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Protective Effects of Cinnamic Acid Against Monosodium Glutamate Toxicity in Rats

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Abstract

Background: Monosodium glutamate (MSG), a common food additive, has demonstrated potential organotoxic effects in animal studies. Cinnamic acid (CA), a naturally occurring phenylpropanoic acid, is known for its antioxidant and anti-inflammatory properties.

Objective: This research aimed to evaluate the protective role of CA against MSG-induced toxicity in rat models.

Methods: The study utilized twenty-five male adult albino rats weighing from 145 to 150 grams, divided into five groups (n=5 each). The groups were: **group I** - control (basal diet); **group II** - MSG oral administration (3.0 g/kg body weight); **group III** - MSG oral administration with CA (40 mg/kg body weight); **group IV** - MSG via intraperitoneal injection (4 mg/kg body weight); **group V** - MSG intraperitoneal injection with CA (40 mg/kg body weight). Post-treatment, serum was analyzed for biochemical changes.

Results: CA administration significantly reduced blood glucose and leptin levels while elevating insulin levels in MSG-treated rats. Furthermore, CA markedly reduced malondialdehyde (MDA) levels and increased superoxide dismutase (SOD) and glutathione (GSH) levels, indicating a reduction in oxidative stress.

Conclusion: The study reveals CA's capability in ameliorating MSG-induced metabolic alterations and oxidative stress, underscoring its potential as a therapeutic agent in managing biochemical disturbances related to MSG exposure.

Keywords: Cinnamic acid, Monosodium glutamate (MSG), Toxicity, Oxidative stress, antioxidant, Lipid profile

1. Introduction:

Numerous artificial pollutants, encompassing food additives and industrial chemicals, are associated with negative health impacts [1]. The burgeoning working class and urban lifestyles have led to a widespread reliance on commercial foods, prized for their time and resource efficiency, yet often lacking in nutritional value. These commercial food products frequently contain additives serving as preservatives or flavor enhancers [2]. One prevalent additive in processed foods is Monosodium Glutamate (MSG), known for enhancing taste and appeal [3].

While MSG is effective in intensifying flavor and stimulating appetite, it is deemed harmful to humans and laboratory animals [4]. Its use not only improves the taste of food but also activates the appetite center, potentially leading to increased body weight [5]. Research has pointed to MSG's role in prompting metabolic alterations, potentially causing serious health issues such as obesity, liver damage, central nervous system and re-

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productive dysfunctions [6]. One such issue is the induction of oxidative stress following MSG consumption [7]. This stress exacerbates conditions like hypercholesterolemia, hypertension, diabetes, and chronic kidney disease [8, 9]. Oxidative stress arises from an imbalance in the production and elimination of free radicals, primarily oxygen radicals and other reactive oxygen species (ROS) [10]. Studies have shown that chronic exposure to MSG in rats leads to reduced levels of key antioxidant enzymes and an increase in lipid peroxidation, particularly in the kidneys [11].

Cinnamic acid (CA), an organic compound belonging to the phenylpropanoic acid family, is primarily found in plants such as Cinnamomum cassia (commonly known as Chinese cinnamon) and Panax ginseng, along with a presence in vegetables, whole grains, fruits, and honey [12]. This compound is noted for its antioxidative capabilities, attributed to its vinyl fragment structure, enabling it to halt radical chain reactions by donating electrons and thereby forming stable compounds [13]. CA is recognized for its diverse biological activities, including anti-inflammatory [14], antimicrobial, antitumoral, and antifungal properties [15]. Furthermore, it demonstrates significant roles in diabetes management and blood sugar regulation by influencing glycogenesis and gluconeogenesis and improving glucose tolerance and insulin secretion [16].

The focus of this research is to explore the protective effects of cinnamic acid against the detrimental impacts caused by monosodium glutamate (MSG) in a rat model. This exploration involves the assessment of serum biomarkers, analysis of oxidative stress levels, and conducting histopathological examinations of the liver, kidneys, and pancreas.

2. Materials and methods

2.1. Chemicals

In the study presented, the chemicals used were of the highest purity and acquired from reputable sources. Specifically, monosodium Glutamate (MSG) with a purity greater than 99%, and Cinnamic Acid (CA), also exceeding 99% purity, were obtained from LOBA CHEMIE PVT LTD.

2.2. Animals

Twenty-five male adult albino rats (sprague-Dawley strains), each with a body weight ranging from 145 to 150 grams, were acquired from the National Research Center of Egypt's (NRC) animal facility. These rats were accommodated in metal enclosures, with five animals per cage, within the NRC's Laboratory Animal House in Egypt. The rats were kept under conditions mimicking natural daylight, with ambient temperatures maintained at 25±2 °C. A two-week acclimatization period was provided prior to the commencement of experimental procedures. The rats had unrestricted access to water and standard rodent feed. All experimental practices involving these animals were conducted in strict compliance with the ethical standards and protocols set by both the National Research Center Ethics Committee and the Faculty of Science Ethics Committee (REC56/2021).

2.3. Experimental Design

Following a 14-day acclimatization period, the subjects were allocated into five distinct groups, each consisting of five rats. **Group I** acted as the normal control, receiving only the standard diet.

Group II was provided with the standard diet, enhanced with 3 g/kg of Monosodium Glutamate (MSG) administered daily through oral gavage for a duration of 45 days [17].

Group III received a similar diet to Group II, but with the addition of 40 mg/kg Cinnamic Acid, also administered daily via oral gavage for 45 days [19].

Group IV was subjected to daily intraperitoneal (IP) injections of 4 mg/kg MSG for 45 days [18].

Lastly, Group V was treated with daily IP injections of 4 mg/kg MSG [18] and oral of 40 mg/kg Cinnamic Acid, continued over 45 days [19].

2.4. Sampling

At the end of the experiment, the rats were fasted for 12 h, then blood will be drained and collected under effect of tetrahydrofuran inhalation anesthesia. Blood was drawn from the retro-orbital venous plexus, followed by centrifugation at 3000 revolutions per minute for 10 minutes. The serum

obtained was clear, promptly separated, and preserved at -20°C for later biochemical analyses. Subsequent to the blood collection, the rats were humanely euthanized. Organ tissues, specifically from the pancreas, liver, and kidneys, were then surgically removed. These tissue samples were preserved in 10% neutral buffered formalin in preparation for histopathological evaluation.

2.5. Blood glucose, insulin levels and HOMA-IR

The concentration of glucose in the serum was measured through an enzymatic colorimetric method, utilizing a kit available for purchase (Catalog Number GL 46861, DIACHEM LTD). Levels of serum insulin were quantified using an ELISA method tailored for rats, employing a specific kit (Catalog Number CSB-E05070r, CUSABIO Company), in accordance with the instructions provided by the manufacturer. Insulin resistance was quantitatively assessed using the homeostasis model assessment (HOMA-IR). This was calculated using the formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/L) / 22.5 [20].

2.6. Lipid profile

Referring to [21]. The serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL), and triglycerides (TG) were evaluated using enzymatic colorimetric kits provided by DIACHEM Ltd Company, Egypt.

2.7. Assay for leptin (ng/ml

Leptin, identified as a peptide hormone, originates from adipose tissue. Its functions are primarily associated with the control of appetite, neuroendocrine activities, and the maintenance of energy balance [22]. The quantification of leptin is performed using a rat leptin ELISA kit provided by CUSABIO Company, under the catalog number CSB-E07433r.

2.8. Determination of reduced glutathione (GSH (mmol/L

Glutathione, an essential intracellular tripeptide comprising glutamic acid, cysteine, and glycine, plays a pivotal role as an antioxidant, safeguarding cells from the detrimental effects of free radicals [23]. The concentration of reduced glutathione was assessed using the Colorimetric Method, utilizing kits from CELL BIOLABS Company (Catalog Number STA-312).

2.9. Assay for lipid peroxide (malondialdehyde (μmol/L

Malondialdehyde (MDA), a product of polyunsaturated fatty acid peroxidation within cells, is indicative of increased free radical activity [24]. MDA levels are commonly used to gauge oxidative stress and the antioxidant status, particularly in patients with cancer. The serum level of MDA was determined through a Colorimetric Method, using commercially available MDA kits (Catalog Number MD STA-330, CELL BIO LABS Company, Egypt).

2.10. Assay for superoxide dismutase (SOD (U/µL

Superoxide, a by-product of oxygen metabolism, can lead to various forms of cellular damage if not adequately regulated [25]. The levels of superoxide dismutase were measured using Colorimetric Method kits (Catalog Number STA-340, CELL BIOLABS Company, Egypt).

2.11. Histopathological examination

After euthanasia, the pancreas, liver, and kidneys were extracted from the rats and then fixed in a 10% neutral-buffered formalin solution for histopathological examination.

2.12. Statistical analysis

The data were analyzed using Graph Pad Prism version 8 for Windows, with results presented as Mean ± SD (n = 5). Statistical analysis involved one-way ANOVA followed by the Tukey test. A p-value of less than 0.05 was considered statistically significant []

3. Results

3.1. Fasting blood glucose level (FBG , insulin Level and HOMA-IR

Administration of MSG, both orally and via intraperitoneal (IP) routes, markedly elevated fasting

blood glucose (FBG) levels as compared to healthy control group ($P < 0.05$), with the oral route inducing a more pronounced increase. Treatment with Cinnamic Acid (CA) notably lowered FBG ($P < 0.05$) in contrast to the MSG-treated groups (groups 2 and 4). In relation to the control group, the MSG-administered groups (groups 2 and 4) showed a significant reduction in insulin levels ($P < 0.05$). In contrast, rats receiving CA treatment for a duration of 45 days demonstrated significantly elevated insulin levels ($P < 0.05$) compared to those subjected to MSG. The IP administration of MSG resulted in a substantial rise in the homeostasis model assessment of insulin resistance (HOMA-IR) relative to the control group ($P < 0.05$). Nevertheless, a month-long CA treatment in rats administered with MSG significantly diminished HOMA-IR, bringing it to levels similar to those in the control group, as illustrated in table 1.

The data presented indicates the average value (mean) with its standard deviation (SD) based on five samples ($n = 5$). In the dataset, values that have different superscript letters in the same row show a significant difference, with a p-value of less than 0.05 ($P<0.05$). FBG refers to Fasting Blood Glucose.

3.2. Lipid profile

Administration of monosodium glutamate (MSG) orally resulted in a notable rise in serum total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-c) levels, when compared to the control group ($P < 0.05$). Concurrent treatment with Cinnamic Acid (CA) effectively reduced the elevations in TC, TG, and LDL-c caused by MSG ($P \leq 0.05$), as detailed in Table 2.

3.3. Leptin level

The administration of Monosodium Glutamate (MSG) led to a marked increase in the levels of circulating leptin compared to the rats in the negative control group. Treatment with Cinnamic Acid (CA) significantly decreased leptin concentrations in groups III and V, in comparison to groups II and IV, which were their respective counterparts.

Every value is indicative of the mean ± standard deviation (SD) for a group size of five ($n = 5$). Within each row, values having unique superscript letters demonstrate a statistically significant variation at a p-value less than 0.05 ($P<0.05$). TC refers to total cholesterol, TG to triglycerides, HDL-C to high-density lipoprotein cholesterol, and LDL-C to low-density lipoprotein cholesterol.

3.4. Lipid Peroxidation and Antioxidants

Oral administration of Monosodium Glutamate (MSG) resulted in a statistically significant elevation ($P < 0.05$) in the level of Malondialdehyde (MDA) when compared with the control group. The administration of Cinnamic Acid (CA) led to a considerable reduction ($P < 0.05$) in MDA levels in comparison to both groups II and IV. Intraperitoneal (IP) administration of MSG at a dosage of 4mg/kg body weight significantly diminished the levels of Superoxide Dismutase (SOD) and Glutathione (GSH) relative to the control rats. There was no notable difference in SOD and GSH levels between the control group and group V, as depicted in Table 3.

Each reported value represents the average ± standard deviation (SD) with a sample size of five ($n = 5$). In the same row, values having distinct superscript letters indicate a significant difference at a p-value of less than 0.05 ($P<0.05$). The abbreviations MDA, SOD, and GSH stand for malondialdehyde, superoxide dismutase, and reduced glutathione, respectively.

3.5. Histopathology :

3.5.1. Liver

The liver of **(group I)** showed normal histological structure of hepatic lobules, each lobule had a centrally located central vein and radiating cords of hepatic cells. Each hepatic cell contained homogenous eosinophilic cytoplasm with prominent centrally located nucleus . On the other hand, **Group II** revealed multiple perilobular vacuolar degeneration of hepatocytes typical to fatty change. Congestion of central veins, mild proliferation of bile ducts and mild focal lymphocytic infiltrations **Group III** exhibited moderate degree of

Table 1: The effect of Cinnammic acid on Glucose, Insulin, and HOMA IR.

Groups experiment	Group I	Group II	Group III	Group IV	Group V
FBG (mg/dL)	$115.5^{c}\pm 3.78$	$171.5^{a}\pm 2.24$	$134.0^{b}\pm 2.23$	$136.8^{b}\pm 1.79$	$118.6^{c}\pm 1.38$
Insulin (nIU/ml)	$68.66^{a}\pm 1.19$	$45.86^{c}\pm 0.80$	$61.15^{b}\pm 0.64$	$61.12^{b}\pm 0.78$	$68.15^{a}\pm 0.55$
HOMA IR	19.50 ± 0.63^{b}	19.39 ± 0.19^{b}	20.22 ± 0.53^{ab}	20.70 ± 0.38^{a}	19.95 ± 0.24^{b}

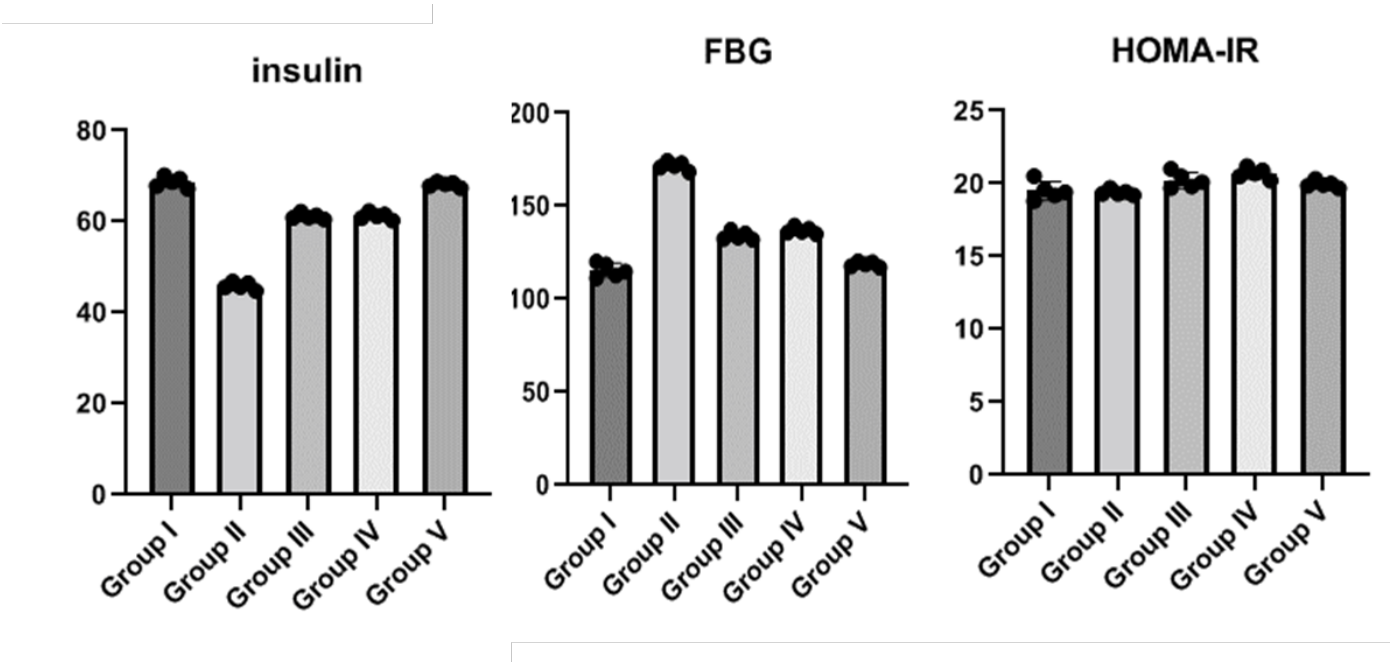

Figure 1: Effect of Cinnamic Acid on Glucose, Insulin, and HOMA-IR in experimental groups.

Table 2: **:The effect of Cinnammic acid on Leptin and lipid profile.**

Groups experiment	Group I	Group II	Group III	Group IV	Group V
TC (mg/dL)	$55.27^{d}\pm 0.67$	$100.0^{a}\pm 2.58$	$64.67^{c}\pm 1.34$	$71.51^{b}\pm 1.42$	$57.41^{d}\pm 1.40$
TG (mg/dL)	$61.42^{d}\pm 1.04$	$117.8^{a}\pm 3.67$	$69.16^{c}\pm 1.88$	$79.70^{b}\pm 1.49$	$64.93^{d}\pm 1.23$
HDL-C (mg/dL)	$15.08^{d}\pm 0.19$	$19.48^{a}\pm 0.15$	$16.56^{b}\pm 0.15$	$16.80^{b}\pm 0.13$	$15.65^{c}\pm 0.14$
LDL-C (mg/dL)	$27.88^{d}\pm 0.77$	$57.00^{a}\pm 2.00$	$34.34^{c}\pm 1.02$	$38.78^{b}\pm 1.01$	$28.78^{d}\pm 1.11$
Leptin (ng/ml)	$2.726^{d}\pm 0.08$	$4.168^{a}\pm 0.06$	$3.208^{c}\pm 0.11$	$3.480^{b}\pm 0.08$	$2.830^{d}\pm 0.08$

Table 3: **The effect of cinammic acid on lipid peroxidation and antioxidant parameters**

Groupsof experiment	Group I	Group II	Group III	Group IV	Group V
MDA (μmol/L)	$0.12^{e}\pm 0.006$	$0.54^{a}\pm 0.01$	$0.25^{b}\pm 0.008$	$0.22^{c}\pm 0.008$	$0.15^{d}\pm 0.006$
SOD (U/μL)	$5.202^{a}\pm 0.03$	$3.810^{c}\pm 0.08$	$4.804^{b}\pm 0.05$	$4.764^{b}\pm 0.06$	$5.032^{a}\pm 0.11$
GSH (mmol/L)	$18.89^{a}\pm 0.10$	$14.07^{c}\pm 0.13$	$18.08^{b}\pm 0.12$	$18.04^{b}\pm 0.16$	$18.89^{a}\pm 0.09$

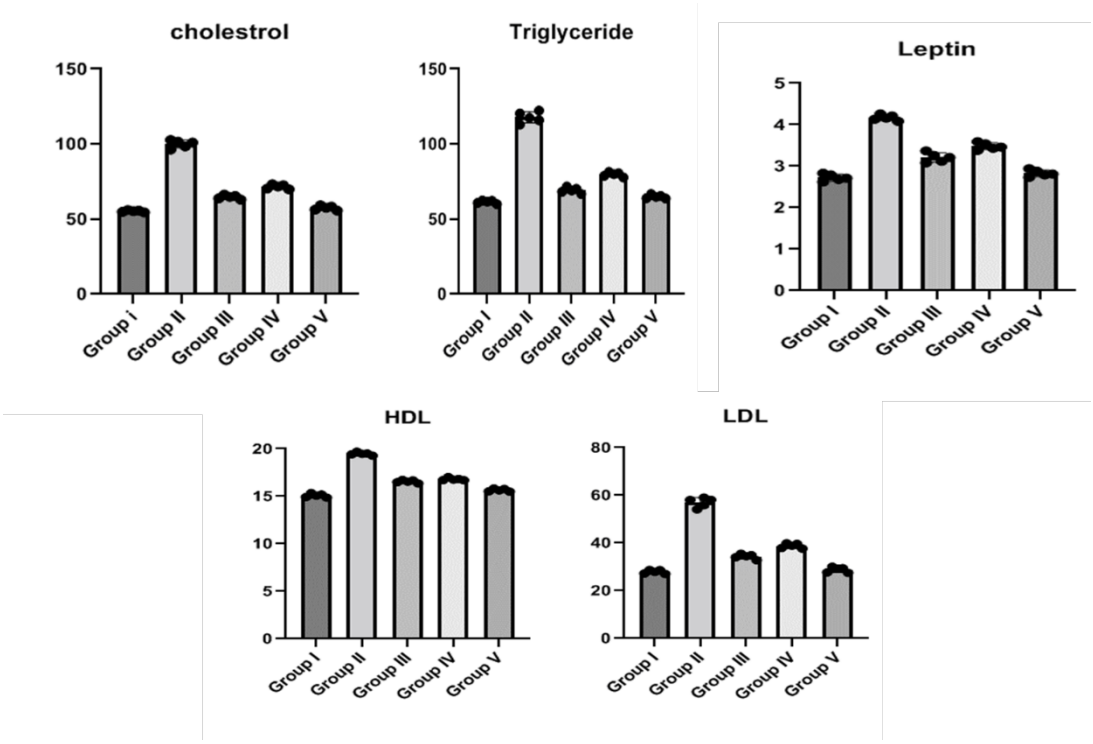

Figure 2: Effect of Cinnamic Acid on Leptin and Lipid Profile in different experimental groups.

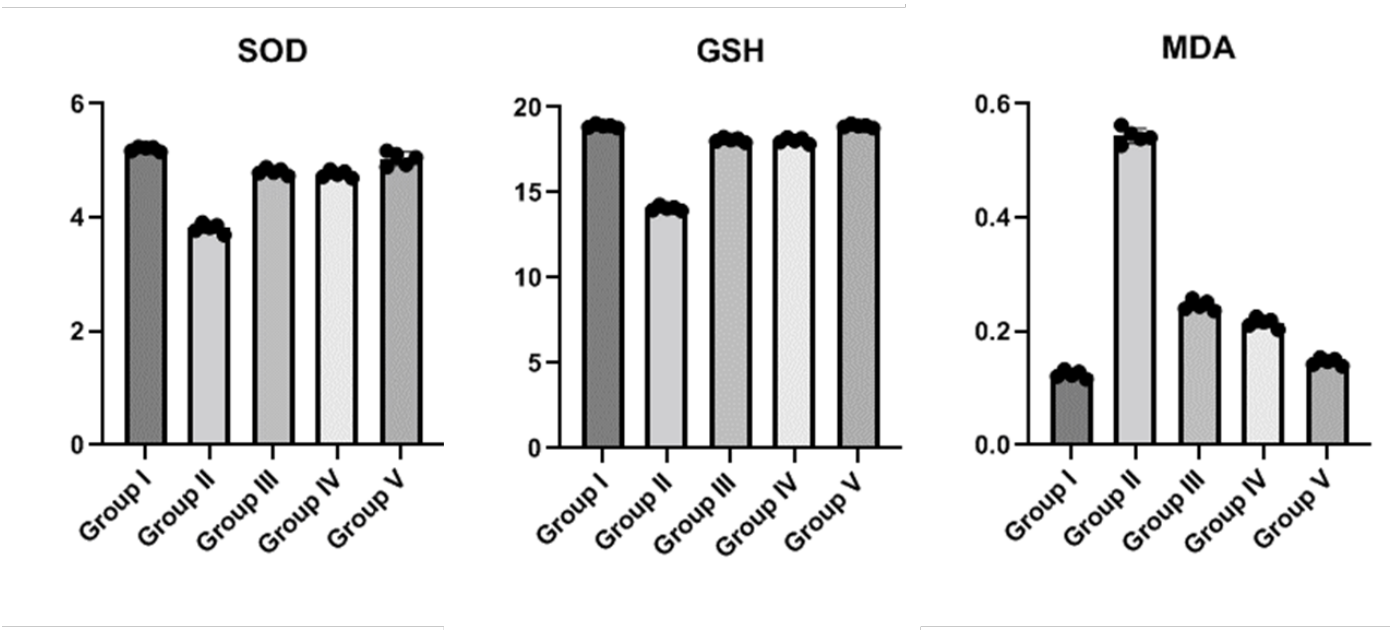

Figure 3: Effect of Cinnamic Acid on Lipid Peroxidation and Antioxidant Parameters in experimental groups

improvements characterized mild to moderate focal areas of fatty infiltration. **Group IV** revealed hyperplasia of bile ducts, perivascular edema and focal vacuolar degeneration of hepatocytes. **Group V** revealed prominent degrees of improvement of the hepatic tissue with mild degenerative changes of some hepatocytes.

3.5.2. Kidney

Kidneys of **group I** showed normal glomeruli and normally intact proximal and distal convoluted tubules that had intact basement membranes and maintained brush borders. The glomeruli of **group II** revealed marked thickening of glomerular capillaries, multifocal degeneration of renal tubular epithelium with indistinct epithelial outlines and loss of brush borders of proximal convoluted tubules. Also, there were focal periglomerular leukocytic infiltrations along with congestion of blood vessels**.Group III** demonstrated pronounced improvement of the kidney lesions. The glomeruli of **Group IV** revealed marked thickening of glomerular capillaries, multifocal degeneration of renal tubular epithelium with indistinct epithelial outlines and loss of brush borders of proximal convoluted tubules. Also, there were focal periglomerular leukocytic infiltrations along with congestion of blood vessels**. Group V** demonstrated pronounced improvement of the kidney lesions.

3.5.3. Pancreas

The pancreas of **group** I showed normal lobules of exocrine glands and normal distribution of well-defined islets of Langerhans that had prominent beta cells . **Group II** revealed marked reduction in both numbers and sizes of pancreatic islets of Langerhans. Islets had poorly defined outlines along with degenerated beta cells, focal area of lymphocytic infiltrations and destruction of necrotic and degenerative changes in exocrine and endocrine cells. **Group III** exhibited both hyperplasia and hypertrophy in the islets of Langerhans, accompanied by a reduction in their quantity. Furthermore, the islet cells demonstrated vacuolation within the cytoplasm and pyknosis in the nuclei. Additionally, the acinar cells revealed slight alterations in their typical structure, alongside vascular congestion and dilation, coupled with the occurrence of edema in the surrounding areas**.** The pancreas of rats treated with **Group IV** revealed mild degenerative changes of pancreatic cells and normal exocrine parts. Whereas the group treated with **CA** showed well demarcated islets outline with mild focal necrotic changes of beta cells**.** Rats treated with **Group V** demonstrated well defined pancreatic outlines and mild degeneration of beta cells with focally necrotic nuclei**.**

4. Discussion

Numerous studies have linked MSG consumption, a common flavor enhancer, with the development of obesity and metabolic syndrome in both humans and animals [26]. This research delved into the metabolic disruptions caused by MSG in rat models and examined the potential mitigating effects of cinnamic acid. The study focused on alterations in critical metabolic indicators such as glucose, insulin, leptin, lipid profiles, and antioxidant markers.

Assessing fasting blood glucose is crucial for diagnosing and treating carbohydrate metabolism disorders. The results revealed a significant rise in glucose levels in rats administered with MSG (groups II and IV), in contrast to control rats. These increases varied between groups, attributed to differing MSG doses and administration methods. A primary factor for hyperglycemia in these rats was a reduction in GLUT 4 protein in adipocytes [27]. These findings align with previous research [28], which showed elevated FBG levels in rats given various MSG doses over eight weeks, due to insulin deficiency. However, these findings contrast with other studies [29] that reported no significant differences in serum insulin levels and glucose tolerance between MSG-treated and untreated rats.

Cinnamic acid (CA) effectively lowered glucose levels, potentially by inhibiting dipeptidyl peptidase-IV and enhancing glucose uptake [30]. These results are consistent with studies suggesting CA derivatives boost glucose uptake in adipocytes and muscle cells [31], indicating CA's anti-diabetic properties through improved glucose tolerance

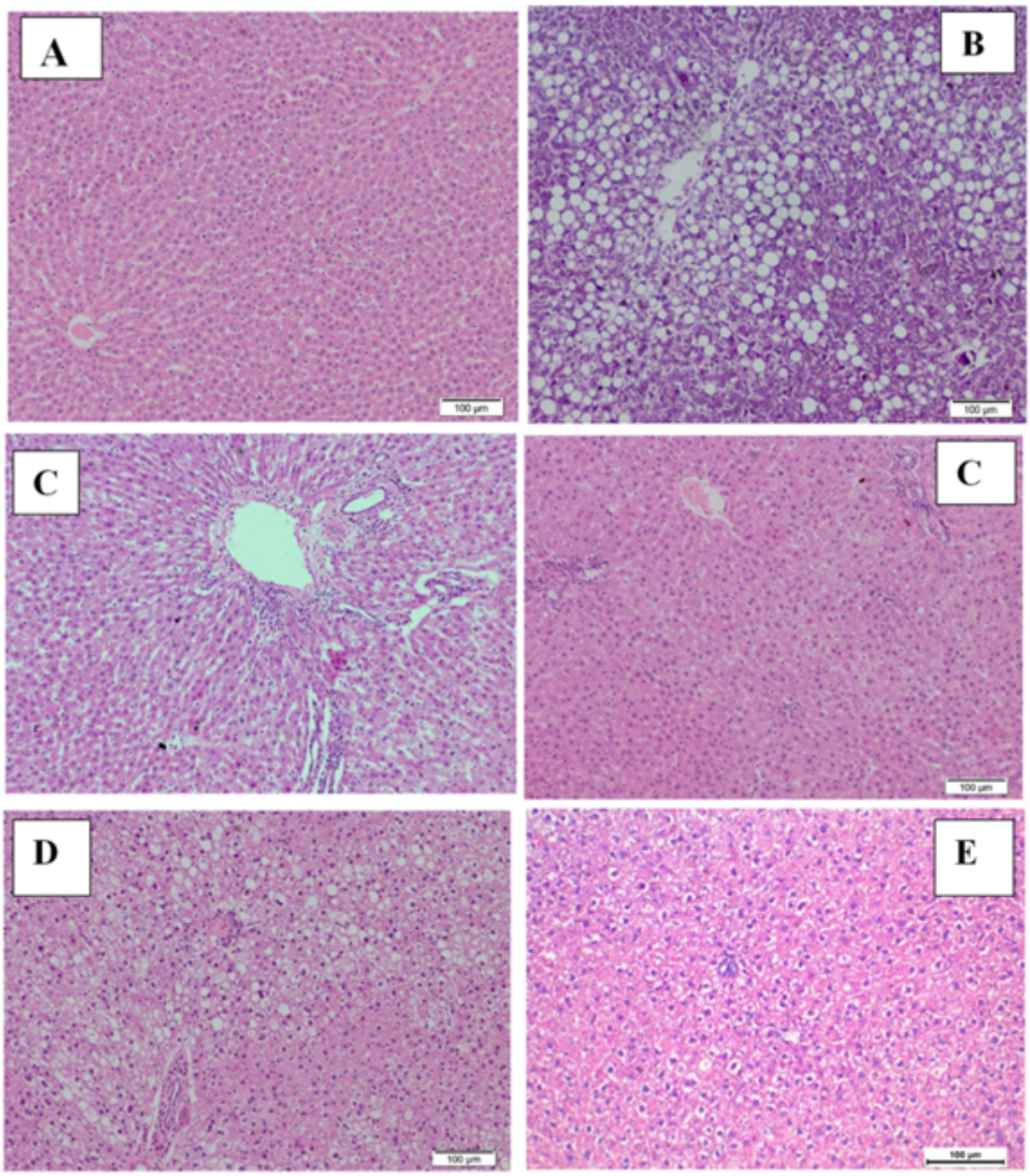

Figure 4: Histopathology of liver tissue in groups I, II, III, IV, and V. Normal intact radiating cords of hepatocytes around normal central veins. H&E was observed in the group I (A). Cytoplasmic fatty vaculation and necrosis of the centrilobular hepatocytes, fatty vaculation of the interlobular hepatocytes in group II (B). Hyperplasia of bile ducts and focal lymphoctic infiltrations in hepatic area in group III (C). Multifocal fat infiltration of hepatocytes along with focal necrosis of some hepatic cells in group IV (D). Mild cytoplasmic vacuolation of hepatic cells in group V (E).

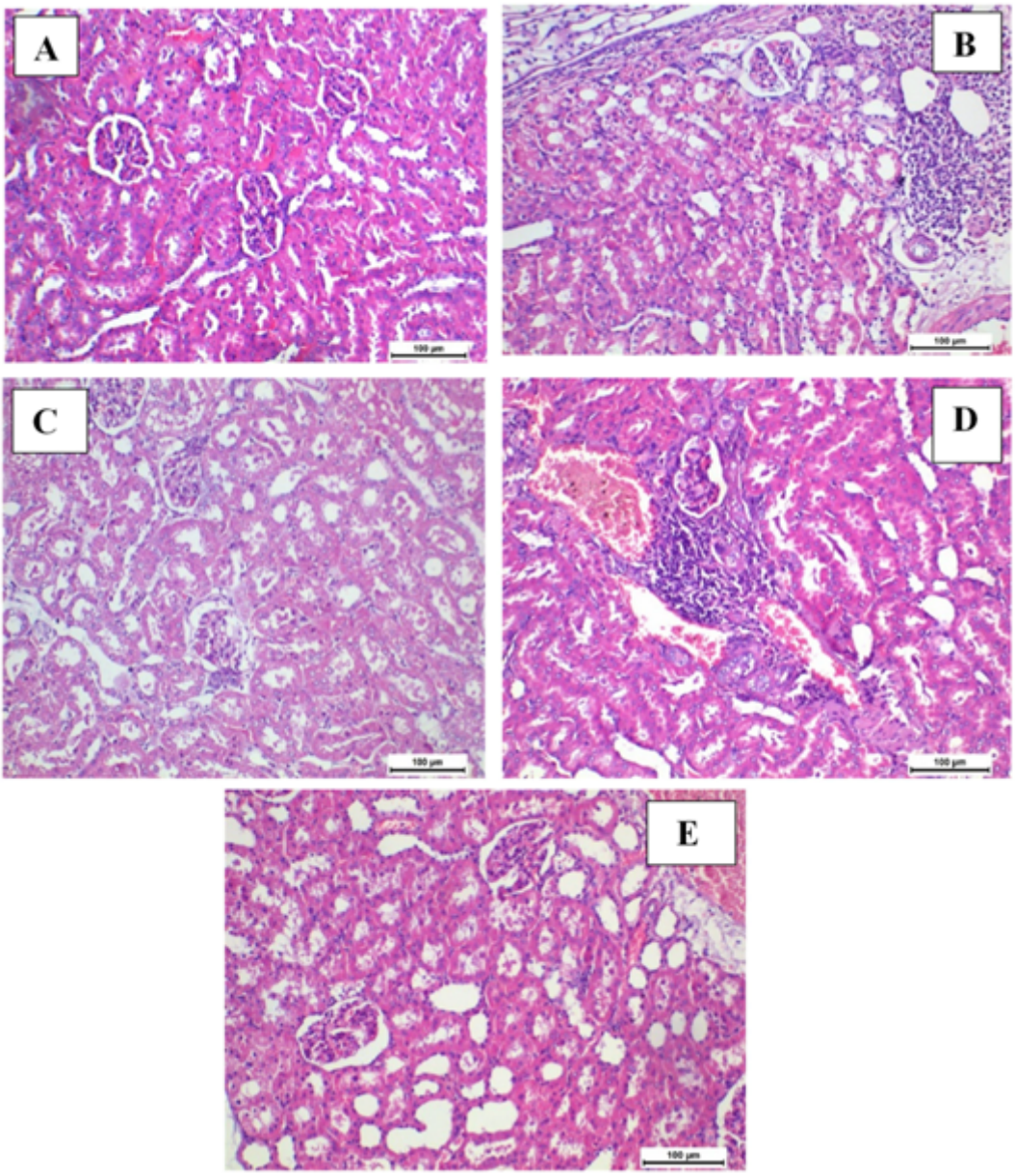

Figure 5: Histopathology ofkidney tissue in groups I, II, III, IV, and V .Normal intact renal tubules and normal glomeruli in group I (A) Dilatation and congestion of blood vessels perivascular edema, lymphocytic infiltration and edema, fatty change and necrosis of some tubules in group II (B). Mild degenerative changes of renal tubule in group III (C).Dilatation and congestion of blood vessels perivascular glomerular lymphocytic infiltration degeneration of some tubules with cystic dilatation in group IV (D).Mild congestion of renal blood vessels and mild degeneration of renal tubulessome tubules in group V (E).

and insulin secretion. CA enhances glucose absorption via PPARγ-mediated GLUT4 translocation in mature 3T3-L1 adipocytes [32] and exhibits insulin-like activity, enhancing hormone pathway functionality [33].

Insulin plays a role in lipid as well as carbohydrate metabolism, with its deficiency linked to hypercholesterolemia and hypertriglyceridemia. This study showed that MSG led to a significant decrease in insulin levels, corroborating with findings that MSG reduces insulin secretory response to glucose [34]. This explains the hyperglycemic state resulting from MSG exposure, though it contrasts with studies indicating MSG-induced hyperinsulinemia [35]. Conversely, CA significantly raised insulin levels compared to MSG-treated rats, sup-

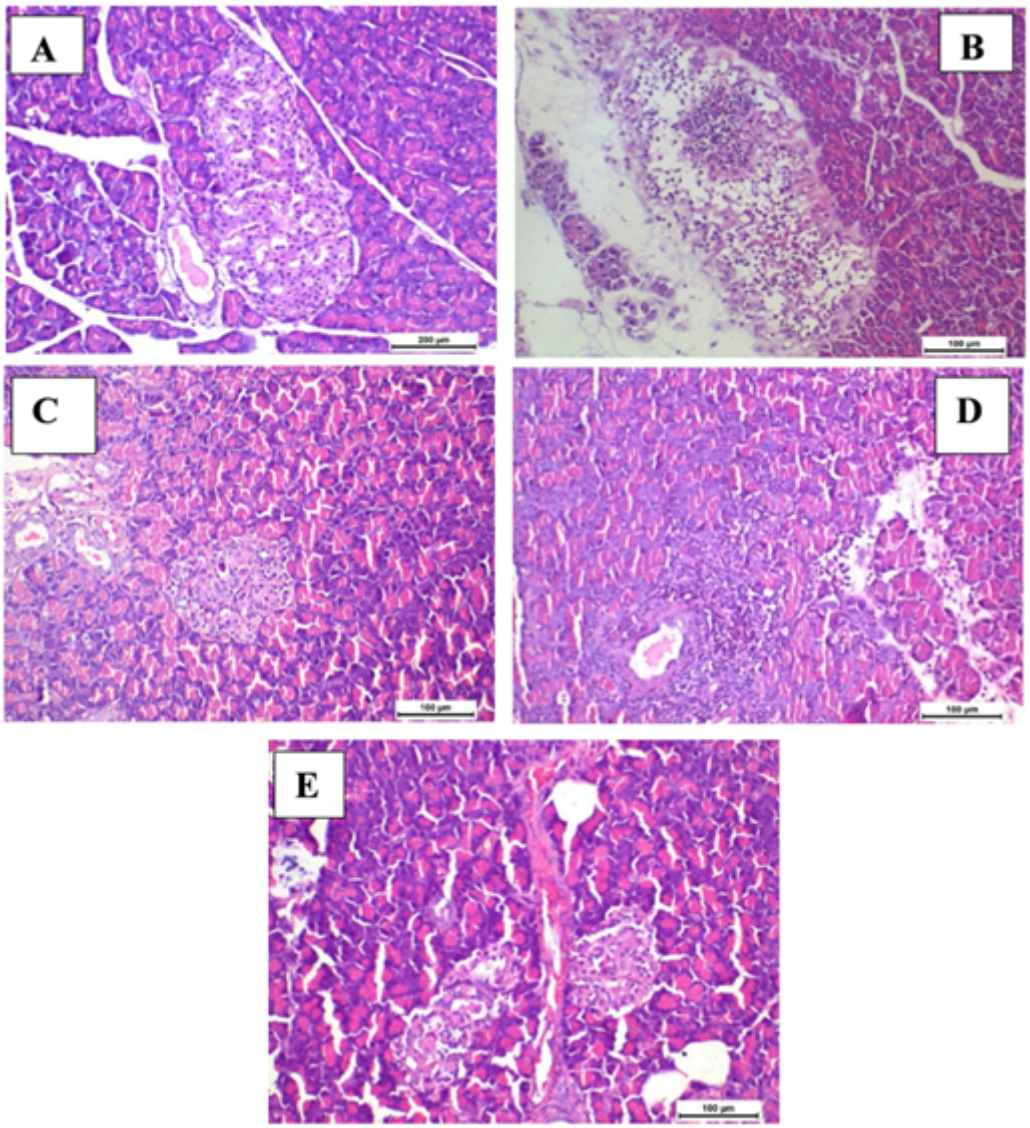

Figure 6: Fig (3) depicts histopathological observations of pancreatic tissues in groups I, II, III, IV, and V. In group I (A), the islets of Langerhans (IL) display typical architecture, interspersed among normal pancreatic acini (SA) and regular blood vessels (BV). Group II (B) shows a disruption in the normal structure of both exocrine and endocrine regions, along with extensive focal necrosis and lymphocytic infiltrations replacing damaged areas. Group III (C) presents with hyperplasia and hypertrophy in the islets of Langerhans, characterized by pyknotic nuclei (P), mild vacuolation (V), edema (E), and congested, dilated blood vessels. Group IV (D) exhibits a loss of normal exocrine and endocrine structure with mild focal necrosis and lymphocytic infiltrations supplanting some acinar cells. Lastly, group V (E) demonstrates hyperplasia and hypertrophy in the islets of Langerhans, along with pyknotic nuclei, mild vacuolation, edema, and congested, dilated blood vessels

porting the hypothesis that CA's anti-diabetic action is mediated by increased insulin secretion [16]. Phenolic compounds, like CA, have been found to alleviate insulin resistance in the liver of high-fat diet-fed rats by unlocking the insulin pathway and ameliorating pro-inflammatory and redox imbalances [36].

Leptin, secreted by adipocytes, is crucial in regulating appetite and body fat. The study found a significant increase in leptin levels in MSG-treated groups (II and IV) compared to controls, with variations due to different MSG doses and administration methods. These findings agree with research suggesting that MSG's toxicity-related hyperphagia might stem from leptin's inability to bind its receptor, thereby raising serum leptin levels [37, 38].

Leptin levels in rats closely correlate with fat depot size [39].

CA reduced leptin levels in groups III and V, aligning with evidence that CA inhibits lipase activity [40], supporting its potential in obesity prevention by hindering key fat metabolism enzymes [41]. This inhibition limits the conversion of dietary triglycerides into absorbable free fatty acids and monoglycerides in the intestine.

Lipid and lipoprotein abnormalities significantly contribute to the development and progression of atherosclerosis and cardiovascular diseases [42]. The study observed a substantial increase in lipid profiles in MSG-treated groups (II and IV) compared to controls, varying due to different MSG doses and administration methods. This aligns with research showing MSG's role in enhancing HMG CoA reductase activity, increasing cholesterol, TG, HDL, and LDL synthesis [43]. Dyslipidemia, a key cardiovascular disease risk factor, primarily arises from metabolic disturbances [44].

CA effectively improved TC, TG, HDL, and LDL levels in groups III and V. Studies have shown that CA, especially at doses like 50mg/kg, reduces cholesterol, TG, and LDL levels [45]. CA reduces dietary TG absorption by inhibiting pancreatic lipase [41], up-regulates LCAT essential for cholesterol esterification [46], and modifies lipoprotein levels [47]. Additionally, CA regulates lipogenic and lipolytic genes [48].

Moderate ROS levels are vital in physiological processes, but excess ROS production causes oxidative stress by disrupting cellular oxidation balance. MDA, an indicator of lipid peroxidation, signifies oxidative damage initiated by ROS, affecting membrane function [49]. This study recorded a significant MDA increase in MSG-treated groups (II and V) compared to controls, matching findings that MSG heightens MDA formation in rat livers and brains [18, 50]. MSG's reactivity induces lipid peroxidation, forming low molecular weight reactive substances like MDA.

CA mitigated oxidative stress (lowered MDA levels) in groups III and V, thanks to its potent antioxidative activity that inhibits cell membrane lipid peroxidation [51]. SOD, produced during oxygen metabolism, prevents various cell damages. The study noted a significant decrease in SOD levels in MSG-treated groups (II and IV), consistent with theories that reduced SOD activity leads to uncontrolled MDA increase due to antioxidant system failure [52].

CA raised SOD levels in groups III and V, supporting previous findings on CA's ability to alleviate oxidative stress in various pathological conditions [53]. CA's ameliorative effect on oxidative stress is attributed to its ROS scavenging activity [54] and its role in upregulating mRNA expression of antioxidant enzymes.

The study observed a significant GSH level decrease in MSG-treated groups (II and IV), aligning with research suggesting MSG-induced lipid peroxidation contributes to GSH depletion [55]. CA's antioxidative properties are mainly due to its lipid oxidation inhibition and free radical scavenging effects. CA derivatives' antioxidant activities stem from the presence of a vinyl fragment, with the strongest properties found in phenyl ring-substituted hydroxyl group compounds [56]. The compound's hydrophobicity determines its antioxidant effectiveness in lipid peroxidation assays, with more hydrophobic compounds generally exhibiting stronger properties [57].

5. Conclusion

The present study demonstrates the potentially detrimental effects of Monosodium Glutamate (MSG) on peripheral organs, particularly the liver, kidney, and pancreas. MSG administration resulted in: diminished antioxidant enzyme levels, signifying reduced cellular defense against reactive oxygen species, decreased insulin secretion, potentially leading to impaired glucose homeostasis, elevated lipid peroxidation, indicative of oxidative stress and potential membrane damage and Increased glucose, lipid profile, and leptin levels, suggestive of metabolic dysregulation. These findings suggest that MSG exposure may induce oxidative stress in the liver, potentially contributing to the development of liver disorders (e.g., dyslipidemia). Notably, this study also presents the first-ever evidence of Cinnamic Acid's (CA) potent ameliorative effects against MSG toxicity.

References

[1] E. G. Helal, Effects of some food additives on some biochemical parameters in young male albino rats and the ameliorative role of royal jelly. The Egyptian Journal of Hospital Medicine 67 (2017) 605–613.

[2] S. P. Chakraborty, Patho-physiological and toxicological aspects of monosodium glutamate. Toxicology mechanisms and methods 29 (2019) 389–396.

[3] H. D. B. Maluly, A. P. Arisseto-Bragotto, F. G. R. Reyes, Monosodium glutamate as a tool to reduce sodium in foodstuffs: Technological and safety aspects, Food Sci Nutr 5 (6) (2017) 1039–1048.

[4] N. Belluardo, G. Mudo, M. Bindoni, Effects of early destruction of the mouse arcuate nucleus by monosodium glutamate on age-dependent natural killer activity, Brain research 534 (1-2) (1990) 225–233.

[5] C. Gobatto, The monosodium glutamate (MSG) obese rat as a model for the study of exercise in obesity. Research communications in molecular pathology and pharmacology 111 (2002) 89–101.

[6] F. Koohpeyma, M. Siri, The effects of L-carnitine on renal function and gene expression of caspase-9 and Bcl-2 in monosodium glutamate-induced rats 22 (2021) 162–162.

[7] S. Mahieu, Monosodium glutamate intake affect the function of the kidney through NMDA receptor. Life sciences 149 (2016) 114–119.

[8] M. Mahmoodi, The protective effect of Zataria multiflora Boiss. hydroalcoholic extract on TNF-α production, oxidative stress, and insulin level in streptozotocin-induced diabetic rats. Avicenna journal of phytomedicine 9 (2019) 72–72.

[9] A. Sharma, Monosodium glutamate-induced oxidative kidney damage and possible mechanisms: a mini-review, J Biomed Sci 22 (2015) 93–93.

[10] N. Bashan, Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species, Physiological reviews (2009).

[11] M. S. Paul, Protective effects of α-tocopherol against oxidative stress related to nephrotoxicity by monosodium glutamate in rats, Toxicology Mechanisms and Methods 22 (8) (2012) 625–630.

[12] S. Chandra, Cinnamic acid activates PPARα to stimulate Lysosomal biogenesis and lower Amyloid plaque pathology in an Alzheimer's disease mouse model, Neurobiology of disease 124 (2019) 379–395.

[13] E. Babaeenezhad, Cinnamic acid ameliorate gentamicin-induced liver dysfunctions and nephrotoxicity in rats through induction of antioxidant activities. Heliyon 7 (2021) 7465–7465.

[14] E. Ugazio, Photodegradation of cinnamic acid in different media, Journal of dispersion science and technology 29 (5) (2008) 641–652.

[15] Y. Akao, Cell growth inhibitory effect of cinnamic acid derivatives from propolis on human tumor cell lines, Biological and Pharmaceutical Bulletin 26 (7) (2003) 1057–1059.

[16] R. M. Hafizur, Cinnamic acid exerts anti-diabetic activity by improving glucose tolerance in vivo and by stimulating insulin secretion in vitro, Phytomedicine 22 (2) (2015) 297–300.

[17] H. A. Khalaf, E. A. Arafat, Effect of different doses of monosodium glutamate on the thyroid follicular cells of adult male albino rats: a histological study, International journal of clinical and experimental pathology 8 (12) (2015) 15498–15498.

[18] E. Farombi, O. Onyema, Monosodium glutamate-induced oxidative damage and genotoxicity in the rat: modulatory role of vitamin C, vitamin E and quercetin, Human & experimental toxicology 25 (5) (2006) 251–259.

[19] Z. Wang, Anti-obesity effect of trans-cinnamic acid on HepG2 cells and HFD-fed mice, Food and Chemical Toxicology 137 (2020) 111148–111148.

[20] D. R. Matthews, Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man, Diabetologia 28 (7) (1985) 412–421.

[21] M. Burstein, H. R. Scholnick, R. Morfin, Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions, J Lipid Res 11 (6) (1970) 583–95.

[22] S. Grinspoon, Serum leptin levels in women with anorexia nervosa, J Clin Endocrinol Metab 81 (11) (1996) 3861–3864.

[23] J. Pizzorno, Glutathione! Integr Med (Encinitas) 13 (2014) 8–12.

[24] S. Gaweł, Malondialdehyde (MDA) as a lipid peroxidation marker, Wiad Lek 57 (9) (2004) 453–458.

[25] J. Fujii, T. Homma, Superoxide Radicals in the Execution of Cell Death 2022.

[26] M. Olguin, Monosodium glutamate affects metabolic syndrome risk factors on obese adult rats: a preliminary study, Journal of Obesity and Weight-Loss Medication 4 (2018) 1–5.

[27] L. Macho, M. Fickova, S. Zorad, Late effects of postnatal administration of monosodium glutamate on insulin action in adult rats, Physiological research 49 (2000) 79–85.

[28] E. O. Ogbuagu, Hyperglycemic and hypocholesterolemic effect of monosodium glutamate in Wistar rats, International Journal of Research and Reports in Hematology 2 (3) (2019) 1–7.

[29] P. Boonnate, Monosodium glutamate dietary consumption decreases pancreatic β-cell mass in adult Wistar rats, PLoS One 10 (6) (2015) 131595–131595.

[30] S. Adisakwattana, Cinnamic Acid and Its Derivatives: Mechanisms for Prevention and Management of Diabetes and Its Complications, Nutrients 9 (2) (2017).

[31] P. K. Prabhakar, M. Doble, Interaction of cinnamic acid derivatives with commercial hypoglycemic drugs on 2-

deoxyglucose uptake in 3T3-L1 adipocytes, J Agric Food Chem 59 (18) (2011) 9835–9879.

[32] P. K. Prabhakar, M. Doble, Interaction of cinnamic acid derivatives with commercial hypoglycemic drugs on 2-deoxyglucose uptake in 3T3-L1 adipocytes, Journal of Agricultural and Food Chemistry 59 (18) (2011) 9835–9844.

[33] M. A. Martín, S. Ramos, Dietary Flavonoids and Insulin Signaling in Diabetes and Obesity. Cells, 2021 10 1474–1474.

[34] T. R. Araujo, Benefits of l-alanine or l-arginine supplementation against adiposity and glucose intolerance in monosodium glutamate-induced obesity, European Journal of Nutrition 56 (6) (2017) 2069–2080.

[35] A. E. Hirata, Monosodium glutamate (MSG)-obese rats develop glucose intolerance and insulin resistance to peripheral glucose uptake, Brazilian Journal of Medical and Biological Research 30 (1997) 671–67.

[36] S. A. Abdulmalek, M. Fessal, M. El-Sayed, Effective amelioration of hepatic inflammation and insulin response in high fat diet-fed rats via regulating AKT/mTOR signaling: Role of Lepidium sativum seed extracts, Journal of ethnopharmacology 266 (2021) 113439–113439.

[37] F. R. Seiva, Quercetin ameliorates glucose and lipid metabolism and improves antioxidant status in postnatally monosodium glutamate-induced metabolic alterations, Food and Chemical Toxicology 50 (10) (2012) 3556–3561.

[38] M. Afifi, A. M. Abbas, Monosodium glutamate versus diet induced obesity in pregnant rats and their offspring, Acta Physiologica Hungarica 98 (2) (2011) 177–188.

[39] S. Wein, Quercetin enhances adiponectin secretion by a PPAR-γ independent mechanism, European Journal of Pharmaceutical Sciences 41 (1) (2010) 16–22.

[40] K. Mnafgui, Anti-obesity and cardioprotective effects of cinnamic acid in high fat diet-induced obese rats, Journal of food science and technology 52 (2015) 4369–4377.

[41] K. Mnafgui, Inhibitory activities of Zygophyllum album: A natural weight-lowering plant on key enzymes in high-fat diet-fed rats. Evidence-based complementary and alternative medicine (2012).

[42] L. W. Scott, Effects of Beef and Chicken Consumption on Plasma Lipid Levels in Hypercholesterolemic Men 154 (1994) 1261–1267.

[43] B. Okediran, Alterations in the lipid profile and liver enzymes of rats treated with monosodium glutamate. Sokoto journal of veterinary sciences 12 (2014) 42–46.

[44] F. Rizvi, M. Iftikhar, J. George, Beneficial effects of fish liver preparations of sea bass (Lates calcarifer) versus gemfibrozil in high fat diet-induced lipid-intolerant rats, Journal of Medicinal Food 6 (2) (2003) 123–128.

[45] H. G. Anlar, Effects of cinnamic acid on complications of diabetes, Turkish Journal of Medical Sciences 48 (1) (2018) 168–177.

[46] R. T. T. Paim, p-Methoxycinnamic acid diesters lower dyslipidemia, liver oxidative stress and toxicity in high-fat diet fed mice and human peripheral blood lymphocytes, Nutrients 12 (1) (2020) 262–262.

[47] P. Rodrigues, Hypolipidemic activity of P-methoxycinnamic diester (PCO-C) isolated from Copernicia prunífera against Triton WR-1339 and hyperlipidemic diet in mice, Environmental Toxicology and Pharmacology 56 (2017) 198–203.

[48] X. Cao, The caffeic acid moiety plays an essential role in attenuating lipid accumulation by chlorogenic acid and its analogues. RSC advances 9 (2019) 12247–12254.

[49] E. Selvakumar, Chemoprotective effect of lipoic acid against cyclophosphamide-induced changes in the rat sperm, Toxicology 217 (1) (2006) 71–78.

[50] V. Pavlovic, Effect of monosodium glutamate on oxidative stress and apoptosis in rat thymus. Molecular and cellular biochemistry 303 (2007) 161–166.

[51] O. A. A. Zaid, F. S. Moawed, Z. A. Ibrahim, Ameliorative effect of Cinnamic acid against L-arginine-induced pancreatitis, Benha Veterinary Medical Journal 37 (1) (2019) 252–255.

[52] S. M. Hazzaa, Monosodium glutamate induces cardiac toxicity via oxidative stress, fibrosis, and P53 proapoptotic protein expression in rats. Environmental Science and Pollution Research 27 (2020) 20014–20024.

[53] A. A. Hemmati, S. Alboghobeish, A. Ahangarpour, Effects of cinnamic acid on memory deficits and brain oxidative stress in streptozotocin-induced diabetic mice, The Korean Journal of Physiology & Pharmacology: Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology 22 (3) (2018) 257–257.

[54] E. Pontiki, D. Hadjipavlou-Litina, Multi-target cinnamic acids for oxidative stress and inflammation: Design, synthesis, biological evaluation and modeling studies, Molecules 24 (1) (2018) 12–12.

[55] O. O. Onyema, Effect of vitamin E on monosodium glutamate induced hepatotoxicity and oxidative stress in rats (2006).

[56] M. Sova, Antioxidant and antimicrobial activities of cinnamic acid derivatives. Mini reviews in medicinal chemistry 12 (2012) 749–767.

[57] S. Son, B. A. Lewis, Free radical scavenging and antioxidative activity of caffeic acid amide and ester analogues: Structure− activity relationship, Journal of agricultural and food chemistry 50 (3) (2002) 468–472.

[58] N. M. White, An observational analysis of the trope "A p-value of< 0.05 was considered statistically significant" and other cut-and-paste statistical methods 17 (2022) 264360–264360.