Molecular Nutrition & Food Research

WILEY-VCH

Molecular Nutrition & Food Research

RESEARCH ARTICLE

Preferential Therapeutic Potential of *Ficus carica* Against Monosodium Glutamate and Metanil Yellow-Evoked Hepato-Renal Injury: In Vivo and In Silico Approaches

Hanaa M. Hassan[1] | Ahmed Abdeen[2] | Magda E. Mahmoud[1] | Nawal H. Almohammadi[3] | Mohamed M. Abdel-Daim[4,5] | Ali H. El-Far[6] | Donia E. F. Zaghamir[7,8] | Mohamed E. Mohamed[9] | Ehab K. Ali[10] | Nashwa H. Aborayah[11,12] | Tabinda Hasan[13] | Nourelhuda A. Mohammed[14] | Dania Abdelhady[15,16] | Heba Allah M. Elbaghdady[17] | Samah F. Ibrahim[18] | Khaled M. A. Hassanein[19]

[1]Department of Agricultural Chemistry, Faculty of Agriculture, Minia University, Minia, Egypt | [2]Department of Forensic Medicine and Toxicology, Faculty of Veterinary Medicine, Benha University, Toukh, Egypt | [3]Department of Basic Medical Science, Faculty of Medicine, Taibah University, Madinah, Saudi Arabia | [4]Department of Pharmaceutical Sciences, Pharmacy Program, Batterjee Medical College, Jeddah, Saudi Arabia | [5]Department of Pharmacology, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt | [6]Department of Biochemistry, Faculty of Veterinary Medicine, Damanhour University, Damanhour, Egypt | [7]College of Nursing, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia | [8]Department of Pediatric Nursing, Faculty of Nursing, Port Said University, Port Said, Egypt | [9]Department of Basic Medical Sciences, College of Medicine, AlMaarefa University, Riyadh, Saudi Arabia | [10]Department of Anatomy and Embryology, Faculty of Medicine, Al-Azhar University, New Damietta, Egypt | [11]Department of Pharmacology, Faculty of Medicine, Benha University, Benha, Egypt | [12]Department of Pharmacology, Faculty of Medicine, Mutah University, Mutah, Jordan | [13]Department of Anatomy, College of Medicine, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia | [14]Department of Physiology, Faculty of Medicine, Zagazig University, Zagazig, Egypt | [15]Department of Physiology, Faculty of Medicine, Benha University, Benha, Egypt | [16]Department of Biomedical Sciences, Dubai Medical College for Girls, Dubai Medical University, Dubai, UAE | [17]Department of Zoology, Faculty of Science, Mansoura University, Mansoura, Egypt | [18]Department of Internal Medicine, College of Medicine, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia | [19]Department of Pathology, Faculty of Veterinary Medicine, Assiut University, Assiut, Egypt

Correspondence: Ahmed Abdeen (ahmed.abdeen@fvtm.bu.edu.eg) | Dania Abdelhady (dania.mohamed@fmed.bu.edu.eg)

Received: 12 November 2024 | **Revised:** 10 January 2025 | **Accepted:** 25 February 2025

Funding: This research was supported via funding from Prince Sattam bin Abudlaziz University project number (PSAU/2024/R/1446), Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2025R127), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Keywords: antioxidant | apoptosis | food additives | hepato-renal injury | oxidative stress

ABSTRACT

Food preservatives can break food safety worldwide; herein, we studied the mitigating effect of *Ficus carica* (FC) on hepato-renal injury resulting from monosodium glutamate (MSG) or metanil yellow (MY) as a common food preservative. Rats were assigned into five groups; Control, MSG (400 mg/kg), MY (200 mg/kg), FC+MSG (received FC plus MSG), and FC+MY group (received FC plus MY). The antioxidant properties of FC were evaluated. The results revealed the antioxidant potency of FC leave extract. MSG/MY evoked a hepato-renal injury indicated by marked elevations in their biochemical functions. Besides, oxidative damage was also initiated represented by significant increases in MDA levels and decreases in GSH content and SOD activity accompanied by apoptotic cascade (increases in Bax/Bcl2 ratio and caspase3 expression). The molecular docking ascertained the interaction between MSG/MY and cellular antioxidants. However, FC was able to reduce the MSG/MY-induced oxidative stress, apoptosis, and histopathological alterations as well as improve the liver and kidney functions. In the molecular docking model, the natural bioactive compounds of FC explored high affinities for binding with Bax and caspase-3 abrogating the induced apoptosis. The antioxidant potential of FC mitigated the hepato-renal damage in rats caused by MSG or MY.

1 | Introduction

Monosodium glutamate (MSG) is the salt of sodium and glutamate. In 1908, seaweed was first utilized in Japan to create MSG, a flavor enhancer [1]. It is used worldwide as a flavor enhancer in contemporary nutrition. Families in Sudan frequently use MSG, and due to its accessibility and affordability especially in light of the nation's dire economic situation, it has recently gained popularity in rural areas [2]. MSG is used as a food ingredient in various meals, whether in hydrolyzed protein or pure monosodium salt. In addition, it is seen as a contentious material. The antioxidant system is implicated in its disruption [3].

Chronic use of MSG leads to renal fibrosis. Renal damage is mostly caused by oxidative stress, which can be caused by either an excess of oxygen radicals and other reactive oxygen species (ROS) or an inadequate removal of free radicals from cells [4, 5]. More focus should be placed on the harmful consequences of color additives because of the unrestricted use of artificial food coloring ingredients which increased significantly in developing countries such as Egypt, particularly in foods intended for children's nutrition [6]. MSG induces hepatotoxicity as well as its oxidant effect so, it must prevented during hepatic diseases [7].

Dyes are used in various ways as food additives and colorants. The yellow azo dye, metanil yellow (MY) is frequently used in the food industry. It is a sodium salt of m-[(p-anilinophenyl)azo]benzenesulphonic acid made from a reaction between diphenylamine and diazotized metanilic acid [8, 9]. Azo dyes act as biological indicators, pH indicators, and research colors in laboratories. Paper, wool, nylon, silk, aluminum, detergent, ink, and other materials can all be colored with MY. The color is prohibited from being used in food because it is dangerous and cannot be consumed. The harmful chemical azo dye is used in different foods due to its inexpensive food coloring agent [9]. MY, an azo dye, is produced by mixing diphenylamine with metanilic acid [7]. MY is not toxic in and of itself, but diphenylamine, one of its metabolites, has a hepatotoxic, nephrotoxic, neurotoxic, carcinogenic, and mutagenic effect. MY is prohibited due to its carcinogenic and genotoxic characteristics [9–11].

Within the Moraceae family, *Ficus carica* (FC) is a rubber tree that grows in tropical and subtropical conditions. FC has been reported to have multiple beneficial pharmacological actions antioxidant, anti-inflammatory, cardioprotective, hepatoprotective, neuroprotective, hypoglycemic, anticancer, antipyretic, and antibacterial activities [12–14]. These activities are attributed to its content of various bioactive components from flavonoids and phenolics including phytosterols, organic acids, phenolic compounds, anthocyanin composition, coumarins, triterpenoids, and volatile molecules, such as hydrocarbons, aliphatic alcohols, and other types of secondary metabolites [12, 15].

This study's goal was to investigate the protective properties of FC leaf extract against hepato-renal injury caused by MSG and MY through the computational modeling platform as well as in vivo investigations including monitoring biochemical markers, oxidative stress, and apoptotic indices.

2 | Experimental Section

2.1 | Molecular Docking Assessment

2.1.1 | Ligand Preparation

The three-dimensional structures of MSG and MY were acquired from the PubChem database [16]. Meanwhile, the bioactive compounds of FC were obtained in SDF format from the LOTUS database [17, 18] and subsequently opened in MOE (Molecular Operating Environment) software [19] for energy minimization and docking with target proteins.

2.1.2 | Preparation of Protein

From the UniProt database [20], the three-dimensional structures of the rat glutathione synthetase, superoxide dismutase-1 (SOD1), superoxide dismutase-2 (SOD2), superoxide dismutase-3 (SOD3), Bax, and caspase-3 were obtained. Target protein energy minimization and MOE 2015.10 [21] tools were used to prepare the target proteins for docking.

2.2 | Chemicals

MSG (Cat. No. G5889; ≥ 99.0% purity) and MY (Cat. No. (Cat. No. G5889; ≥ 70% purity) were obtained from Sigma-Aldrich Co., MO, USA. DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate; Cat. No. D9132; ≥ 99.0% purity), ABTS (2,2-azino-bis 3-ethylbenzothiazoline-6-sulfonic acid; Cat. No. A1888; ≥ 98.0% purity), AAPH (2, 2'-azobis (2-methylpropionamidine) dihydrochloride; Cat. No. 440914; ≥ 97.0% purity) were obtained from Sigma-Aldrich, USA. AST (Cat. No. AS1061), ALT (Cat. No. AL1031), urea (Cat. No. UR2110), creatinine (Cat. No. CR1250), and ALP (Cat. No. AP1021) were procured from Laboratory Biodiagnostics, Cairo, Egypt.

2.3 | Preparation of Plant FC Materials

Fresh FC leaves were collected on July 15, 2022, from Al-Minia University's Agricultural Farm, Al-Minia, Egypt. The leaves were cleaned, dried, and finely pulverized, then stored in a closed metal container. Next, they extracted according to Ao et al. [22], with minor modifications. Briefly, 20 g of dried leaves were added to 100 mL methanol (100%) and kept under shaking at 25°C for 3 days and then filtered by Whatman paper No. 1 (Thomas Scientific, USA). Next, methanol was evaporated using a rotating evaporator (at 45°C/100 mbar), and the extract was stored in an amber glass container at 4°C for the following analysis.

2.4 | Assessment of the Antioxidant Capacity of FC Extract

2.4.1 | Estimating the Total Amount of Flavonoids and Phenols

Total flavonoid content (TFC) was determined by a colorimetric assay, while total phenolic content (TPC) was determined by a Folin–Ciocalteu photometric assay [23].

2.4.2 | DPPH Assay

Using the procedure outlined by Boly et al. [24], the capacity of the FC extract to scavenge DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) was ascertained.

2.4.3 | ABTS Assay

The capacity of FC extract to scavenge the free radical ABTS (2,2-azino-bis 3-ethylbenzothiazoline-6-sulfonic acid) was determined by using the methodology described by Arnao et al. [25].

2.4.4 | Ferric Reducing Ability of Plasma (FRAP) Assay

Benzie and Strain [26] evaluated the FC extract's reduction power using the ferric-reducing antioxidant power (FRAP) assay to evaluate the antioxidant capacity of the FC extract.

2.4.5 | Oxygen Radical Absorbance Capacity (ORAC) Assay

In ORAC assay, 2,2'-azobis (2-methylpropionamidine) dihydrochloride (AAPH) functioned as the ROS generator. A peroxyl free radical was produced when AAPH was heated. This interaction has biological relevance since the body contains many such free radicals. The fact that AAPH reacts with lipid-soluble and water-soluble substances makes it possible to test overall antioxidant capability. The ORAC assay was used according to Liang et al. [27].

2.4.6 | Assessment of the Chelating Activity of Iron (II)

Fe^{2+} chelation capacity of FC extract was investigated using the minor modified protocol as described by Santos et al. [28].

2.5 | Animal Study

Male Sprague-Dawley rats (180–200 g) were kept for 2 weeks for acclimatization in the Biological Lab, Department of Chemistry, Faculty of Agriculture, Minia University, Egypt. Rats were housed in well-ventilated cages with a standard temperature of $22.5 \pm 2°C$, a relative humidity of 60 ± 10%, and 12 h of light/dark cycles for 2 weeks before the experiment. Next, all rats were assigned into five groups (four rats each) as follows: Control group, rats received normal saline; MSG group, rats were orally administered daily 400 mg/kg b.wt. of MSG [29]; MY group, rats were orally received 200 mg/kg b.wt. of MY daily [10]; FC+MSG group, rats were received oral doses of 200 mg/kg b.wt. [30] and 400 mg/kg b.wt. of FC extract and MSG, respectively; and FC+MY group, animals were administered 200 mg/kg b.wt. of FC and MY extract orally every day.

After 30 days, all animals were starved overnight followed by a collection of blood samples from the retro-orbital plexus under the effect of isoflurane anesthesia. Serum was collected after coagulation of blood for 15 min at room temperature, then centrifuged for 15 min at 3000 rpm at 4°C. The serum was preserved at −20°C for further biochemical analyses.

2.5.1 | Biochemical Assessment of Hepato-Renal Function and Oxidative Stress Markers

Serum ALT, AST, ALP, creatinine, and urea were determined. Moreover, specimens of liver and kidney tissues were homogenized. Homogenates were employed to test the amounts of total superoxide dismutase (SOD), glutathione (GSH), and malondialdehyde (MDA). All procedures were carried out according to the manufacturer's instructions (Laboratory Biodiagnostics, Cairo, Egypt).

2.5.2 | Histopathological Examination

The excised tissue samples from the liver and kidneys were washed with saline and fixed in 10% buffered formalin, and then dehydrated with different concentrations of ethyl alcohol and clarified with xylene before being trapped in paraffin. Tissues were sectioned into 4–5 μm thickness and stained with hematoxylin and eosin stains. Next, lesions were scored based on the following criteria: no lesions, + lesions in 3–6 sections, ++ lesions in 7–19 sections, and +++ lesions in 20–30 sections.

2.5.3 | Immunohistochemical Examination

Sections were cut into 4–5 μm lengths and rehydrated on poly-l-lysine-coated slides. Microwave-induced epitope retrieval was conducted for 15 min, followed by protein and endogenous peroxidase blocking. Primary antibodies (caspase-3, Bax, and Bcl2) were treated with tissue slices, as described in Table S1. After washing, a goat anti-rabbit secondary antibody (Cat. No. K4003, EnVision+TM System Horseradish Peroxidase Labelled Polymer; Dako) was applied to the slides and left for 30 min at room temperature. After examining the slides with the 3,3'-diaminobenzidine (DAB) kit, Mayer's hematoxylin was used as a counterstain. The staining index for the caspase-3 and Bax antibodies was determined and displayed as the mean of positive cells in eight high-power fields. In contrast, the Bcl2 antibody was determined using Image J analysis software to assess positive expression per area [31].

2.6 | Statistical Analyses

OriginPro (version 2019b, OriginLab Co., MA, USA) was used for analyses and visualization of the obtained data which were expressed as mean ± S.E.M., and the comparison of treatment means was done by one-way ANOVA and Tukey's test as a post-hoc. ANOVA techniques were used to perform variance analyses. When the p value was less than 0.05 was considered significant. Moreover, R version 4.0.2 of RStudio was employed to generate the principal component analysis (PCA), debiased sparse partial correlation (DSPC) network, correlation heatmap, and variable importance in projection (VIP) scores.

role of FC bioactive ingredients is confirmed by the immunohistochemistry in the current study. Similarly, by lowering the expression levels of Bax, caspase-3, and other apoptotic markers, the extract of FC leaves reduced pancreatic β-cell apoptosis [66]. The proposed mechanisms located behind the protective activity of FC toward the MSG or MY-induced hepato-renal damage are summarized in Figure 11.

Interestingly, the multivariate analyses assert the above-mentioned data; where the PCA and clustering heatmap confirm the occurrence of liver and kidney injury in response to MSG or MY insult which could be distinctively differentiated from the other groups protected by FC supplementation. These data strongly suggest the potential protective activity of FC against the damaging action of MSG or MY in liver and kidney tissues. Moreover, the DSPC network confirms the rationale interrelationship between the studied parameters. Besides, the VIP scores indicated that oxidative damage and apoptotic indices were the top influencing variables in the current study. Collectively, these data robustly corroborated the hepato-renal protective potential of FC for MSG/MY-induced liver and kidney injury. The multivariate analyses document the influencing effect of oxidative stress and apoptosis in the current study which encourages the idea of employing the antioxidant potential FC on future clinical bases. However, more research is required to investigate the pharmacological action of the individual FC fraction rather than whole extracts.

5 | Conclusion

The obtained findings from the current study concluded that MSG or MY could provoke a toxic injury in the liver and kidney tissues; thereby, the hepatic and kidney functions along with oxidative damage and apoptosis were initiated. However, co-administration of FC leaf extract could arrogate the MSG/MY-induced oxidative and apoptotic damaging actions. These protective activities might be attributed to the potential antioxidant capacity of FC. Therefore, FC could be used as a potent food supplement as a plant-derived antioxidant to counterpart the harmful action of such kind of food additives.

Acknowledgments

The appreciation is extended to the Researchers Supporting Project number (MHIRSP2024006), AlMaarefa University, Riyadh, Saudi Arabia. Moreover, this work supported via funding from Prince Sattam bin Abudlaziz University project number (PSAU/2024/R/1446). The authors' profound appreciation also goes to Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2025R127), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Ethics Statement

According to OIE regulations for using animals in research, the animal ethics committee of Assiut University's, Veterinary Medicine Collage, Assiut, Egypt, has authorized the experiment's methods. The committee's approval No: 06/2022/0020.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Upon request, the corresponding authors can supply the data that was utilized to confirm the study's findings.

References

1. Z. Kazmi, I. Fatima, S. Perveen, and S. S. Malik, "Monosodium Glutamate: Review on Clinical Reports," *International Journal of Food Properties* 20 (2017): 1807–1815.

2. S. I. Y. A. N. A. S. I. A. A. A. S. Shareef, *Al Neelain Journal of Science and Technology* 3 (2019): 07–14.

3. O.-L. Moldovan, C.-E. Vari, A. Tero-Vescan, et al., "Potential Defence Mechanisms Triggered by Monosodium Glutamate Sub-Chronic Consumption in Two-Year-Old Wistar Rats," *Nutrients* 15 (2023): 4436.

4. A. Sharma, V. Prasongwattana, U. Cha'on, et al., "Monosodium Glutamate (MSG) Consumption Is Associated With Urolithiasis and Urinary Tract Obstruction in Rats," *PLoS ONE* 8 (2013): e75546.

5. N. Bashan, J. Kovsan, I. Kachko, H. Ovadia, and A. Rudich, "Positive and Negative Regulation of Insulin Signaling by Reactive Oxygen and Nitrogen Species," *Physiological Reviews* 89, no. 1 (2009): 27–71.

6. M. M. Hashem, A. H. Atta, M. S. Arbid, S. A. Nada, and G. F. Asaad, "Immunological Studies on Amaranth, Sunset Yellow and Curcumin as Food Colouring Agents in Albino Rats," *Food and Chemical Toxicology* 48 (2010): 1581–1586.

7. D. Ghosh, P. S. Singha, S. B. Firdaus, and S. Ghosh, "Metanil Yellow: The Toxic Food Colorant," *Asian Pacific Journal of Health Sciences* 4 (2017): 65–66.

8. U. K. Sharma, R. Kumar, A. Gupta, et al., "Ameliorating Efficacy of Eugenol Against Metanil Yellow Induced Toxicity in Albino Wistar Rats," *Food and Chemical Toxicology* 126 (2019): 34–40.

9. P. P. Nath, K. Sarkar, M. Mondal, and G. Paul, "Metanil Yellow Impairs the Estrous Cycle Physiology and Ovarian Folliculogenesis in Female Rats," *Environmental Toxicology* 31 (2016): 2057–2067.

10. W. M. Elwan, "Effect of Long-Term Administration of Metanil Yellow on the Structure of Cerebellar Cortex of Adult Male Albino Rat and the Possible Protective Role of Anise Oil: A Histological and Immunohistochemical Study," *Egyptian Journal of Histology* 41 (2018): 27–38.

11. I. S. Khan, M. N. Ali, R. Hamid, and S. A. Ganie, "Genotoxic Effect of Two Commonly Used Food Dyes Metanil Yellow and Carmoisine Using Allium cepa L. as Indicator," *Toxicology Reports* 7 (2020): 370–375.

12. O. S. Arvaniti, Y. Samaras, G. Gatidou, N. S. Thomaidis, and A. S. Stasinakis, "Review on Fresh and Dried Figs: Chemical Analysis and Occurrence of Phytochemical Compounds, Antioxidant Capacity and Health Effects," *Food Research International* 119 (2019): 244–267.

13. M. I. Barolo, N. R. Mostacero, and S. N. López, "Ficus carica L. (Moraceae): An Ancient Source of Food and Health," *Food Chemistry* 164 (2014): 119–127.

14. A. M. Abdel-Aty, M. B. Hamed, W. H. Salama, M. M. Ali, A. S. Fahmy, and S. A. Mohamed, "Ficus carica, Ficus sycomorus and Euphorbia tirucalli Latex Extracts: Phytochemical Screening, Antioxidant and Cytotoxic Properties," *Biocatalysis and Agricultural Biotechnology* 20 (2019): 101199.

15. B. Salehi, A. Prakash Mishra, M. Nigam, et al., "Ficus Plants: State of the Art From a Phytochemical, Pharmacological, and Toxicological Perspective," *Phytotherapy Research* 35 (2021): 1187–1217.

16. National Library of Medicine, PubChem, Explore Chemistry (2024).

17. Lotus, Natural Products Online (2024).

18. A. Rutz, M. Sorokina, J. Galgonek, et al., "The LOTUS Initiative for Open Knowledge Management in Natural Products Research," *Elife* 11 (2022): e70780.

19. S. Vilar, G. Cozza, and S. Moro, "Medicinal Chemistry and the Molecular Operating Environment (MOE): Application of QSAR and Molecular Docking to Drug Discovery," *Current Topics in Medicinal Chemistry* 8 (2008): 1555–1572.

20. Uniprot, Find Your Protein (2024).

21. B. Salim and M. Noureddine, "Identification of Compounds from Nigella sativa as New Potential Inhibitors of 2019 Novel Corona Virus (Covid-19): Molecular Docking Study," *Chemrxiv* 19 (2020): 1–12.

22. C. Ao, A. Li, A. A. Elzaawely, T. D. Xuan, and S. Tawata, "Evaluation of Antioxidant and Antibacterial Activities of Ficus microcarpa L. fil. Extract," *Food Control* 19 (2008): 940–948.

23. K. M. Yoo, C. H. Lee, H. Lee, B. Moon, and C. Y. Lee, "Relative Antioxidant and Cytoprotective Activities of Common Herbs," *Food Chemistry* 106 (2008): 929–936.

24. R. Boly, T. Lamkami, M. Lompo, J. Dubois, and I. Guissou, "DPPH Free Radical Scavenging Activity of Two Extracts from Agelanthus dodoneifolius (Loranthaceae) Leaves," *International Journal of Toxicological and Pharmacological Research* 8 (2016): 29–34.

25. M. B. Arnao, A. Cano, and M. Acosta, "The Hydrophilic and Lipophilic Contribution to Total Antioxidant Activity," *Food Chemistry* 73 (2001): 239–244.

26. I. F. F. Benzie and J. J. Strain, "The Ferric Reducing Ability of Plasma (FRAP) as a Measure of 'Antioxidant Power': The FRAP Assay," *Analytical Biochemistry* 239 (1996): 70–76.

27. Z. Liang, L. Cheng, G.-Y. Zhong, and R. H. Liu, "Antioxidant and Antiproliferative Activities of Twenty-Four Vitis vinifera Grapes," *PLoS ONE* 9 (2014): e105146.

28. J. S. Santos, V. R. A. Brizola, and D. Granato, "High-Throughput Assay Comparison and Standardization for Metal Chelating Capacity Screening: A Proposal and Application," *Food Chemistry* 214 (2017): 515–522.

29. H. E. S. Mostafa, I. M. M. Ammar, D. A. El-Shafei, A. N. A. Allithy, N. A. Abdellatif, and E. A. A. El-Din, "Pathological and Immunopathological Studies on Broiler Chicks Infected With Chicken Anemia Virus," *Advances in Animal and Veterinary Sciences* 9 (2021): 700–708.

30. A. El Ghouizi, D. Ousaaid, H. Laaroussi, et al., "Ficus Carica (Linn.) Leaf and Bud Extracts and Their Combination Attenuates Type-1 Diabetes and Its Complications via the Inhibition of Oxidative Stress," *Foods* 12 (2023): 759, https://doi.org/10.3390/foods12040759.

31. S. Saber, R. M. Khalil, W. S. Abdo, D. Nassif, and E. El-Ahwany, "Olmesartan Ameliorates Chemically-Induced Ulcerative Colitis in Rats via Modulating NFκB and Nrf-2/HO-1 Signaling Crosstalk," *Toxicology and Applied Pharmacology* 364 (2019): 120–132.

32. M. E. İnal, G. Kanbak, and E. Sunal, "Antioxidant Enzyme Activities and Malondialdehyde Levels Related to Aging," *Clinica Chimica Acta* 305 (2001): 75–80.

33. D. Zeyuan, T. Bingyin, L. Xiaolin, H. Jinming, and C. Yifeng, "Effect of Green Tea and Black Tea on the Blood Glucose, the Blood Triglycerides, and Antioxidation in Aged Rats," *Journal of Agricultural and Food Chemistry* 46 (1998): 3875–3878.

34. K. Singh and P. Ahluwalia, "Effect of Monosodium Glutamate on Lipid Peroxidation and Certain Antioxidant Enzymes in Cardiac Tissue of Alcoholic Adult Male Mice," *Journal of Cardiovascular Disease Research* 3 (2012): 12–18.

35. E. Padmini and B. T. Sundari, "Erythrocyte Glutathione Depletion Impairs Resistance to Haemolysis in Women Consuming Alcohol," *Journal of Clinical Biochemistry and Nutrition* 42 (2008): 14–20.

36. P. Chaudhary, V. B. T. Malik, S. Puri, and P. Ahluwalia, "Studies on the Effects of Monosodium Glutamate on Hepatic Microsomal Lipid Peroxidation, Calcium, Ascorbic Acid and Glutathione and Its Dependent Enzymes in Adult Male Mice," *Toxicology Letters* 9 (1996): 71–76.

37. S. E. Tawfeek, A. M. Shalaby, M. A. Alabiad, A.-A. A. A. Albackoosh, K. M. M. Albakoush, and M. M. A. Omira, "Metanil Yellow Promotes Oxidative Stress, Astrogliosis, and Apoptosis in the Cerebellar Cortex of Adult Male Rat With Possible Protective Effect of Scutellarin: A Histological and Immunohistochemical Study," *Tissue & Cell* 73 (2021): 101624.

38. J. Li and J. Yuan, "Caspases in Apoptosis and Beyond," *Oncogene* 27 (2008): 6194–6206.

39. E. E. Ragab, "The Possible Protective Effect of Vitamin C on Monosodium Glutamate Induced Renal Toxicity in Male Albino Rats," *Egyptian Journal of Histology* 41 (2018): 386–397.

40. Y. Fukuzawa, Y. Watanabe, D. Inaguma, and N. Hotta, "Evaluation of Glomerular Lesion and Abnormal Urinary Findings in OLETF Rats Resulting From a Long-Term Diabetic State," *Journal of Laboratory and Clinical Medicine* 128 (1996): 568–578.

41. N. H. Al-Mousawi, "Study on Effect of Glutamate Monosodium Exposure on Some Blood and Biochemical Parameters in Adult Albino Rats," *Journal of Entomology and Zoology Studies* 5 (2017): 1029–1031.

42. M. Shukry, A. M. El-Shehawi, W. M. El-Kholy, et al., "Ameliorative Effect of Graviola (Annona muricata) on Mono Sodium Glutamate-Induced Hepatic Injury in Rats: Antioxidant, Apoptotic, Anti-inflammatory, Lipogenesis Markers, and Histopathological Studies," *Animals* 10 (2020): 1996.

43. H. I. Mahmoud, M. E. Mahamed, H. A. Ismail, and H. M. Hassan, "The Effect of Some Natural and Synthetic Colorants on Blood Parameters of Male Albino," *Journal of Environment and Bio-Sciences* 5 (2010): 537–554.

44. B. Saxena and S. Sharma, "Food Color Induced Hepatotoxicity in Swiss Albino Rats, Rattus norvegicus," *Toxicology International* 22 (2015): 152.

45. H. M. Shosha, H. M. Ebaid, E. A. Toraih, H. M. A. Abdelrazek, and R. A. Elrayess, "Effect of Monosodium Glutamate on Fetal Development and Progesterone Level in Pregnant Wistar Albino Rats," *Environmental Science and Pollution Research* 30 (2023): 49779–49797.

46. A. Z. Dorreia, A. D. Mohamed, A. Hanaa, and M. O. Salwa, "Effects of Monosodium Glutamate on the Liver of Male Adult Albino Rat and the Possible Protective Role of Vitamin C (Light and Electron Microscopic Study)," *The Medical Journal of Cairo University* 86 (2018): 3407–3418.

47. S. I. Othman and M. Bin-Jumah, "Histomorphological Changes in Mono-Sodium Glutamate Induced Hepato-Renal Toxicity in Mice," *International Journal of Pharmacology* 15 (2019): 449–456.

48. F. Conforti, G. Menichini, L. Zanfini, et al., "Evaluation of Phototoxic Potential of Aerial Components of the Fig Tree Against Human Melanoma," *Cell Proliferation* 45 (2012): 279–285.

49. B. M. Silva, P. B. Andrade, P. Valentão, F. Ferreres, R. M. Seabra, and M. A. Ferreira, "Quince (Cydonia oblonga Miller) Fruit (Pulp, Peel, and Seed) and Jam: Antioxidant Activity," *Journal of Agricultural and Food Chemistry* 52 (2004): 4705–4712.

50. B. Halliwell, M. V. Clement, and L. H. Long, "Hydrogen Peroxide in the Human Body," *FEBS Letters* 486 (2000): 10–13.

51. M. Marrelli, G. A. Statti, R. Tundis, F. Menichini, and F. Conforti, "Fatty Acids, Coumarins and Polyphenolic Compounds of Ficus carica L. cv. Dottato: Variation of Bioactive Compounds and Biological Activity of Aerial Parts," *Natural Product Research* 28 (2014): 271–274.

52. T. Takahashi, A. Okiura, K. Saito, and M. Kohno, "Identification of Phenylpropanoids in Fig (Ficus carica L.) Leaves," *Journal of Agricultural and Food Chemistry* 62 (2014): 10076–10083.

53. I. E. Orhan, O. Üstün, and B. Şener, "Estimation of Cholinesterase Inhibitory and Antioxidant Effects of the Leaf Extracts of Anatolian Ficus carica var. Domestica and Their Total Phenol and Flavonoid Contents," *Natural Products Communications* 6 (2011): 1934578X1100600315.

54. I. N. Rôças and J. F. Siqueira Jr, "Characterization of Microbiota of Root Canal-Treated Teeth With Posttreatment Disease," *Journal of Clinical Microbiology* 50 (2012): 1721–1724.

55. A. P. Oliveira, P. Valentão, J. A. Pereira, B. M. Silva, F. Tavares, and P. B. Andrade, "Ficus carica L.: Metabolic and Biological Screening," *Food and Chemical Toxicology* 47 (2009): 2841–2846.

56. Z. Li, Y. Yang, M. Liu, et al., "A Comprehensive Review on Phytochemistry, Bioactivities, Toxicity Studies, and Clinical Studies on Ficus carica Linn. Leaves," *Biomedicine & Pharmacotherapy* 137 (2021): 111393.

57. A. Javed, K. Iffat, K. Salman, and I. Danish, "Evaluation of Antioxidant and Antimicrobial Activity of Ficus Carica Leaves: An In Vitro Approach," *Journal of Plant Pathology & Microbiology* 4 (2013): 1000157.

58. M. Jayachandran, Z. Wu, K. Ganesan, S. Khalid, S. M. Chung, and B. Xu, "Isoquercetin Upregulates Antioxidant Genes, Suppresses Inflammatory Cytokines and Regulates AMPK Pathway in Streptozotocin-Induced Diabetic Rats," *Chemico-Biological Interactions* 303 (2019): 62–69.

59. Z. Sang, K. Wang, J. Shi, et al., "Apigenin-Rivastigmine Hybrids as Multi-Target-Directed Liagnds for the Treatment of Alzheimer's Disease," *European Journal of Medicinal Chemistry* 187 (2020): 111958.

60. M. Imran, A. Rauf, T. Abu-Izneid, et al., "Luteolin, a Flavonoid, as an Anticancer Agent: A Review," *Biomedicine & Pharmacotherapy* 112 (2019): 108612.

61. R. M. Hussein, W. R. Mohamed, and H. A. Omar, "A Neuroprotective Role of Kaempferol Against Chlorpyrifos-Induced Oxidative Stress and Memory Deficits in Rats via GSK3β-Nrf2 Signaling Pathway," *Pesticide Biochemistry and Physiology* 152 (2018): 29–37.

62. O. Belguith-Hadriche, S. Ammar, M. del Mar Contreras, et al., "HPLC-DAD-QTOF-MS Profiling of Phenolics From leaf Extracts of Two Tunisian Fig Cultivars: Potential as a Functional Food," *Biomedicine & Pharmacotherapy* 89 (2017): 185–193.

63. S. Ammar, M. del Mar Contreras, O. Belguith-Hadrich, A. Segura-Carretero, and M. Bouaziz, "Assessment of the Distribution of PhenolicCompounds and Contribution to the Antioxidant Activity in Tunisian Fig Leaves, Fruits, Skins and Pulps Using Mass Spectrometry-Based Analysis," *Food Function* 6 (2015): 3663–3677.

64. G. K. Mohan, E. Pallavi, R. Kumar, M. Ramesh, and S. Venkatesh, "Hepatoprotective Activity of Ficus caricaLinn Leaf Extract Against Carbon Tetrachloride-Induced Hepatotoxicity in Rats," *DARU Journal of Pharmaceutical Sciences* 15 (2007): 162–166.

65. N. Aghel, H. Kalantari, and S. Rezazadeh, "Hepatoprotective Effect of Ficus Carica Leaf Extract on Mice Intoxicated With Carbon Tetrachloride," *Iranian Journal of Pharmaceutical Research* 10 (2011): 63–68.

66. Y. Zhang, Y. Li, P. Ma, J. Chen, and W. Xie, "Ficus carica Leaves Extract Inhibited Pancreatic β-Cell Apoptosis by Inhibiting AMPK/JNK/caspase-3 Signaling Pathway and Antioxidation," *Biomedicine & Pharmacotherapy* 122 (2020): 109689.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.