RESEARCH ARTICLE

Ameliorative effects of cape gooseberry (*Physalis peruviana* L.) against monosodium glutamate (MSG)–induced toxicity: genetic and biochemical approach

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Abstract

In this study, the toxic effects of monosodium glutamate (MSG), which is the sodium salt of glutamic acid and used as a flavor-enhancing additive in foods, and the protective role of cape gooseberry (*Physalis peruviana* L.) extract against these effects were investigated using *Allium cepa* L. test material with physiological, cytogenetic, and biochemical parameters. In the study, physiological changes were evaluated by determining root length, weight gain, and rooting percentage; genetic changes were evaluated by chromosomal abnormalities, micronucleus (MN) formation, mitotic index ratio (MI), and DNA damage. Oxidative stress was evaluated by determining the levels of malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). Further, the relationships between oxidative stress and other parameters in the study were investigated. The antimutagenic effect of *P. peruviana* L. extract was evaluated as inhibition caused by MSG-induced chromosomal abnormalities (CAs) and DNA damage. In the study, six groups, including one control and five applications, were formed. The bulbs of *Allium cepa* L. in the control group were treated with tap water; the bulbs in the administration groups treated with 1000 mg/L MSG, 125 mg/L, and 250 mg/L concentrations of *P. peruviana* L. extract and MSG (1000 mg/L) in combination with *P. peruviana* L. extracts (125 mg/L and 250 mg/L) for 72 h. At the end of the application, compared to the control group, MSG application caused decreases in rooting percentage, weight gain, root length and MI, increases in frequencies of MN formation, chromosomal abnormalities, and DNA damage. In the biochemical analysis, it was determined that there were increases in MDA, SOD, and CAT levels and a decrease in GSH level. *P. peruviana* L. extract ameliorated MSG toxicity by showing improvement in all these parameters depending on the application concentration. As a result, considering the toxic effects of MSG, it has been understood that the use as a food additive should be abandoned and the use of *P. peruviana* L. in addition to daily nutrition has been found to be a good antioxidant nutrient in reducing the effects of exposed toxic substances.

Keywords Monosodium glutamate · *Physalis peruviana* L. · Chromosomal abnormalities · Comet assay · Micronucleus · Mutagenicity · Antimutagenicity · *Allium cepa* L. test

Introduction

Along with the increase in global populations, the increase in the consumption of nutrients leads manufacturers to the use of various chemicals. These substances can be classified according to their basic functions as colorants, preservatives, antioxidants, stabilizers, emulsifiers, sweeteners, flavor enhancers, thickeners, and food additives used for a wide range of purposes (Spellman and Price-Bayer 2019; Partridge et al. 2019).

Monosodium glutamate (MSG), one of the most common, non-natural amino acids, is the glutamic acid sodium salt. MSG is a natural salt found in low concentrations in seaweed, soybeans, and sugar beets. Refined MSG is used to enhance the flavor of certain foods, especially red meat, poultry, and fish. For this purpose, it is widely used by the processed food industry, Asian restaurants, Chinese and Japanese people. The most common processed foods used in MSG are meat products (gravy, curls, soups, and pre-packaged meals), condiments, brines, confectionery, and baked products (Harte

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et al. 1991; Whitney and Rolfes 2018; Lokesh et al. 2019). MSG is a chemical compound with the molecular formula $C_5H_8NNaO_4$, molecular weight 187.127 g/mol, dissolves more than 100 mg/mL at 20 °C, and is known as sodium glutamate and the Chinese salt (PubChem 2019; Cameo Chemicals 2020). MSG is manufactured industrially from sugar cane and beet, starch, and corn by fermentation. The cleavage and modification of naturally bound glutamate into several free glutamate forms produce a white glassy powder in a free form and has an aroma boosting effect in food (FSANZ 2003). MSG is the most common example of chemicals used in our novel foods. It is applied as pure monosodium salt to the food or as part of a combination of small peptides and amino acids that are the product of acid or enzymatic hydrolysis of proteins. The body utilizes glutamate as a transmitter of nerve impulses in the brain, as well as glutamate-sensitive areas of the body (Schwartz 2004). Since there was no confirmation of the role of MSG in Chinese restaurant syndrome, the JECFA did not define the acceptable daily intake (ADI) level of glutamic acid and its salts (Walker and Lupien 2000). When the effects of MSG are examined, it has been revealed that by increasing the flavor of foods, it disrupts the leptin-mediated hypothalamus signal chain, potentially leading to obesity and causing an impaired energy balance (Araujo et al. 2017). MSG has been reported to cause liver damage symptoms (Onyema et al. 2006), renal damage (Dixit et al. 2014) and reproductive system damage (Mondal et al. 2018). Also, since glutamates are an important stimulating neurotransmitter, they can cause neuronal damage and excitotoxicity in extreme cases and may cause chronic conditions such as amyotrophic lateral sclerosis, multiple sclerosis, and Parkinson's disease (Lau and Tymianski 2010).

Physalis peruviana L. (fam. Solanaceae) is a semi-shrub plant that occurs in subtropical zones, herbaceous, and perennial. It can grow to a height of 0.6 to 0.9 m and it is rarely observed to grow to 1.8 m. The fruit is an oval-shaped juicy fruit and has a diameter of between 1.25 and 2.50 cm, and a weight between 4 and 10 g, with about 100–200 small seeds. The fruit is completely preserved with calyx (Fries and Tapia 2007). They grow in nature in Asia, America, and Europe. It has been used by the public in Taiwan for medical purposes because of its anti-inflammatory, diuretic, antidotal, antipyretic, cough suppressant, and antitumor effects (Lee et al. 2008). It is reported that *P. peruviana* L. contains various phytochemical compounds such as kaempferol, quercetin, folic acid, lucenin-2, and betulin (Al-Olayan et al. 2014). The total phenol, flavonoid, saponin, and antioxidant capacity of *P. peruviana* L. methanol extract were investigated and reported as 525 mg gallic acid, 61 mg quercetin, and 395 mg antioxidant capacity in 100 g, respectively (Wahdan et al. 2019). *P. peruviana* L. has been used as a protector against different toxic effects of many chemicals and used as a preservative in the prevention of liver inflammation and insulin resistance in dietary-induced obese mice (Nocetti et al. 2020), against different toxic effects caused by different agents such as inhibition of carbon tetrachloride (CCl_4) induced toxicity in rat testicles (Abdel Moneim 2016) and as a preventive in the inhibition of ovalbumin-induced airway inflammation (Park et al. 2019).

Of the 148 substances assessed by the *Allium cepa* L. test, 76% gave consistent results with other studies and were therefore accepted as a standard test to identify genetic damage caused by chemicals (Fiskesjö 1985; Grant 1982). *A. cepa* L. is an effective model for evaluating environmental pollutants in terms of cytotoxic, genotoxic, and mutagenicity and evaluating them with different parameters such as rooting, growth, mitotic index, and chromosomal aberrations (Grant, 1994). Similar results obtained from in vivo animal tests and in vitro cell culture tests of the results of genotoxicity and cytotoxicity studies performed with *A. cepa* L. test indicate the reliability of this test. For example, Hanada (2011) reported that paraquat caused chromosomal damage in leukocyte cell culture; Acar et al. (2015) also reported that paraquat caused chromosomal damage in *A. cepa* L. root tip cells. Kılıç et al. (2018) investigated the genotoxicity of trifluralin and pendimethalin herbicides in V79 and human peripheral lymphocyte cells with comet assay and micronucleus tests, and they reported that both herbicides showed genotoxic effects and increased MN frequency on both cell lines. Similarly, in studies conducted with *A. cepa* L. test material, it was reported that pendimethalin caused chromosomal abnormalities (Verma and Srivastava 2018) and trifluralin herbicide caused MN formation (Fernandes et al. 2007). *A. cepa* L. has been used as a model organism to investigate the effects of many environmental pollutants such as water pollution (Wijeyaratne and Wadasinghe 2019), pesticides (Rosculete et al. 2019), wastewater (Yadav et al. 2019; Kumar and Ghosh 2019), heavy metals (Sarac et al. 2019; Sabeen et al. 2020), and other industrial pollutants (Acar et al. 2020). Therefore, *A. cepa* L. test material was preferred in this study because of its reliable results and its use in investigating the effects of many toxic agents.

Although there is no comprehensive study investigating the genetic effects of MSG, the lack of studies investigating the antimutagenic effect of *P. peruviana* L. extract with an in vivo mutagenic agent has led to the idea of investigating both effects with this study. In this study, the genetic and biochemical effects of MSG, antimutagenic activity, and the protective role of *P. peruviana* L. extract against these effects were investigated with *Allium cepa* L. test material.

Materials and methods

Plant materials

Fully ripe fruits of *P. peruviana* L. were collected from Giresun between June and August 2019 and pesticide

application has not been applied to the collection area before, and the areas where the plant grows naturally were preferred. *Allium cepa* L. bulbs were obtained from the local market. The plant material has been authenticated using taxonomic characters in the Department of Botany, Faculty of Science and Art, Giresun University, Giresun, Turkey.

In previous studies, the methanol extract was found rich in phytochemical components and was therefore chosen for the experiment (Othman et al. 2014; Abdel Moneim et al. 2014). *P. peruviana* L. fruits were separated from their calyxes, 10 g of sample were taken, chopped, homogenized, and extracted in 500 mL of methanol (99.9%) in a shaker incubator for 1 day at room temperature. The extract was filtered with filter paper (Whatman No. 1) to eliminate solid particles at the end of the incubation period and the filtrate was centrifuged for 10 min at $16,100 \times g$. After centrifugation, the liquid phase was evaporated with the aid of an evaporator and a semi-solid extract mass was obtained and stored at -20 °C before use. In the preparation of the study concentrations, it was prepared by dissolving in pure water (Yalçın et al. 2017).

Concentrations used

Since plants are not the target organism of MSG directly, there is no study determining the IC_{50} value. LD_{50} value was reported as 15 to 18 g/kg body weight in rodents (Walker and Lupien 2000). However, in the literature, the IC_{50} range of MSG wastewater has been reported as the highest values as 32,432 and 3320 mg/L, respectively, according to seed germination and root elongation (Liu et al. 2007). Estimated MSG consumption in the average daily diet in developed countries has been reported to range from 0.3 to 1.0 g/day (Geha et al. 2000). Due to the high LD_{50} values of MSG and IC_{50} values of the wastewater, the lower 1000 mg/L concentration was preferred as the study concentration.

There is no study in the literature on the protective effect of *P. peruviana* L. extract against DNA damage. Considering the protective effects of *P. peruviana* L. extract against renal damage, inflammation, cancer formation, and oxidative stress caused by toxic agents in the literature; 125 mg/L and 250 mg/L concentrations, which were thought to be low and effective, were preferred (Ahmed 2014; Castro et al. 2015; El-Meghawry et al. 2015; Dewi and Sulchan 2018).

Experimental design

In this study, 1000 mg/L MSG, 125 mg/L, and 250 mg/L *P. peruviana* L. extract were applied. Six groups were created including equal-sized and healthy *A. cepa* L. bulbs and treated with tap water (control), MSG, and *P. peruviana* L. extract at 24 °C for 72 h. As given in Table 1, a total of six (6) groups, one (1) control and five (5) treatment groups, were formed.

Measurement of physiological parameters

The root lengths of *A. cepa* L. bulbs were calculated on the basis of the radicle shape using the millimeter ruler and the weight gain was determined using the precision scale. Weight increase was determined by weight differences before and after application using precision scales. The percentage of rooting and relative injury rates were calculated by using Eqs. 1 (Atik et al. 2007) and 2 (Praveen and Gupta 2018).

$$\text{Rooting percentage } (\%) = \frac{\text{Rooted bulbs}}{\text{Total number of bulbs}} \quad (1)$$

$$\text{Relative injury rate} = \frac{\%RP \text{ in control} - \%RP \text{ in each group}}{\%RP \text{ in control}} \quad (2)$$

Chromosomal abnormalities, mitotic index, and micronucleus test

A total of 1–2 cm samples taken from root tips of *A. cepa* L. were fixed in Clarke's solution (ethanol and glacial acetic acid, 3:1) for 2 h and kept in 96% ethanol for 15 min. They were stored in 70% ethanol at 4 °C for analysis procedures. For micronucleus (MN) and mitotic index (MI) analysis, the roots were treated with 1N HCl for 17 min at 60 °C, incubated in 45% acetic acid for 30 min, stained in acetocarmine for 24 h, and then compressed at 45% acetic acid. The preparations were observed for mitotic cells and counted under a research microscope (Staykova et al. 2005). The evaluation of the presence of MN was determined according to Fenech et al. (2003). A total of 1000 cells were counted in each group for MN frequency and chromosomal abnormalities and 10,000 cells in each group for MI.

Comet assay (single-cell gel electrophoresis)

The protocol of Chakraborty et al. (2009) was performed for alkaline single-cell gel electrophoresis (Bio-Rad, Mini-Sub

Table 1 Application groups

Groups	Application
Group I	Tap water
Group II	125 mg/L *P. peruviana* L. extract
Group III	250 mg/L *P. peruviana* L. extract
Group IV	1000 mg/L MSG
Group V	1000 mg/L MSG + 125 mg/L *P. peruviana* L. extract
Group VI	1000 mg/L MSG + 250 mg/L *P. peruviana* L. extract

Cell GT) with slight modifications. In 400 μL cold Tris-buffer (0.4 M, pH 7.5) and a combination of 1:1 nuclear suspension and 1% low melting point agarose (LMPA) in phosphate-buffered saline (PBS) on pre-coated sheets, the roots were quickly crushed down with a raster tool. The coverslip was covered at 40 °C with 1% normal melting point agarose (NMPA). After completing the gelling step of the LMPA, the coverslip was slowly extracted. LMPA-embedded nuclei slides were moved for 15 min to a horizontal gel electrophoresis tank with a fresh and cooled electrophoresis buffer, accompanied by a 4-min electrophoresis at 4 °C of 0.7 V/cm (20 V, 300 mA). Slides had been rinsed with purified water three times and neutralized by Tris-buffer (0.4 M Tris, pH 7.5). The nuclei were stained with 80 μL SYBR green for 5 min following immersion in cold water for 5 min. The preparations are washed with cold water to extract excess stain and sealed with a coverslip. All steps were done in low light to prevent DNA damage and analyzed with fluorescence microscopy. DNA damaged cells displayed as comets were evaluated with the Comet Assay software version 1.2.3b (Końca et al., 2003) with the parameters of tail DNA percentage, tail moment, and olive tail moment, and 500 cells were calculated for each group. The tail DNA percentage, tail moment, and olive tail were used as the measure of DNA damage.

Evaluation of the antimutagenic effect

Equation 3 was used to determine the antimutagenic effect of *P. peruviana* L. extract application. Chromosomal abnormality (CAs) frequencies and the tail DNA percentage in the comet assay were used to determine the antimutagenic effects.

$$\text{Mutagenicity inhibition (\%)} = \frac{\text{MSG group damage (\%)} - \text{MSG with } P.\ peruviana \text{ L. extract group damage (\%)}}{\text{MSG group damage (\%)} - \text{Control group damage (\%)}} \times 100 \quad (3)$$

Malondialdehyde level

Lipid peroxidation was determined with the protocol of Ünyayar et al. (2006). Approximately, 0.5 g of root tissue taken from the groups, root tips were split into small parts and homogenized in 5% trichloroacetic acid (TCA), and homogenates were centrifuged at 23,182×*g* for 15 min at 24 °C. Supernatant, thiobarbituric acid (0.5%) TCA solution (20%) were transferred to a new tube and 25 min incubated at 96 °C, transferred to the ice bath and 5 min centrifuged at 16,100×*g*. The absorbance was determined at 532 nm; the extinction coefficient 155 mM/cm was used to determine the malondialdehyde (MDA) content and MDA levels are expressed as mean μmol/g fresh weight (FW) ± standard error (SE).

Glutathione level

Glutathione (GSH) levels were determined by using the protocol described by Sedlak and Lindsay (1968) with slight modifications. Briefly, the root tips (0.5 g) were homogenized in 0.2 M EDTA (pH 4.7). In total, 0.02 M EDTA (0.9 mL), 0.2 M Tris- EDTA buffer (1.0 mL), and 10 mM DTNB (20 μL) were added to homogenate and the mixture was vortexed. At room temperature, the reaction mixture incubated and centrifuged for 30 min. The supernatant absorbance was recorded at 412 nm and the GSH level was estimated as mean μmol/mg FW ± SE.

Superoxide dismutase and catalase analysis

A total of 0.5 g root material homogenized with 5 mL 50 mM (pH 7.8) chilled sodium phosphate buffer. Homogenates are centrifuged for 20 min at 16100×*g* and the supernatant is used for the analysis of enzymes. Superoxide dismutase (SOD) activity was measured by making some modifications to the method to Beauchamp and Fridovich (1971). The reaction mixture contained 1.5 mL 0.05 M sodium phosphate buffer (pH 7.8), 0.3 mL 130 mM methionine, 0.3 mL 750 μM nitroblue tetrazolium chloride (NBT), 0.3 mL 0.1 mM EDTA-Na$_2$, 0.3 mL of 20 μM riboflavin, 0.01 mL of enzyme extract, 0.01 mL of 4% (w/v) insoluble polyvinylpyrrolidone, and 0.28 mL of deionized water. The reaction was started by placing the tubes under two 15 W fluorescent lamps for 10 min and terminated by keeping the tubes in the dark for 10 min. Absorbance was measured at 560 nm and a unit SOD enzyme activity was determined as the amount of SOD enzyme required for 50% inhibition of NBT reduction under application conditions. SOD enzyme activity is expressed as mean units per milligram FW ± SE (U/mg FW).

Catalase (CAT) activity was determined by a UV-Vis spectrophotometer at 25 °C in 2.8 mL a reaction mixture including 0.3 mL 0.1 M H$_2$O$_2$, 1.0 mL deionized water, and 200 mM sodium phosphate buffer (1.5 mL) prepared just before use. The reaction was triggered by adding 0.2 mL of supernatant CAT activity by calculating the absorbance decrease (240 nm) resulting from the ingestion of H$_2$O$_2$. CAT activity was determined by the protocol of Beers and Sizer (1952), and measured in units per minute and expressed as the absorbance obtained per 1 g of FW in a minute; the change of 0.1 at an

absorbance of 240 nm was specified as one unit of CAT activity (OD$_{240nm}$/min.g FW) ± SE.

Concentration-response relationship

The evaluation of the concentration-response relationship of *P. peruviana* L. extract against MSG toxicity was performed by calculating the healing effect of *P. peruviana* L. extract as a percentage against changes in all parameters due to MSG toxicity. Since the healing effect will only be positive, it has been evaluated as an increase or decrease in value and for this purpose, the absolute value of the change is taken. For this, Eq. 4 was used and evaluated with the logarithmic values of the concentrations.

$$\text{Recovery effect of } P. peruviana \text{ L.}(\%) = \frac{|\text{ MSG with } P. \ peruviana \text{ L.extract group parameter}-\text{MSG group parameter }|}{\text{MSG group parameter}} \times 100 \qquad (4)$$

Statistical analysis

The IBM SPSS Statistics 23 was used to perform statistical analyses. Data were expressed as mean ± SD (standard deviation) in the tables and mean ± SE in the graphs. The statistical significance between the means was calculated using the one-way ANOVA method and Duncan's test, and the p value < 0.05 was statistically significant.

Results

Physiological parameters

In this study, the physiological effects of MSG and the protective role of *P. peruviana* L. extract against these effects were investigated by rooting percentage, root length, weight gain, and relative injury rate parameters. The effects of MSG on rooting percentage and relative injury rate and the protective role of *P. peruviana* L. extract against these effects are given in Table 2. The rooting percentage was 100% in the control group (group I) and in group II and group III treated with 125 and 250 mg *P. peruviana* L. extract, respectively. In other words, it has been determined that *P. peruviana* L. extract applied alone did not affect the rooting percentage. In group IV treated with 1000 mg/L concentration of MSG, the rooting percentage dramatically decreased and the rooting percentage was determined as 47%. In group V and group VI, administration of *P. peruviana* L. extracts in combination with MSG (1000 mg/L) at concentrations of 125 mg/L and 250 mg/ L, respectively, partially compensated for this decrease depending on the extract concentration and the rooting percentage increased to 60% and 75%, respectively. The relative injury rate due to MSG (1000 mg/L) application was found to be 0.53 in group IV, and this value decreased in groups V and VI to 0.40 and 0.25, respectively. Along with increasing *P. peruviana* L. extract concentration, a concentration-related improvement occurred in the relative injury rate. MSG application also affected root elongation. In group I treated with tap water, the root length was measured as an average of 9.70 cm. The mean root length was 11.68 cm and 12.75 cm in group II and group III, where two different concentrations of *P. peruviana* L. extract were applied, respectively. In group V, where only 1000 mg/L concentration of MSG was applied, the average root length decreased sharply and was measured as 4.57 cm on average. An increment in the mean root lengths was observed in group V and group VI, where *P. peruviana* L. extract was administered with MSG at a concentration of 125 mg/L and 250 mg/L, and was determined to be 5.53 cm and 6.82 cm, respectively. Although *P. peruviana* L. application tolerated reductions in root length caused by MSG depending on the concentration, values in the control group could not be reached. But the increase in root length showed a positive correlation with the *P. peruviana* L. concentration.

The effects of MSG and *P. peruviana* L. extract on weight gain are given in Table 3. The highest weight gains were observed in group I as 9.50 g, group II as 17.54 g, and group III as 11.63 g treated with tap water, 125 mg/L *P. peruviana* L. extract, and 250 mg/L *P. peruviana* L. extract, respectively. In group IV, where MSG (1000 mg/L) was administered alone, minimal weight gain occurred and was found to be 3.07 g. A concentration-dependent increase in weight gains occurred in group V and group VI, where *P. peruviana* L. extract was applied at concentrations of 125 and 250 mg, in combination with MSG administration (1000 mg/L), and weight gains determined as 4.34 g and 5.70 g, respectively. In addition to MSG administration, there were increases in weight gains in groups V and group VI, where *P. peruviana* L. extract was administered at 125 mg/L and 250 mg/L concentrations and was determined to be 4.34 g and 5.70 g, respectively.

Genetic parameters

Genetic effects of MSG on root tip cells of *A. cepa* L. and the possible protective role of *P. peruviana* L. extract were evaluated by determining MI rate, MN, and chromosomal abnormality formation and percentage of tail DNA formation. The effect of MSG application on MN formation and MI and the

Table 2 Effect of MSG and *P. peruviana* L. extract on rooting, root length and relative injury rate

Groups	Rooting percentage (%)	Relative injury rate	Minimum root length	Maximum root length	Mean root length
Group I	100	-	9.02	10.38	9.70 ± 0.95^c
Group II	100	-	11.20	12.15	11.68 ± 0.66^b
Group III	100	-	12.17	13.32	12.75 ± 0.80^a
Group IV	47.50	0.53	3.95	5.19	4.57 ± 0.87^f
Group V	60	0.40	4.85	6.20	5.53 ± 0.95^e
Group VI	75	0.25	6.27	7.37	6.82 ± 0.77^d

Group I, tap water (control); group II, 125 mg/L *P. peruviana* L. extract; group III, 250 mg/L *P. peruviana* L. extract; group IV, 1000 mg/L MSG; group V, 1000 mg/L MSG + 125 mg/L *P. peruviana* L. extract; group VI, 1000 mg/L MSG + 250 mg/L *P. peruviana* L. extract. Data are shown as mean ± standard deviation (SD). The averages shown with different letters in the same column are statistically significant ($P < 0.05$)

protective role of *P. peruviana* L. on these effects are given in Table 4. A few MN formations were observed in group I, which is in the control group, and there was no MN formation in group II and group III, where *P. peruviana* L. extract applied alone at concentrations of 125 mg/L and 250 mg/L. There was no statistically significant difference between the control group (group I) and the *P. peruviana* L. extracts applied alone groups (groups II and III) in terms of MN frequency. However, the administration of MSG alone at a concentration of 1000 mg in group IV caused the most frequent MN formation and was detected at an average frequency of 35.40. In group V, where 125 mg/L *P. peruviana* L. extract was administered in addition to MSG (1000 mg/L), MN formation frequency was detected as an average of 24.70. In group VI, where *P. peruviana* L. extract application concentration was 250 mg/L with MSG (1000 mg/L), MN formation decreased to an average of 22.18. The data obtained showed that the application of *P. peruviana* L. extract exhibited a protective role against the genotoxicity induced by MSG and reduced the MN formation. It was determined that the differences in the

MN rate between groups IV and VI were statistically significant ($p < 0.05$).

Mitotic index data were analyzed and the mean MI rate in group I was determined as 9.30%. Different concentrations of *P. peruviana* L. application did not cause a statistically significant change in MI in group II and group III ($p > 0.05$). In group IV, where 1000 mg/L concentration of MSG was administered alone, the MI rate was found to be 4.91% and was the lowest among these groups. In group V and group VI, there was a concentration-dependent increase in MI with the administration of *P. peruviana* L. extract (125 mg/L and 250 mg/L, respectively) in combination with MSG at a concentration of 1000 mg/L. Changes in MI rate showed that MSG administration suppressed cell division and *P. peruviana* L. administration resulted in improvement in this effect depending on the application concentration.

The chromosomal abnormalities caused by MSG application and the protective role of *P. peruviana* L. extract against these are given in Table 5 and Fig. 1. No chromosomal abnormalities were observed in group I (control), except for a few fragments and sticky chromosomes, and no chromosomal abnormality was formed in groups II and III, where *P. peruviana* L. extract was administered alone at 125 mg/L and 250 mg/L concentrations, respectively. There was no statistical significance between the values obtained from these three groups ($p > 0.05$). The highest chromosomal abnormality occurrence was observed in group IV, where MSG has applied alone at a concentration of 1000 mg/L. These chromosomal abnormalities occurred in the order of frequency in the form of the fragment, sticky chromosome, bridge, unequal distribution of chromatin, and nucleus with vacuoles. Administration of *P. peruviana* L. extract at concentrations of 125 mg/L and 250 mg/L in combination with MSG (group V and group VI) inhibited MSG-induced chromosomal abnormalities in a concentration-dependent manner. Mutagenicity inhibition of *P. peruviana* L. extract against MSG was calculated in the groups in which *P. peruviana* L. extracts were administered in combination with MSG (1000 mg/L).

Table 3 The effect of MSG on weight gain and the protective role of *P. peruviana* L. extract

Groups	Initial weight	Final weight	Weight gain
Group I	7.10 ± 0.83^g	16.60 ± 0.66^c	+ 9.50
Group II	6.90 ± 0.91^g	17.54 ± 0.98^b	+ 10.64
Group III	7.11 ± 0.98^g	18.74 ± 1.35^a	+ 11.63
Group IV	6.92 ± 0.94^g	9.99 ± 0.87^f	+ 3.07
Group V	6.99 ± 0.86^g	11.33 ± 0.99^e	+ 4.34
Group VI	7.11 ± 0.83^g	12.81 ± 0.59^d	+ 5.70

Group I, tap water (control); group II, 125 mg/L *P. peruviana* L. extract; group III, 250 mg/L *P. peruviana* L. extract; group IV, 1000 mg/L MSG; group V, 1000 mg/L MSG + 125 mg/L *P. peruviana* L. extract; group VI, 1000 mg/L MSG + 250 mg/L *P. peruviana* L. extract. Data are shown as mean ± standard deviation (SD). The averages shown with different letters in the same column are statistically significant ($P < 0.05$)

Table 4 Effects of MSG and *P. peruviana* L. application on MN formation and mitotic index (MI)

Groups	Lower Bound (MN)	Upper Bound (MN)	Mean (MN)	Mitotic index (MI)	Mitotic index rate (%)
Group I	0.03	0.77	0.40 ± 0.52[d]	929.80 ± 18.65[a]	9.30
Group II	0.00	0.00	0.00 ± 0.00[d]	933.80 ± 16.45[a]	9.34
Group III	0.00	0.00	0.00 ± 0.00[d]	940.30 ± 11.24[a]	9.40
Group IV	30.35	40.45	35.40 ± 7.06[a]	491.40 ± 44.13[d]	4.91
Group V	19.93	29.47	24.70 ± 6.67[b]	548.20 ± 16.29[c]	5.48
Group VI	16.82	22.18	19.50 ± 3.75[c]	671.60 ± 35.76[b]	6.72

Group I, tap water (control); group II, 125 mg/L *P. peruviana* L. extract; group III, 250 mg/L *P. peruviana* L. extract; group IV, 1000 mg/L MSG; group V, 1000 mg/L MSG + 125 mg/L *P. peruviana* L. extract; group VI, 1000 mg/L MSG + 250 mg/L *P. peruviana* L. extract. Data are shown as mean ± standard deviation (SD). The averages shown with different letters in the same column are statistically significant ($P < 0.05$)

Mutagenicity inhibition was determined as 31.47% and 49% in group V and group VI, which were administered *P. peruviana* L. extract at 125 and 250 mg doses, respectively, in combination with MSG. This increase in mutagenicity inhibition means the reduction in chromosomal abnormalities and is due to the concentration of *P. peruviana* L. administered. Besides, the decrease in chromosomal abnormalities was found statistically significant ($p < 0.05$). The chromosomal abnormality inhibition was accepted as the mutagenicity inhibition of *P. peruviana* L. In other words, it provided an evaluation of the antimutagenic effect of *P. peruviana* L.

DNA damage caused by MSG in nuclei of root cells of *A. cepa* L. and the protective role of *P. peruviana* L. extract against this damage were evaluated using single-cell gel electrophoresis with tail DNA (%), tail moment, and olive tail moment. Figure 2 and Table 6 show the effects of MSG and *P. peruviana* L. extract applications on DNA in nuclei of root cells of *A. cepa* L. There is no statistically significant difference was found in the tail DNA percentage, tail moment, and olive tail moment formation occurring between groups I and III ($p > 0.05$). In group IV, where MSG was applied at a concentration of 1000 mg/L alone, the percentage of tail DNA was 53.39, the tail moment was 56.74, and the olive tail moment was 29.52; and these values are the highest among the groups. In group V and group VI, where 125 mg/L and 250 mg/L *P. peruviana* L. extracts were administered in combination with MSG (1000 mg/L), respectively, the tail moment percentage was 32.72 and 24.44, the tail moment was 25.36 and 9.02, and the olive tail moment was 15.92 and 8.25, respectively. Depending on the application concentration, *P. peruviana* L. application reduced DNA damage caused by MSG; caused a decrease in the tail DNA percentage, tail moment, and olive tail moment. The antimutagenic effect was evaluated by the decrease in tail DNA formation and the antimutagenic effect of *P. peruviana* L. extract applications were determined as 41.22% in group V (MSG + 125 mg/L *P. peruviana* L. extract) and 57.33% in group VI (MSG + 250 mg/L *P. peruviana* L. extract). It was determined that MSG application caused DNA damage in *A. cepa* L. root nuclei, and this damage showed a concentration-related improvement with *P. peruviana* L. application. The resulting DNA damage and improvement in this damage may have

Table 5 Chromosomal abnormalities induced by MSG and the protective role of *P. peruviana* L. extract

	Group I	Group II	Group II	Group IV	Group V	Group VI
FRG	0.20 ± 0.42[d]	0.00 ± 0.00[d]	0.00 ± 0.00[d]	54.70 ± 6.70[a]	35.20 ± 5.05[b]	26.30 ± 2.50[c]
SC	0.10 ± 0.32[d]	0.00 ± 0.00[d]	0.00 ± 0.00[d]	31.60 ± 5.85[a]	22.40 ± 3.37[b]	15.20 ± 3.05[c]
B	0.00 ± 0.00[d]	0.00 ± 0.00[d]	0.00 ± 0.00[d]	18.40 ± 4.20[a]	14.30 ± 2.83[b]	11.50 ± 3.03[c]
UDC	0.00 ± 0.00[d]	0.00 ± 0.00[d]	0.00 ± 0.00[d]	12.40 ± 2.01[a]	8.30 ± 2.31[b]	6.20 ± 2.15[c]
NV	0.00 ± 0.00[d]	0.00 ± 0.00[d]	0.00 ± 0.00[d]	13.80 ± 3.12[a]	9.60 ± 2.84[b]	7.70 ± 2.31[c]
Total CAs	0.30 ± 0.48[d]	0.00 ± 0.00[d]	0.00 ± 0.00[d]	130.90 ± 13.22[a]	89.80 ± 10.05[b]	66.90 ± 6.90[c]
CAs (%)	0.03	0	0	13.09	8.98	6.69
Mutagenicity inhibition (%)	-	-	-	-	31.47	49.00

Group I, tap water (control); group II, 125 mg/L *P. peruviana* L. extract; group III, 250 mg/L *P. peruviana* L. extract; group IV, 1000 mg/L MSG; group V, 1000 mg/L MSG + 125 mg/L *P. peruviana* L. extract; group VI, 1000 mg/L MSG + 250 mg/L *P. peruviana* L. extract. Data are shown as mean ± standard deviation (SD). The averages shown with different letters in the same line are statistically significant ($P < 0.05$). *FRG*, fragment; *SC*, sticky chromosome; *B*, bridge; *UDC*, unequal distribution of chromatin; *NV*, nucleus with vacuoles

Fig. 1 Chromosomal abnormalities caused by MSG (**a** MN. **b** Fragment. **c** Sticky chromosome. **d** Unequal distribution of chromatin. **e** Bridge. **f** Nucleus with vacuoles)
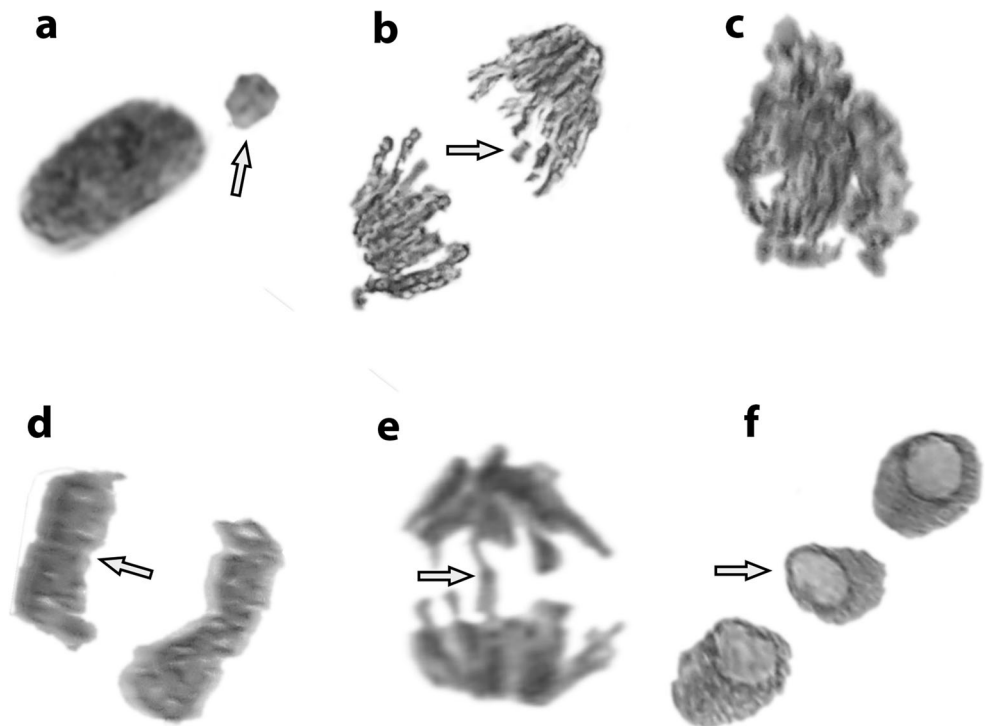
resulted from the induction of the oxidative DNA damage of the MSG application and the interaction of the *P. peruviana* L. application with the DNA repair processes.

Antioxidant-oxidant balance

The effects of MSG and *P. peruviana* L. extract administration on root MDA and GSH levels are shown in Fig. 3 and Fig. 4. In the control group (group I), the MDA level was determined as 7.54 μmol/g FW and the GSH level as 6.15 μmol/g FW. The differences between the control group (group I) and the *P. peruviana* L. extract applied alone groups (group II and group III) were not statistically significant

($p > 0.05$). In other words, *P. peruviana* L. extract applied alone did not cause any important changes in MDA and GSH levels in these groups. In group IV, where MSG was applied alone at a concentration of 1000 mg/L, the level of MDA increased dramatically to 7.54 μmol/g FW and the GSH level decreased significantly to 3.73 μmol/g FW. The findings showed that MSG caused oxidative damage and changes in lipid peroxidation. *P. peruviana* L. administration resulted in an improvement in MDA and GSH levels. In group V and group VI, where *P. peruviana* L. concentrations of 125 mg/L and 250 mg/L were administered respectively, MDA levels were measured as 16.94 μmol/g FW and 12.72 μmol/g FW, and GSH levels as 4.35 μmol/g FW and 5.26 μmol/g FW,

Fig. 2 Comet assay in nuclei isolated from *A. cepa* L. root meristems (**a** Control. **b** 125 mg/L *P. peruviana* L. **c** 250 mg/L *P. peruviana* L. **d** 1000 mg/L MSG. **e** 1000 mg/L MSG + 125 mg/L *P. peruviana* L. **f** 1000 mg/L MSG + 250 mg/L *P. peruviana* L.)
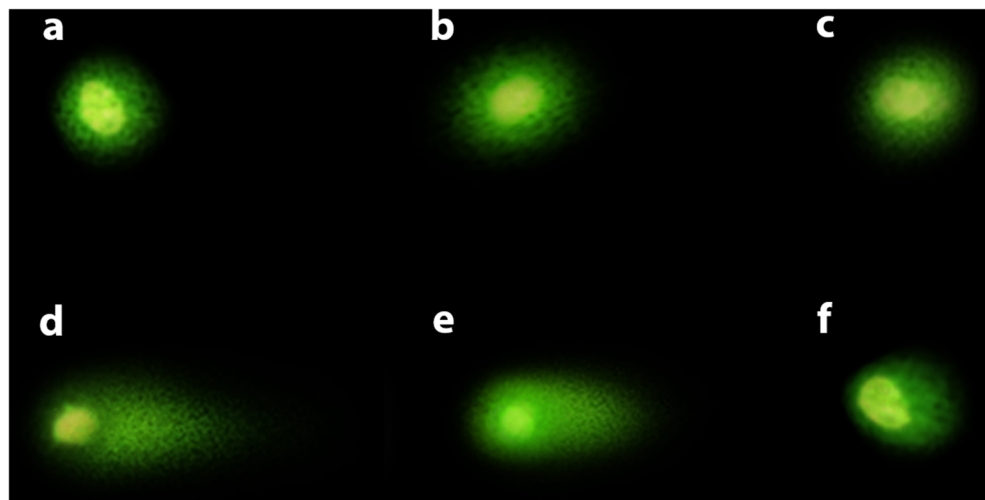
Table 6 Detection of DNA damage caused by MSG in the nuclei of *A. cepa* root cells

Groups	Head DNA (%)	Tail DNA (%)	Tail Moment	Olive tail moment	Mutagenicity inhibition (%)
Group I	96.76 ± 1.27^a	3.24 ± 1.27^d	0.34 ± 0.06^d	0.91 ± 0.08^d	-
Group II	97.16 ± 1.76^a	2.84 ± 1.76^d	0.22 ± 0.08^d	0.77 ± 0.10^d	-
Group III	98.23 ± 1.15^a	1.77 ± 1.15^d	0.09 ± 0.04^d	0.45 ± 0.06^d	-
Group IV	46.61 ± 6.02^d	53.39 ± 6.02^a	56.74 ± 9.15^a	29.52 ± 8.23^a	-
Group V	67.28 ± 5.23^c	32.72 ± 5.23^b	25.36 ± 8.54^b	15.92 ± 5.05^b	41.22
Group VI	75.56 ± 5.94^b	24.44 ± 5.94^c	9.02 ± 2.46^c	8.25 ± 3.76^c	57.73

Group I, tap water (control); group II, 125 mg/L *P. peruviana* L. extract; group III, 250 mg/L *P. peruviana* L. extract; group IV, 1000 mg/L MSG; group V, 1000 mg/L MSG + 125 mg/L *P. peruviana* L. extract; group VI, 1000 mg/L MSG + 250 mg/L *P. peruviana* L. extract. Data are shown as mean ± standard deviation (SD). The averages shown with different letters in the same column are statistically significant ($P < 0.05$)

respectively. In other words, *P. peruviana* L. application showed a concentration-dependent decrease in MDA level and a concentration-dependent increase in GSH level, resulting in an improvement in these parameters. The changes in MDA and GSH levels among groups IV–VI were found to be statistically significant ($p < 0.05$).

The effect of MGS and *P. peruviana* L. extract applications on SOD and CAT levels are given in Fig. 5 and Fig. 6. In the presence of superoxide anion, the SOD is induced and the free radical is transformed into H_2O_2 and O_2 to reduce the radical influence (Terevinto et al. 2015). Hydrogen peroxide, which triggers lipid peroxidation but is removed by the CAT enzyme, is harmful to proteins and DNA (Bahmani et al. 2015). SOD levels in group I, group II, and group III were determined as 65.54 U/mg FW, 67.16 U/mg FW, and 64.15 U/mg FW, and CAT levels were determined as 1.37 OD_{240nm}/min.g FW, 1.33 OD_{240nm}/min.g FW, and 1.29 OD_{240nm}/min.g FW, respectively. In group IV, where 1000 mg/L concentration of MSG was administered alone, the SOD level increased to 169.24 U/mg and the CAT level increased to 3.75 OD_{240nm}/min.g FW. In combination with MSG, the application of *P. peruviana* L. extract showed a concentration-dependent improvement in SOD and CAT levels, resulting in a decrease in these levels. Although there

were decreases in SOD and CAT levels, these values were higher than the control group and were statistically significant compared to the control group ($p < 0.05$). In other words, *P. peruviana* L. extract inhibited the oxidative stress induced by MSG partially and depending on the application concentration. SOD levels in group V and group VI decreased to 145.75 U/mg and 127.43 U/mg and CAT levels to 2.97 OD_{240nm}/min.g FW and 2.18 OD_{240nm}/min.g FW, respectively. The development of adaptive responses and increased detoxification ability can be correlated with increased SOD and CAT levels after the administration of MSG.

Concentration-dependent curative role of *P. peruviana* L. extract

The curative effects of *P. peruviana* L. extract on all parameters investigated against MSG toxicity, depending on the application concentration, are given in Fig. 7. The concentration-response improvement curves in the graphic show that the *P. peruviana* L. extract shows an enhancement effect depending on the application concentration in all parameters studied. *P. peruviana* L. extract at 250 mg/L concentration showed the highest protection, with improvement between 36.67 and 57.89% in all parameters except SOD, GSH, and weight gain

Fig. 3 Effects of MSG and *P. peruviana* L. on MDA levels. (Data were shown as mean ± SE. The averages shown with different letters are statistically significant ($P < 0.05$))
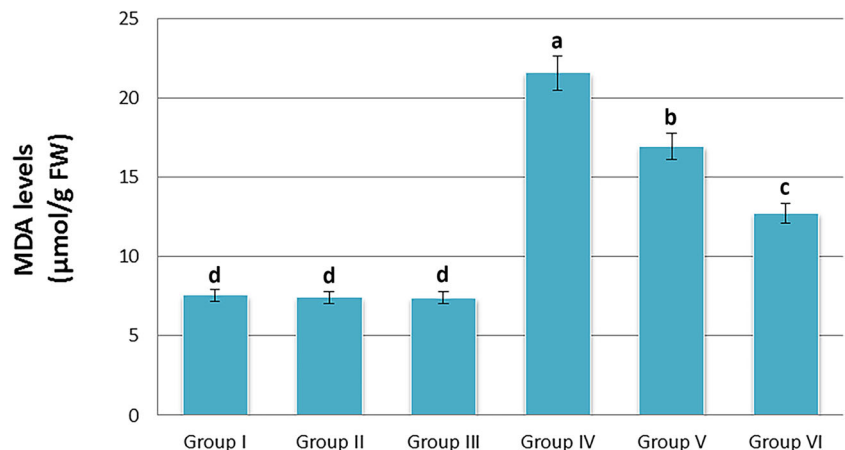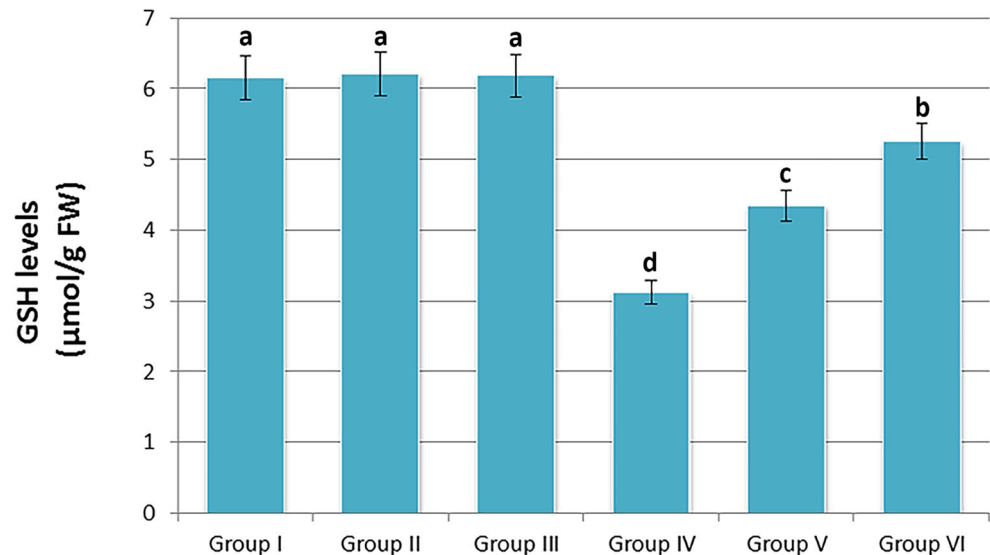
Fig. 4 Effects of MSG and *P. peruviana* L. on GSH levels. (Data were shown as mean ± SE. The averages shown with different letters are statistically significant ($P < 0.05$))

parameters. The improvement in the SOD parameter was below this range at 24.7%, while the improvements in GSH and weight gain were 68.59% and 85.67%, respectively, above this range. As shown in the graph, the healing effects occurring in most parameters depending on the application of *P. peruviana* L. extract are dose-dependent and in a similar range, which is another proof that these parameters are directly or indirectly related to each other.

Discussion

In this study, the toxic effects of MSG, a common food additive, and the protective role of *P. peruviana* L. extract against these effects were investigated with physiological, genetic, and biochemical parameters. At the end of the study, it was determined that MSG caused a decrease in physiological parameters such as rooting percentage, root length, and weight gain, whereas *P. peruviana* L. extract caused an increase in these parameters again depending on the application concentration. Other studies are supporting these findings. Zedan et al. (2017) investigated the effects of MSG, black pepper, and cumin application on germination in *Vicia faba* L. seeds and a decrease in the germination rate was reported due to MSG application. Besides, it has been reported that black pepper and cumin applications inhibit MSG toxicity, causing an increase in the germination rate again. In a study carried out by Liu et al. (2007), the physiological effects on wheat, tomato, and Chinese cabbage of MSG wastewater application were investigated, and as a result, it was reported that the application reduced the germination rate and weight increase in all plants, especially tomatoes. In a study by Singh et al. (2009), industrial wastewater of MSG was applied to *Zea mays* L. and *Brassica rapa* L., as a result, reported that increasing application concentrations caused a decrease in biomass recovery.

Fig. 5 Effects of MSG and *P. peruviana* L. on SOD levels. (Data were shown as mean ± SE. The averages shown with different letters are statistically significant ($P < 0.05$))
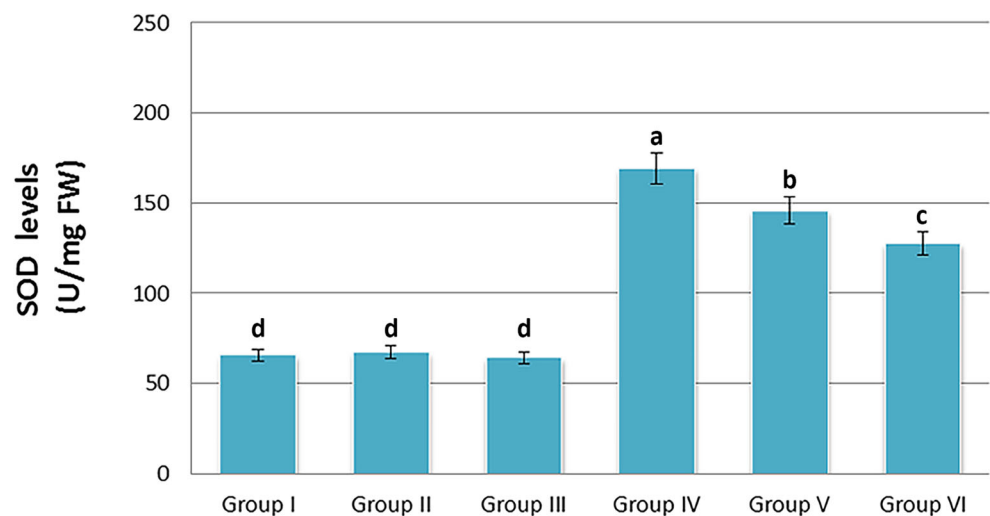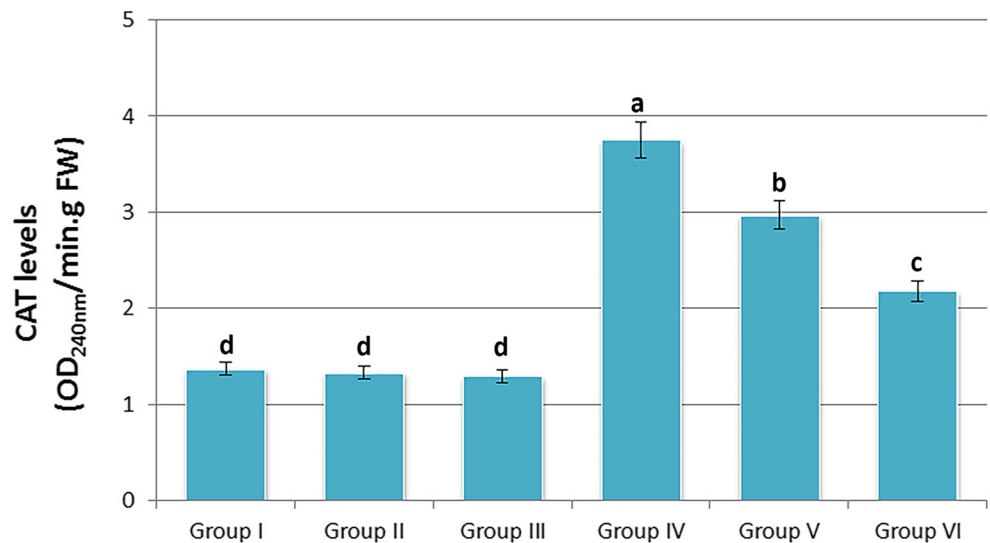
Fig. 6 Effects of MSG and *P. peruviana* L. on CAT levels. (Data were shown as mean ± SE. The averages shown with different letters are statistically significant ($P < 0.05$))

The genetic effects of MSG administration and therapeutic effects of *P. peruviana* L. extract were investigated with MI percentage, MN formation, CA frequency, and DNA damage. The determination of DNA damage was evaluated based on the formation of the DNA tail by the comet test. The comet assay allows DNA strand breaks to be observed in a single-cell. The migration of DNA indicates the extent of DNA damage in the cell and the degree of tail development (Speit and Hartmann 2005). The genetic effects of MSG application were a decrease in MI percentage, an increase in DNA tail formation percentage, and formation of CAs and MN. On the other hand, *P. peruviana* L. extract showed a therapeutic effect depending on the concentration in all these genetic parameters and caused an increase in the MI percentage and a decrease in the frequency of CAs, MN, and DNA tail formation percentage. Other studies in the literature support our findings. In the study conducted by Duran and Aki (2017), different

concentrations of MSG were applied to the *A. cepa* L. test material and it was reported that the application caused a concentration-dependent reduction in the mitotic index. Ataseven et al. (2016) reported that MSG application decreases MI frequency by showing an inhibitory effect on cell division. Ataseven et al. (2016) investigated the effect of six different concentrations of MSG in human lymphocyte cells, and as a result, MSG was reported to increase chromosome abnormalities, sister-chromatid changes, and MN depending on the concentration. In a study by Nagat and Hoda (2015), MSG and two different medicinal plant, *Origanum majorana* L. and *Ruta chalepensis*, extracts were applied to *Allium* bulbs; as a result, it was reported that the content of the nuclear DNA raised due to MSG application, and both medicinal plant extracts reversed this effect and showed antimutagenic effects. In a study by Türkoğlu (2015), MSG tested on *A. cepa* L. was reported to produce important chromosomal abnormalities,
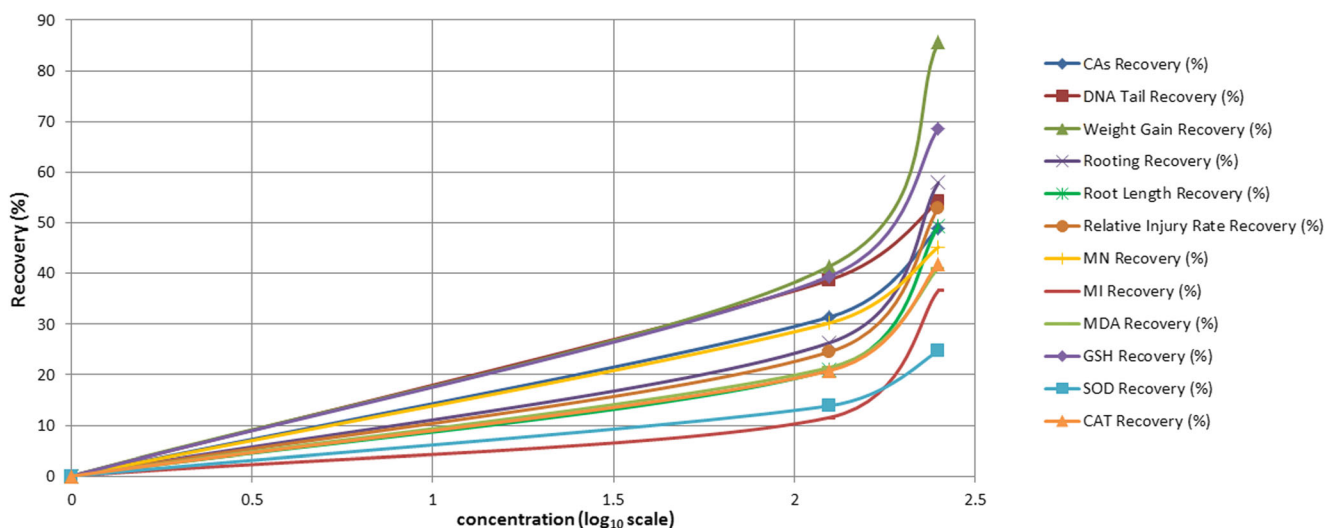

Fig. 7 Concentration-response recovery curves of *P. peruviana* L. extract against MSG toxicity

such as fragments, bridges, discomfort, sticky chromosomes, and other morphological abnormalities such as the expansion of cells at the root tips. Khatab and Elhaddad (2015) applied MSG and additionally the extracts of *Ruta chalepensis* and *Origanum majorana* L. medicinal plants to *A. cepa* L. bulbs, and as a result, reported that MSG caused chromosomal abnormalities in the form of sticky chromosomes, disturbance, bridges, fragments, and morphological abnormalities. It has been reported that plant extracts suppress MSG toxicity, show antimutagenic, and antigenotoxic effects by raising the mitotic index and reducing the chromosomal abnormality rate. Nan et al. (2016) reported that oxidative stress can cause DNA damage, and the formation of excessive reactive species is the main cause of DNA damage. This confirms the findings we obtained in the study. Studies with different tissues and organisms have also revealed that MSG causes DNA damage. It has been reported that MSG administration causes DNA damage in the testicular cells of male rats (Hamza et al., 2020), human neuroblastoma cells (Shah et al. 2019), and liver cells of male rats (Albrahim and Binobead, 2018). It is known from studies that *P. peruviana* L. has a protective role against DNA damage. Similar to the findings of the research, in a study conducted by Çakir et al. (2014), *P. peruviana* L. extract was reported to prevent DNA damage. Ramadan et al. (2015) reported that *P. peruviana* L. shows pharmacological, biological, and antimutagenic activity, and the source of this is the high amount of terpenes and high levels of isoeugenol in its content. Research reports that terpenes and isoeugenol have antimutagenic effects (Ogata et al. 2000; Di Sotto et al. 2008; Bound et al. 2020). These phytochemicals are thought to be the source of the antimutagenic effect exhibited by *P. peruviana* L. in the study.

MSG application caused lipid peroxidation in root tip tissues of *A. cepa* L. bulbs and increases in antioxidant enzyme activities occurred. MSG application caused an increase in MDA, SOD, and CAT levels and a decrease in GSH level. *P. peruviana* L. extract resulted in a decrease in MDA, SOD, and CAT levels and an increase in GSH levels, depending on the application concentration. In other words, it has tolerated the lipid peroxidation and antioxidant enzyme activity increases caused by MSG application. Raised levels of MDA, reduced levels of GSH are associated with the toxicity of MSG and fluctuations of antioxidant enzyme activities. The synthesis of superoxide anion, reactive oxygen species (ROS), and hydrogen peroxide in the plant cells have been induced by MSG and its intermediate molecules (Tseng and Lin 2015). Glutathione is the substrate of enzymes such as glutathione transferase, glutathione reductase, and glutathione peroxidase, and the change in glutathione levels will cause a change in the activity of these enzymes. In short, an imbalance will occur in the antioxidant system, and in this case, an increase in oxidant molecules such as hydrogen peroxide and a decrease in

antioxidant molecules such as total thiol may be observed (Moron et al. 1979). The protective mechanism of *P. peruviana* L. is known to consist of its ability to clean ROS and improve the antioxidant system (El-Beltagi et al. 2019). Similarly, Arun and Asha (2007) reported that CCl$_4$ application increased MDA level and decreased GSH level, and *P. peruviana* L. extract applied in combination with CCl$_4$ showed an improvement again in all these levels, and decreased MDA level and increased GSH level again. In another study, Erman et al. (2017) reported that the administration of *P. peruviana* L. extract caused an improvement in MDA-GSH levels. Similarly, Hamza and Al-Baqami (2019) stated that MSG application increased the MDA level, decreased SOD and CAT levels significantly depending on the dose, and ellagic acid application in combination with MSG caused improvement in these parameters. In a study conducted by Farombi and Onyema (2006), it was reported that MSG administration caused an increase in liver SOD and CAT levels in rats, and quercetin administration decreased these levels. The fact that *P. peruviana* L. contains quercetin in its content has been previously reported (Al-Olayan et al. 2014) provides an understanding of the decrease in SOD-CAT levels caused by MSG with *P. peruviana* L. application.

Conclusion

As a purpose, this research is designed to evaluate MSG toxicity and the therapeutic potential of *P. peruviana* L. extract together for the first time. Whereas MSG application caused significant adverse effects on all parameters, *P. peruviana* L. extract administration partially inhibited toxicity by showing dose-dependent therapeutic effects. Considering all the data in the study as a whole, MSG application inhibited the physiological growth parameters in *A. cepa* L. bulbs, caused the formation of MN, chromosomal abnormalities, DNA damage, MI, reduction in MI, and oxidative stress determined by biochemical parameters. *P. peruviana* L. extract administration showed concentration-dependent therapeutic effects by reducing the toxicity occurring in all these parameters. The study has shown that MSG affects DNA by causing oxidative stress, which affects the growth and division of cells and negatively affects physiological growth. On the other hand, *P. peruviana* L. extract decreased oxidative stress and DNA damage depending on the concentration, and this also manifested itself in physiological parameters.

Consequently, considering the genetic damage caused and oxidative stress by MSG, it has been found that its use as a food additive should be abandoned and the use of *P. peruviana* L. as a supplement in addition to daily nutrition to be a good antioxidant in reducing the effects of exposed toxic substances.

Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Ethics approval and consent to participate   Not applicable

Consent for publication   Not applicable

Conflict of interest   The author declares that he has no conflict of interest.

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