were stained with H&E for standard light microscopy and histological examination (Henwood, 2017).

Total RNA was extracted from kidney tissue samples of each rat embryo with Trizol reagent. RNA yield and purity were measured using a NanoDrop spectrophotometer (Nano Spectrostar, BMG LABTECH). cDNA was synthesized with a reverse transcription kit, and random primers (Thermo Scientific, Hudson, NH, USA; cat# AB-1453/B) following the manufacturer's guidelines. All DNA contamination was eradicated utilizing the buffer included in the cDNA synthesis kit.

For the qPCR reaction, The Primer3 software (version 0.2.0) was utilized for the creation of primers for each gene under investigation (Koressaar & Remm, 2007). Table 1 displays the primer sequences for each gene. Quantitative PCR was conducted using the Bio-Rad iCycler detection system utilizing cDNA samples diluted 80-fold. The qPCR reaction was conducted with a SYBR green master mix (Thermo Scientific, Hudson, NH, USA). The cDNA templates (0.006 µg/µl) were included in the master mix alongside the forward and reverse primers at a concentration of 0.1 nM/µl (Paneru *et al*., 2016). PCR was initiated with denaturation at 95 °C for 7 min, followed by 40 amplification cycles consisting of 95 °C for 10 s, annealing at 57–64 °C according to primer Tm, and a final extension step at 60 °C for 5 min. The β-actin gene in mice serves as a housekeeping gene utilized for normalization (Asif *et al*., 2021). The relative gene expressions were determined using the 2^-ΔΔC technique (Livak & Schmittgen, 2001) (Table 1).

Table 1: Primers used in RT-PCR

Gene	Forward Primer	Reverse Primer	Accession No
TNF-α	5`AAATGGGCTCCCTCTCATCAGTTC 3`	5`TCCGCTTGGTGGTTTGCTACGAC 3`	NM_012675.3
IL-6	5`GACTTCCAGCCAGTTGCCTTCTTG 3`	5`TGGTCTGTTGTGGGTGGTATCCTC 3`	NM_012589.2
Act-b	5`AGAAGAGCTATGAGCTGCCTGACG 3	5`CTTCTGCATCCTGTCAGCGATGC 3`	NM_031144.3

For the statistical analysis, results are presented as mean ± standard error (SE). The Kruskal-Wallis H test software was utilized in the statistical analysis (Lee & Lee, 2018) to detect significant differences in the independent variable of fetal weight among the various groups. A post hoc analysis (Dunn's test) was employed for statistical comparison of groups (Fabiana *et al*., 2015). The values exhibited statistical significance at $p < 0.05$.

RESULTS AND DISCUSSION

1. Morphological Observations:

The administration of MSG resulted in a notable reduction in maternal body weight in the treated groups relative to the control group. A minimal reduction in maternal body weight was observed in G4, where dams were administered a daily oral dose of 1.6 g/kg MSG from the 1st to the 20th day of gestation (**Fig. 2**). The Kruskal-Wallis H test revealed a substantial disparity in the dependent variable among the several groups, $\chi2(5) = 39.49$, $p < .001$, with mean rank scores of 39 for the control group, 31.36 for Group 1, 10.79 for Group 2, 18 for Group 3, 4.21 for Group 4, and 25.64 for Group 5. The greatest maternal body weight reduction occurred in G4, consistent with findings reported by George *et al*. (2013) and Khaled *et al.* (2016). Conversely, G1 (Pg. J-treated) maintained normal weight and length. Groups G3 and G5, receiving MSG combined with Pg. J, showed improved body weight and length compared to MSG-only groups, aligning with findings by Ahmed *et al*. (2015), Noori *et al*. (2016), and EL-Rahmany *et al*. (2019).

Statistical analysis indicated that the average gravid uterine weight was markedly greater in the control group than in the MSG-treated groups, with a significant difference in the dependent variable across the groups, $\chi2(5) = 32.11$, $p < 0.001$. The mean rank scores were 36.64 for C, 33.36 for G1, 12.14 for G2, 23.71 for G3, 8.21 for G4, and 14.93 for G5, as determined by the Kruskal-Wallis H test (Fig. 3a, b). The average rankings of the pairs C-G2, C-G4, C-G5, G1-G2, G1, and G4 exhibited significant differences, as determined by the post-hoc Dunn's test with a Bonferroni-adjusted alpha of $p < 0.0002$. Large fetuses that are naturally encapsulated are observed in both the control and G1 uteri. In G2 and G4, a reduced number of fetuses were observed in a diminutive uterus, with some being reinstated. G3 and G4 exhibited bigger uterine sizes compared to G2 and G4. MSG caused irregular implantation across the two horns of uterus, accompanied by premature embryonic mortality. This agrees with (Tawfeeq & Jarjees, 2013, and Abu Elnaga *et al*., 2019).

In this study, G4 showed a significant reduction in gravid uterine weight compared to the control group, is in contrast with Koffuor (2013), who reported increased uterine weigh. Also, Adamo & Ratner (1970) and Abdulghani *et al*. (2022), who found no significant changes. Pomegranate juice supplementation reduces the effect of MSG on the uterus weight.

The injection of MSG elevated the incidence of fetal mortality and diminished the count of live births. Fisher's exact test with a p-value < 0.05 indicated a significant difference in fetal mortality between the control-G4 and G1-G4 groups (p-value = 0.004) for both comparisons. It also demonstrates non-significant disparities in fetal mortality across the other groups. This outcome demonstrated that G4, the high dose of MSG (1.6 g/kg), experienced the most significant adverse effects (Fig. 4). This

study found that MSG-treated pregnant rats exhibited reduced placental weights and altered implantation site distribution in uterine horns. The total number of fetuses per dam decreased significantly compared to controls, though this effect was attenuated by pomegranate juice (Pg. J) supplementation. These findings align with **George *et al.* (2013),** who reported reduced embryo numbers and increased resorptions with low-dose MSG (0.4 g/kg b.w), and Abu Elnaga *et al*. (2019), who reported abnormalities in placental morphology accompanied by impaired fetal development following daily MSG exposure (7 g/10 mL/kg b.w). The negative effects were minimal in the Pg. J-treated group.

MSG resulted in a significant decrease in fetal body weight. The Kruskal-Wallis H test revealed a significant difference in the dependent variable between the groups, $\chi 2(5) = 37.77$, $p < 0.001$, with mean rank scores of 32.43 for C, 38 for G1, 14.43 for G2, 25.57 for G3, 4.36 for G4, and 14.21 for G5 (Fig. 5). The mean ranks of the following pairs exhibited significant differences, as determined by the post-hoc Dunn's test with a Bonferroni corrected alpha of $P<0.0002$: C-G4, G1-G2, G1-G4, G1-G5, G3, and G4. MSG may inhibit the cellular development of embryonic cells, perhaps leading to reduced fetal body weight (Zanfirescu *et al*., 2019, and Shosha *et al*., 2023). In this study, fetal body weight was significantly reduced in treated groups, particularly G4 and G2, relative to controls. These findings align with Khaled *et al.* (2016), who observed significant weight loss in MSG-treated rabbits (8 mg/kg daily for 12 weeks), and George *et al*. (2013), who reported decreased weight in rats after MSG administration (0.4 and 4 g/kg b.w. for 15 days). Tawfeeq and Jarjees (2013) similarly documented reduced ovarian weight and decreased pup weight and length following MSG treatment (4 g/kg b.w).

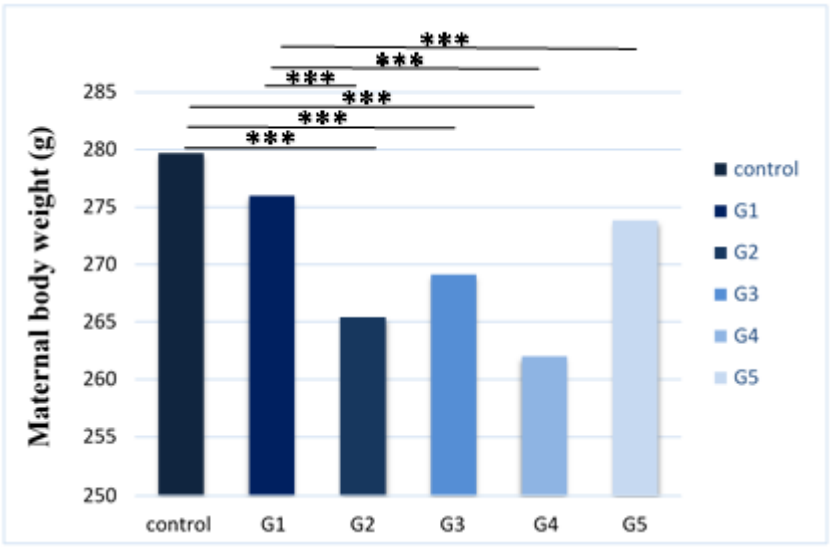

Fig. 2: The histogram represents the P-values evaluating the effect of MSG on the body weight (g) of pregnant rat dams orally treated from gestational day 1 to 20 in comparison to the control group. Data are presented as mean ± S.E. $P < 0.05$, *$P < 0.01$, ***$P < 0.001$. G1 represents Pg. J group, G2 = MSG L.D group, G3=MSG L.D +Pg. J group, G4=MSG H.D group and G5=MSG H.D+Pg. J group.

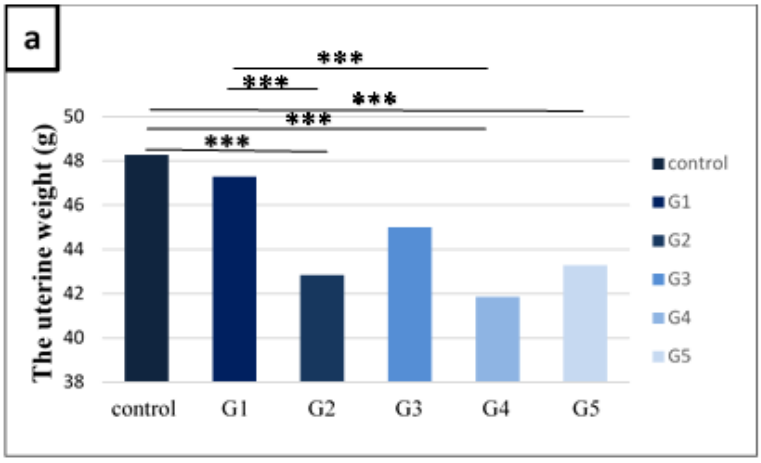

Fig. 3a: The histogram represents the *P*-values evaluating the effect of MSG on the uterine weight (g) of pregnant rats treated orally from gestational days 1–20, compared to control group. Data are expressed as mean ± S.E. $P < 0.05$, * P < 0.01, and *** P < 0.001.

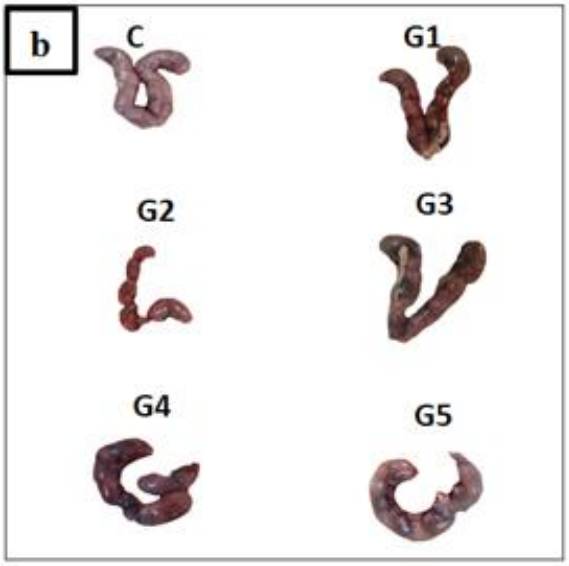

Fig. 3b: Ventral view of the uteri shows the control and maternally treated groups. The arrows referred to resorbed bodies and change in normal distribution of embryos in uterine horns.

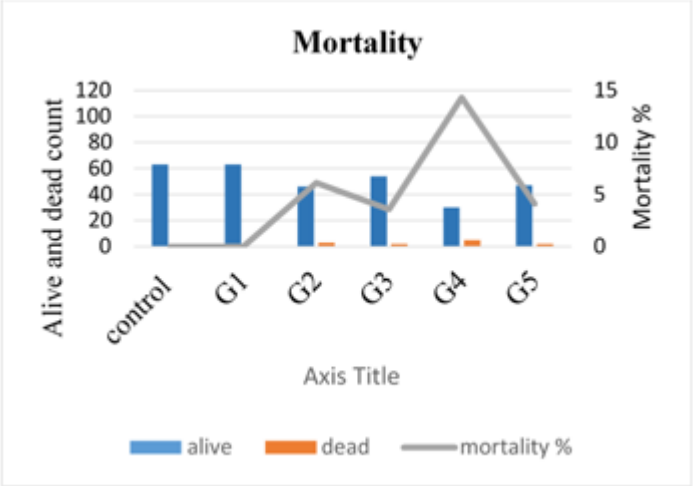

Fig. 4: The histogram represents *P*-values evaluating the effect of MSG on the fetal mortality rate of pregnant rats treated orally from gestational day 1-20, in comparison to the control group.

2. Histopathological Observations:

The microscopic analysis of hematoxylin and eosin-stained sections (Fig. 6a, b) demonstrated that both the control and G1 groups exhibited normal heart constituents, including cardiac muscle fibers with a single nucleus and typical striations. G2 exhibited histological changes characterized by degeneration of cardiac fibers and leukocytic infiltration, with certain myocardial muscle fibers displaying pyknotic nuclei, centrally positioned nuclei, and necrotic regions (Fig. 6c). Paul *et al*. (2012) demonstrated that heart muscle fibers exhibited hazy edema, fiber separation, and vascular congestion in adult male rats fed (MSG). Furthermore, G3 demonstrated significant protective efficacy on cardiac muscle fibers with centrally positioned nuclei (Fig. 6d). The most pronounced histological alterations in heart muscle tissue included extensive vacuolation, vascular congestion, leukocytic infiltration, and degradation of myocardial fibers. Absence of striations in the perinuclear area, Pyknotic nuclei, and necrotic regions were identified in the myocardial muscle fibers of G4 (Fig. 6e). Research conducted by Mustafa *et al*. (2017), Zanfirescu *et al*. (2019), and Mokhtar & Sewelam (2021) corroborated these findings. G5 had a little enhancement in histological alterations compared to the preceding group. Characterized by degradation of cardiac fibers and leukocytic infiltration (Fig. 6f). This contribution may be ascribed to the presence of ascorbic acid, total anthocyanins, total phenolics, and total antioxidant activity in Pg. J (Aksu *et al*., 2017).

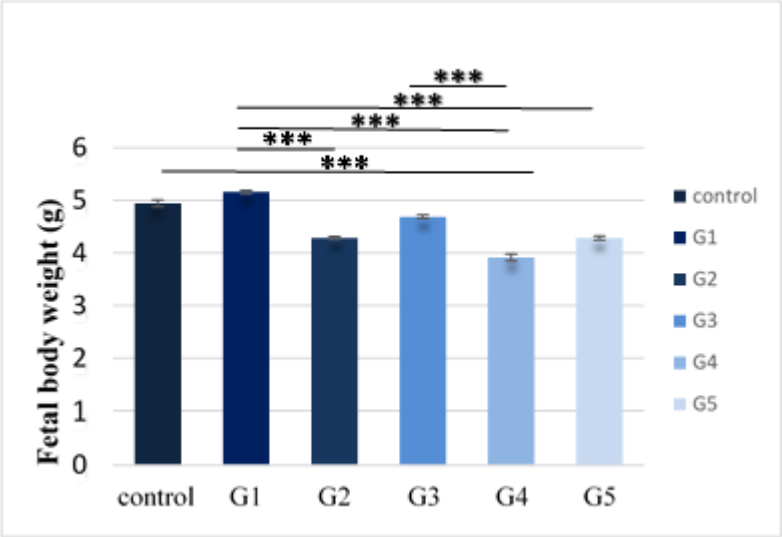

Fig. 5: The histogram represents *P*-values evaluating the effect of MSG on the fetal body weight (g) of pregnant rats treated orally from gestational day 1-20, in comparison to the control group.

The present study demonstrated the cardiotoxic effects of MSG on the heart tissue of 20-day-old *Rattus norvegicus domesticus* fetuses, which was consistent with previous reports (Paul *et al*., 2012; Mirzakhani *et al*., 2020; Hazzaa *et al*., 2020; Mokhtar and Sewelam, 2021). MSG exposure increased oxidative stress markers, reduced antioxidant enzyme activity (Paul *et al*., 2012), and induced cardiac edema, inflammation, myocardial fiber disruption, necrosis, vascular congestion, and collagen deposition (Mirzakhani *et al*., 2020; Hazzaa *et al*., 2020; Mokhtar and Sewelam, 2021). In the current study, Ventricular sections from groups treated with pomegranate juice (Pg. J),

alone or combined with MSG (G1, G3, G5), exhibited significant myocardial structural improvement compared to MSG-only groups. This cardio protection is likely due to Pg. J's antioxidant constituents, including ascorbic acid, anthocyanins, phenolics, and high total antioxidant capacity, which mitigate oxidative stress and myocardial injury (Aksu *et al*., 2017).

The kidneys constitute a pair of excretory organs. The kidneys' elevated blood flow and oxygen consumption increase their susceptibility to circulatory exposure and subsequent damage from excessive pollutants (Radi, 2019). The microscopic analysis indicated that both the control and G1 groups exhibited normal kidney constituents (Fig. 7a, b). Analysis of the kidney sections from G2 revealed significant histological alterations (Fig. 7c). These findings corresponded with earlier studies conducted by Singh *et al*. (2015), Mustafa *et al*. (2017), and Eid *et al*. (2019). Concurrently, G3 exhibited slight histological changes in the distal and proximal tubules (Fig. 7d). The renal histology slice from G4 indicated that certain glomeruli were atrophied or deteriorated (Fig. 7e). Furthermore, G5 demonstrated less significant changes in comparison to group 4. Additionally, necrosis was observed in the epithelial lining of the tubules (Fig. 7f). Numerous investigations demonstrated a significant correlation between MSG exposure and renal consequences (Eid *et al*., 2019; Yousef *et al*., 2019 and Shosha *et al*., 2023). Elshama *et al*. (2016) also noted renal atrophy in fetuses and degradation of Malpighian corpuscles. Sharma *et al*. (2013) documented substantial kidney histological alterations with MSG treatment. Likewise, Mirzakhani *et al*. (2020) demonstrated congestion, hazy edema, and glomerular atrophy in the renal sections. In the current study, histopathological analysis of fetal kidneys at gestational day 20 revealed severe structural damage in MSG-treated groups, including degeneration of distal tubules, glomeruli, epithelial destruction, hydropic degeneration, hemorrhage, and nuclear necrosis, indicating pronounced nephrotoxicity. These findings align with previous reports associated with MSG exposure (Elshama *et al*., 2016; Sharma *et al*., 2013; Eiya & Inneh, 2022; Joshi *et al*., 2023). Biochemical studies further support these histological changes, with reported elevated serum urea, creatinine, and liver enzymes further support MSG-induced renal impairment, primarily driven by oxidative stress, inflammation, and apoptosis (Tawfik & Al-Badr, 2012; Al-Khatawi *et al*., 2019).

In contrast, rats receiving daily pomegranate juice (Pg. J) exhibited significantly reduced renal damage, consistent with its antioxidant and renoprotective properties reported in models of nephrotoxicity (Cekmen *et al*., 2013; Yilmaz *et al.,* 2016; Abdel Moneim & El-Khadragy, 2013). Pg. J's protective effects are attributed to enhanced antioxidant defenses, reduced lipid peroxidation, and improved renal function.

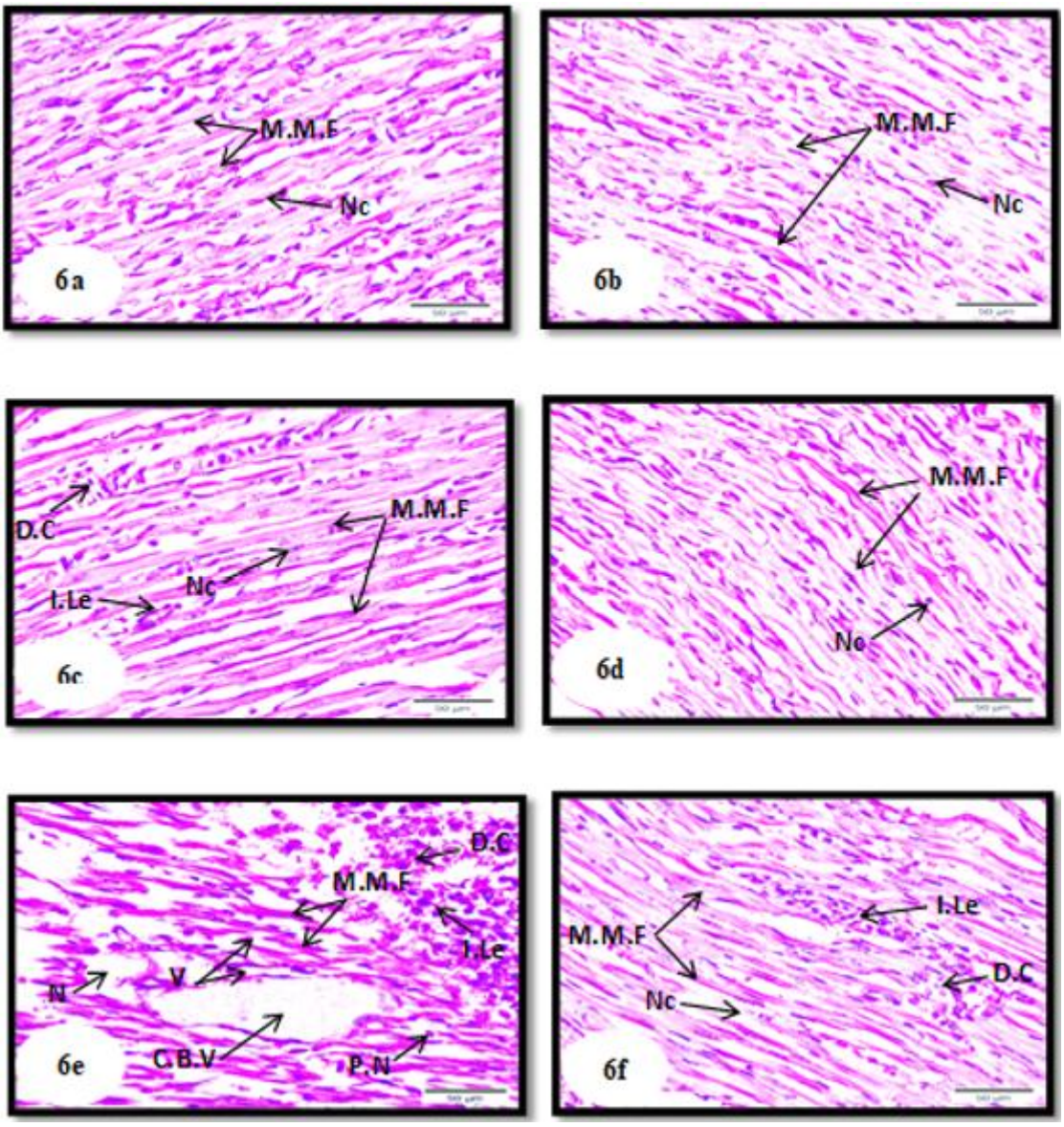

Fig. 6: Photomicrograph of a transverse section in the ventricular myocardial muscle of the heart of a 20th-day maternally treated *Rattus norvegicus domesticus* fetus. Figure 6a represents control group, 6b=Pg. J, 6c=MSG L.D, 6d=MSG L.D +Pg. J, 6e= MSG H.D, 6f= MSG H.D +Pg. J

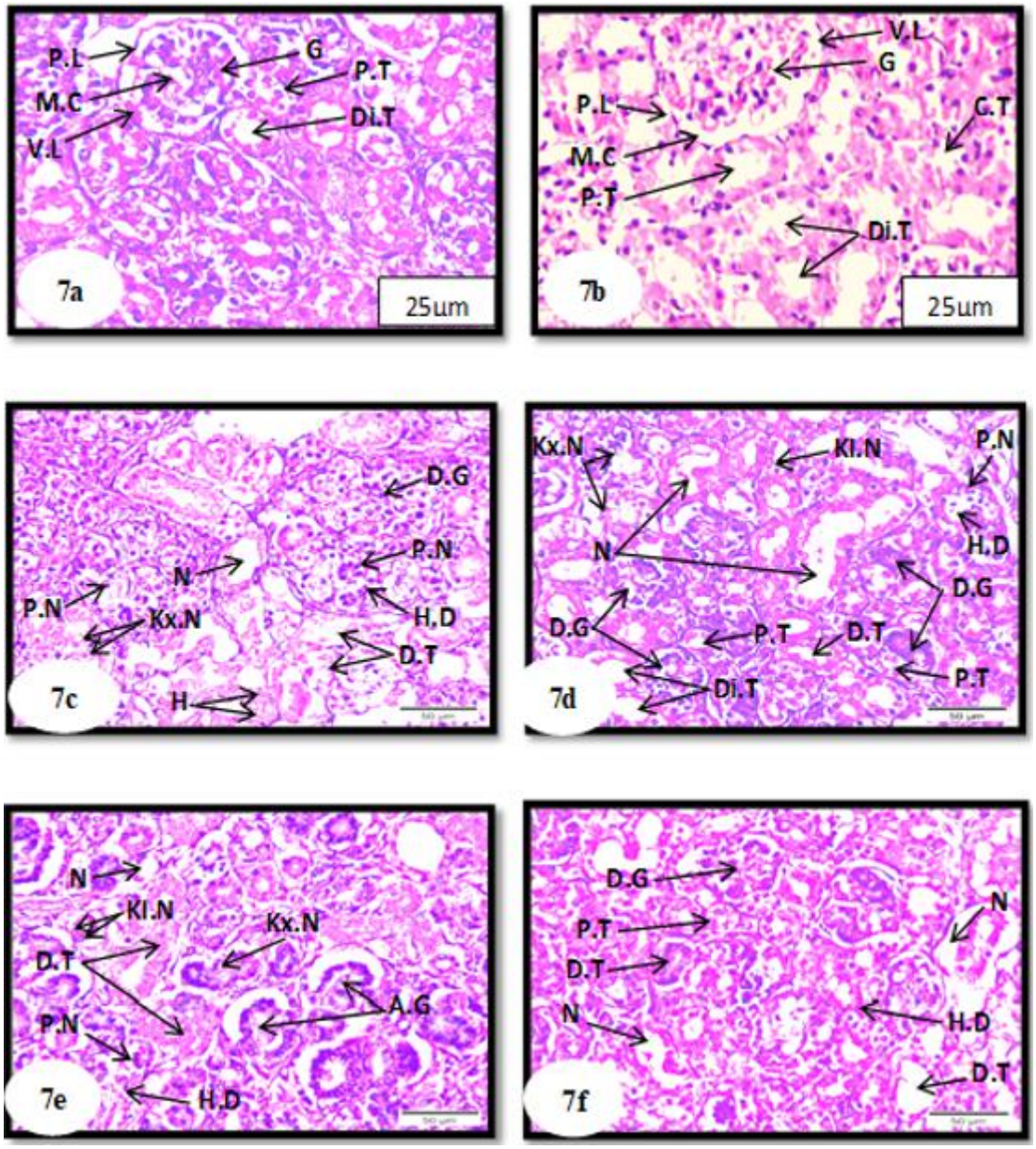

Fig. 7: Photomicrograph of a transverse section in the kidney of a 20th-day *Rattus norvegicus domesticus* maternally treated fetus. Figure 7a represents control group, 7b=Pg. J, 67c=MSG L.D, 7d=MSG L.D +Pg. J, 7e= MSG H.D, 7f= MSG H.D +Pg. J

3. Molecular Biological Observations:

To assess the inflammatory response elicited by MSG exposure during gestation and the possible moderating effect of Pg. J, the expression levels of TNF-α and IL-6 genes were assessed via qPCR. A statistically significant difference in TNF-α gene expression was detected across the experimental groups on gestational day 20, as validated by the Kruskal-Wallis H test, $H = 14.11$, $p = 0.015$. The average rank scores were as follows: control (9), G1 (2), G2 (15), G3 (5), G4 (14), and G5 (12). Group 1 (Pg. J only) exhibited a notable downregulation of TNF-α in comparison to MSG-treated groups, signifying the anti-inflammatory and protective properties of Pg. J. Groups 2 and 4 (MSG only, low and high dosages, respectively) demonstrated significantly increased expression levels relative to the control, indicating MSG-induced inflammatory activity. Groups 3 and 5, which underwent combination treatments of MSG and Pg. J, exhibited reduced TNF-α expression relative to MSG-only groups, indicating a partial ameliorative impact of Pg. J when co-administered. Dunn's test with

Bonferroni correction revealed significant differences across the following group pairs: G1–G2, G1–G4, G1–G5, G2–G3, and G3–G4 (Fig. 8).

IL-6 expression exhibited considerable variation among groups (Kruskal-Wallis H = 14.02, p = 0.015), with mean rank scores as follows: Control (8.33), G1 (4), G2 (11.33), G3 (10.33), G4 (16), and G5 (1.5). Group 1 (pomegranate juice only) exhibited a significant reduction in the IL-6 gene product relative to the control group. Groups 2 and 3 had increased expression levels, but to a lesser extent than Group 4. Group 4 (high-dose MSG) demonstrated the greatest IL-6 expression, greatly surpassing all other groups. Group 5 (high-dose MSG + Pg. J) had the lowest expression, succeeded by Group 1 (Pg. J only), underscoring Pg. J's inhibitory effect on IL-6. The co-administration of Pg. J in G3 and G5 demonstrated modification of IL-6 expression, with a more pronounced effect observed in the high-dose Pg. J group (G5).

Marked disparities were identified among the following group pairs: G1–G4, G2–G5, and G4–G5, signifying distinct expression patterns in Group 4 that diverged from the overarching trends noted in the other groups. This indicates that G4 may represent a unique inflammatory response to high-dose MSG, unaffected by other treatment combinations, and therefore deviates from conventional behavioral patterns (Fig. 9). Research conducted by Banerjee *et al*. (2021a) demonstrated that MSG elevated tumor necrosis factor (TNF-α) and interleukin (IL-6) levels following administration of three distinct doses (200, 400, and 600 mg/kg b.w. orally) during a 28-day period in rats. Banerjee *et al*. (2020) and Mirzakhani *et al*. (2020) reported analogous findings, confirming that MSG induced inflammatory responses, evidenced by elevated TNF-α levels and histopathological alterations in the liver and kidneys of exposed rats. MSG was found to intensify hepatic and renal inflammation, as indicated by increased IL-1β and TNF-α levels, along with upregulated NF-κB expression in both organs (Kassab *et al*., 2022). In contrast to the pro-inflammatory effects of MSG, the administration of Pg. J markedly reduced the levels of TNF-α and IL-6 in the kidneys of rats subjected to MSG treatment. This conclusion aligns with the research conducted by Sohrab *et al*. (2014). Pomegranate supplementation markedly decreased C-reactive protein (CRP), IL-6, and TNF-α (Wang *et al*., 2020).

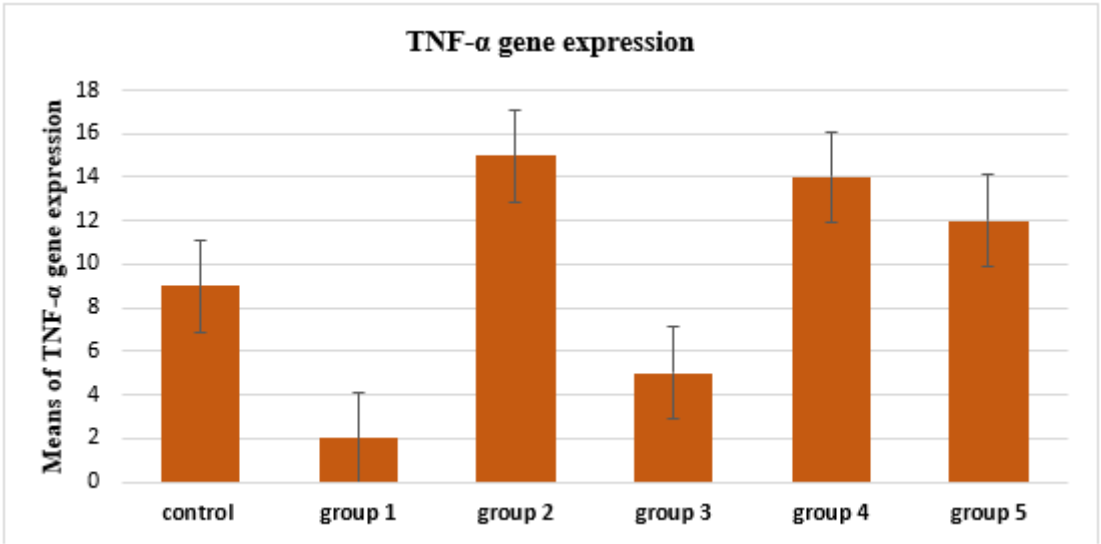

Fig. 8. Bar chart showing the mean change of TNF-α gene expression level in fetal kidney tissues of treated groups (G1, G2, G3, G4, and G5) vs. the control group on the 20th day of gestation (H = 14.02, p = 0.015). Expression was standardized for Act-b and quantified via RT-qPCR. Data are presented as mean rank scores ± SE (n = 5). $p < 0.05$.

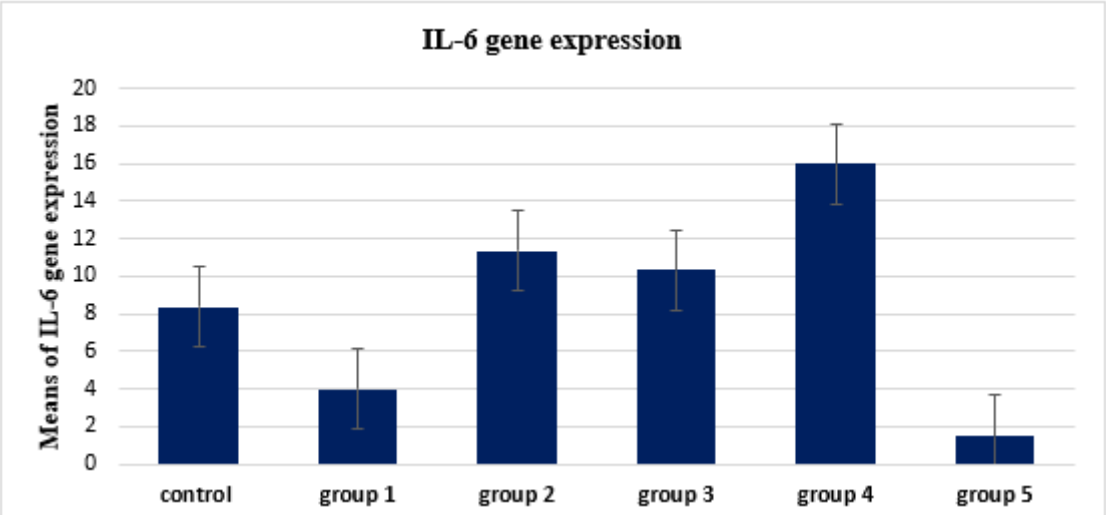

Fig. 9: Bar chart showing the mean change of IL-6 gene expression level in fetal kidney tissues of treated groups (G1, G2, G3, G4, and G5) vs. control groups on the 20th day of gestation (H = 14.11, p = 0.015). Expression was standardized for Act-b and quantified via RT-qPCR. Data are presented as mean rank scores ± SE (n = 5). $p < 0.05$.

Conclusions

Based on our findings, maternal exposure to monosodium glutamate (MSG) during gestation can lead to substantial developmental, histological, and inflammatory harm to fetal cardiac and renal tissues, as evidenced by elevated TNF-α and IL-6 gene expression. Pomegranate juice exhibited a protective effect by diminishing these negative outcomes, indicating its potential as a dietary intervention to alleviate MSG-induced toxicity during pregnancy.

Declarations:

Ethics Approval: Benha University's local ethics committee issued guidelines for the use of animals in investigations (ZD/FSc/BU IACUC/2023-19b) with permit numbers (BUFS-REC-2024-260 Zoo).

Conflict of Interest: The authors declare no conflict of interest.

Author contribution: Mervat K. Iskandar: data interpretation, study design and preparation of the manuscript. Vivian N. Shawky: data interpretation, study design and preparation of the manuscript. Ragaa M. El-Balshy: preparation of the manuscript and revision of the manuscript. Amal M. Abdel-Kareim: data interpretation, study design and preparation of the manuscript. All authors have read and agreed to the published version of the manuscript.

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