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ORIGINAL

The preventive effect of taxifolin on acrylamide-induced heart damage in rats

O efeito preventivo da taxifolina em danos cardíacos induzidos por acrilamida em ratos

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ABSTRACT

Objective

Acrylamide is a toxic compound widely used in industrial sectors. Acrylamide causes reactive oxygen species formation and the subsequent lipid peroxidation reaction, which plays an important role in the pathogenesis of oxidative damage. Taxifolin is a flavonoid with antioxidant properties that inhibit reactive oxygen species formation. In this study, we aimed to investigate the preventive effect of taxifolin on acrylamide-induced oxidative heart damage.

Methods

The rats were divided into three groups: Acrylamide, Acrylamide+Taxifolin , and Healthy group. Water and food intake and body weight alterations were recorded daily. Malondialdehyde, total glutathione, nuclear factor kappa-B, total oxidant status, and total antioxidant status levels were analyzed from the heart tissue. Troponin-I levels, the parameter known as a cardiac biomarker, were analyzed from the blood sample. The cardiac histopathologic examination was also performed.

Results

In the Acrylamide group animals, the malondialdehyde, nuclear factor kappa-B, total oxidant status, and troponin-I levels were significantly higher compared to the ones of Acrylamide+Taxifolin and Healthy groups. The levels of total glutathione and total antioxidant status were significantly lower compared to Acrylamide+Taxifolin and Healthy groups'.

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Additionally, in the Acrylamide group, body weight gain, food and water intake, significantly declined compared to the Acrylamide+Taxifolin and Healthy groups. However, in the Acrylamide+Taxifolin group, taxifolin supplementation brought these values close to Healthy group ones. Furthermore, taxifolin treatment ameliorated structural myocardial damage signs induced by acrylamide.

Conclusion

Acrylamide exposure significantly induced oxidative damage to rat heart tissue. Taxifolin was able to improve the toxic consequences of acrylamide biochemically and histopathologically, possibly due to its antioxidant properties.

Keywords: Acrylamide. Oxidative heart damage. Rat. Taxofilin.

RESUMO

Objetivo

A acrilamida é um composto tóxico amplamente utilizado em setores industriais. Ela causa a formação de reativas de oxigênio e subsequente reação de peroxidação lipídica, que desempenham um papel importante na patogênese do dano oxidativo. A taxifolina é um flavonóide com propriedades antioxidantes que inibe a formação de reativas de oxigênio. Neste estudo, o objetivo foi investigar o efeito preventivo da taxifolina no dano cardíaco oxidativo induzido por acrilamida.

Métodos

Os ratos foram divididos em três grupos: Acrilamida, Acrilamida+Taxifolina e grupo Saudável. Ingestão de água e comida e alterações de peso corporal dos animais foram registradas diariamente. Malondialdeído, glutationa total, fator nuclear kappa-B, estado oxidante total e estado antioxidante total foram analisados no tecido cardíaco dos ratos. Os níveis de troponina-I, – parâmetro conhecido como biomarcador cardíaco, foram analisados a partir de amostra de sangue. Um exame histopatológico cardíaco também foi realizado.

Resultados

Nos animais do grupo Acrilamida, os níveis de malondialdeído, fator nuclear kappa-B, estado oxidante total e troponina-I foram significativamente maiores em comparação com os do grupo Acrilamida+Taxifolina e Saudável. Os níveis de glutationa total e estado antioxidante total foram significativamente mais baixos em comparação com grupos Acrilamida+Taxifolina e Saudável. Além disso, no grupo Acrilamida, o ganho de peso corporal e a ingestão de alimentos e água diminuíram significativamente em comparação com os animais dos grupos Acrilamida+Taxifolina e Saudável. No entanto, no grupo Acrilamida+Taxifolina, a suplementação com taxifolina aproximou esses valores aos do grupo Saudável. Além disso, o tratamento com taxifolina melhorou os sinais de dano miocárdico estrutural induzidos pela acrilamida.

Conclusão

A exposição à acrilamida induziu significativamente o dano oxidativo do tecido cardíaco dos ratos. A taxifolina foi capaz de melhorar as consequências tóxicas da acrilamida bioquímica e histopatologicamente, possivelmente devido às suas propriedades antioxidantes.

Palavras-chave: *Acrilamida. Dano oxidativo ao coração. Rato. Taxofilina.*

INTRODUCTION

The dietary factor is a significant weight behind the rise of foodborne illnesses. Acrylamide is a toxic compound widely used in industrial sectors, generally formed by overheating high-carbohydrate and low-protein foods [1]. Acrylamide (ACR, CH2 = CHCONH2) is colorless, odorless, and highly water-soluble crystals are formed by the hydration of acrylonitrile with sulfuric acid monohydrate. The exposure of food to high temperatures, as in frying and oven-cooking (Maillard reaction), accelerates the formation of acrylamide that can rapidly be absorbed by the gastrointestinal system [2,3]. Acrylamide is also formed during the burning of tobacco at high temperatures and is taken into the body by inhaled smoke [4].

Previous papers stated that acrylamide exposure is associated with unfavorable outcomes such as neurotoxicity, cardiotoxicity, and cancer formation [5-7]. However, the exact mechanism of these associations is not entirely clear; experiments point out that acrylamide causes the overproduction of Reactive Oxygen Species (ROS), leading to Lipid Peroxidation (LPO) and oxidative stress, which play an important role in the pathogenesis of toxicity [8]. Huang *et al*. showed that acrylamide exposure resulted in oxidative heart damage in zebrafish embryos [9]. Acrylamide exposure reduces antioxidant levels such as glutathione (GSH) and increases oxidative stress parameters such as malondialdehyde (MDA) in the heart tissue, as well as causing inflammatory cell infiltration and necrosis in myocardial fibrils [10]. The low antioxidant content in myocardial cells may facilitate the development of tissue damage [11]. In experimental methods, acrylamide chronic exposure caused heart failure and conduction of abnormalities due to mitochondrial dysfunction and oxidative damage [10].

Since acrylamide formation is often triggered by cooking methods and duration, its unfavorable impact may be reversed by natural antioxidants taken with food. Taxifolin is an antioxidant flavonoid that is abundantly found in onions, french maritime pine barks, milk thistles, and tamarind seeds [12]. Research reveals that taxifolin has antioxidant, anti-inflammatory, antiviral, antibacterial, anticancer, and neuroprotective effects [13-16]. In experimental studies, taxifolin was able to decrease oxidative tissue damage by inhibiting the overproduction of ROS [17,18]. In light of these data, we aimed to investigate the preventive biochemical or histopathological effects of taxifolin on the possible acrylamide-induced heart damage in rats.

METHODS

Animals

Eighteen male albino Wistar rats weighing between 280 and 293 grams were used in the experiment. All rats were obtained from the Atatürk University Medical Experimental Application and Research Center. The animals were housed at average room temperature (22 °C). Animals were fed *ad libitum* during the experiment and were maintained on a 12:12h light/dark cycle. All phases of our study have been approved by the Atatürk University Animal Experiments Local Ethics Committee in April 30, 2020, Meeting no 4/58).

Chemicals

Thiopental sodium was obtained from IE Ulagay (Turkey), taxifolin from Evalar (Russia), and acrylamide from the Sigma-Aldrich Chemical Company (USA) for the experiment.

Experimental groups

The animals were divided into three groups of six rats each: Acrylamide (ACL; 20 mg/kg acrylamide), Acrylamide+Taxifolin (TACL; 20 mg/kg acrylamide and 50 mg/kg taxifolin), and Healthy Group (HG).

Experimental procedures

Taxifolin was administered to the Acrylamide+Taxifolin (TACL) (n-6) group animals with a catheter directly to the stomach at a 50 mg/kg dose per day for 60 days. During this time, HG (n-6) and ACL (n-6)

group animals received an equal volume of distilled water as a solvent in the same way. One hour after delivering taxifolin and distilled water, acrylamide was administered to the TACL and ACL groups at the dose of 20 mg/kg with a catheter, directly to the stomach. This procedure was repeated once a day for two months [13]. Bodyweight alterations, food and water intake were recorded daily. None of the animals died during the experimental period. At the end of the two months, all animals were sacrificed with 50 mg/kg thiopental sodium, and their hearts were removed. The Troponin I (TP-I) level was determined from blood samples taken from tail veins before the anesthesia. The removed heart tissues were examined biochemically and histopathologically. All group results obtained from the experiment were compared.

Biochemical analysis of heart tissue

Supernatant portions of homogenates prepared from heart tissues were used for the biochemical analysis. Prior to the dissection, all tissues were rinsed with a phosphate-buffered saline solution. The tissues were homogenized in ice-cold phosphate buffers (50 mM, pH 7.4) that were appropriate for the variable to be measured. The tissue homogenates were centrifuged at 10,000 rpm for 20min at 4 °C, and the supernatants were extracted to analyze MDA, GSH, Nuclear Factor Kappa-B (NF-ĸB), Total Oxidant Status (TOS), and Total Antioxidant Status (TAS). All tissue results were expressed by dividing by g protein. All spectrophotometric measurements were performed via a microplate reader (Bio-Tec, USA).

Malondialdehyde (MDA) *levels* – MDA analyses were performed as defined by Ohkawa *et al.* [19].

Total Glutathione (tGSH) *levels* – The mechanism was defined by Sedlak J and Lindsay RH [20].

Nuclear factor kappa-B (NF-ĸB) *levels* – Tissue-homogenate NF-ĸB concentration was measured using a rat-specific sandwich enzyme-linked immunosorbent assay. Rat NF-ĸB ELISA immunoassay kits (Cat. nº 201-11-0288, SunRed).

Measurements of Total Oxidant Status (TOS) *and total antioxidant status* (TAS) *levels* – The TOS and TAS levels of tissue homogenates were determined using a novel automated measurement method and commercially available kits (Rel Assay Diagnostics, Turkey), both developed by Erel [21,22].

Biochemical analysis of blood samples

Troponin-I (TP-I) *levels* – TP-I levels were measured in the VIDAS Troponin I Ultra kit by utilizing the Enzyme-Linked Fluorescent Assay (ELFA) technique.

Histopathological examination

The cardiac tissues removed from the rats were fixed in a 10% formalin solution for 24 hours. Samples were then treated with a conventional grade of alcohol (70%, 80%, 90%, and 100%) to remove the water within the tissues. Tissues were then passed through xylol and embedded in paraffin. After routine tissue treatment, 4-5 micron thick sections were obtained from the paraffin blocks and stained with Hematoxylin & Eosin. All sections were evaluated under a light microscope (Olympus BX 52, Tokyo, Japan) by two pathologists who were blind to treatment protocols.

Statistical analysis

The normal distribution of the data was tested using the one-sample Kolmogorov–Smirnov test. Continuous variables were presented as mean±SD. An analysis of variance was utilized to compare multiple

group means. The following post hoc evaluation was made by the least significant differences method. $p<0.05$ values were considered to be statistically significant. Statistical analyses were performed using the SPSS 20.0 software for Windows (SPSS Inc, Chicago, IL).

RESULTS

Bodyweight, food and water intake alteration results

Acrylamide administration caused a significant decline in weight gain in the ACL group rats. A considerable decline in body weight gain was recorded from the end of the fifth week and a further decline persisted until the end of the second month, compared to the TACL and HG ($p<0.01$). However, in the TACL, in terms of body weight gain, there was no significant difference at the end of the first and second months compared to the HG ($p>0.05$) (Figure 1A). A significant reduction in food and water intake was recorded in the ACL group at the beginning of the 4th week and a further reduction persisted until the end of the second month ($p<0.01$), compared to the TACL and HG. However, in the TACL group, food and water intake were found to be similar to HG both at the end of the first and second months ($p>0.05$). In the TACL group, animals pretreatment with taxifolin caused a constant increase in food and water consumption by the end of the first month and further at the end of the second month, compared to the acrylamide-alone exposed group ($p<0.01$) (Figures1A, and 1B).

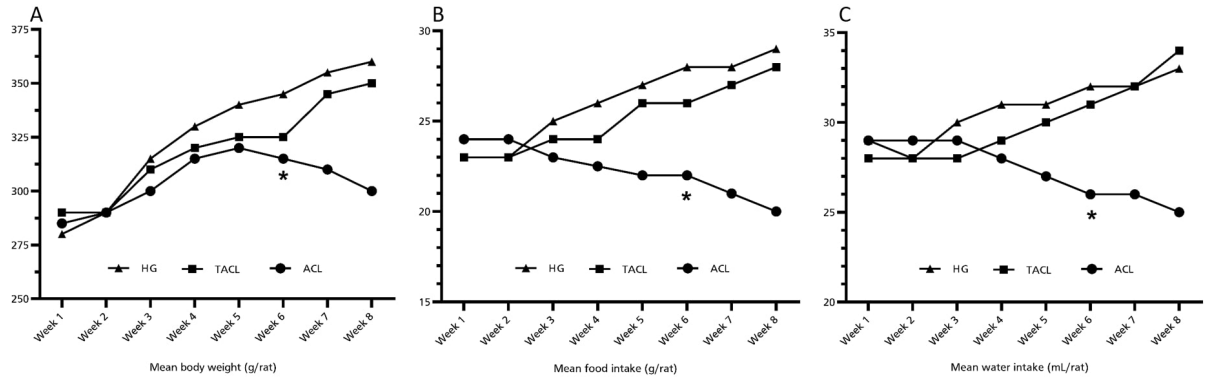

Figure 1 – Bodyweight, food and water intake alteration results of the experimental groups. Erzurum, Turkey, 2021.
Note: A: Bodyweight gain over two months in Acrylamide (ACL), Acrylamide+Taxifolin (TACL), and Healthy Group (HG) animals. In the ACL group animals, a significant decrease in body weight gain was recorded both by the end of the first month and at the end of the second month. B: Food intake over two months in ACL, TACL, and HG animals. In the ACL group animals, a significant decrease in food intake was recorded both by the end of the first month and at the end of the second month. C: Water intake over two months in ACL, TACL, and HG animals. In the ACL group animals, a significant water intake decrease was recorded both by the end of the first month and at the end of the second month.

Biochemical results

Malondialdehyde (MDA), tGSH, NF-ĸB, TOS, and TAS levels were analyzed from the heart tissue. Results showed that the MDA, NF-ĸB, and TOS levels in the ACL group animals significantly increased compared to HG and TACL groups ($p<0.001$). The difference in the MDA, NF-ĸB, and TOS levels between

HG and TACL groups was statistically insignificant ($p>0.05$). The tGSH and TAS levels of the ACL group animals were significantly lower compared to the HG and TACL groups ($p<0.001$). However, the tGSH and TAS levels were found to be similar in HG and TACL groups ($p>0.05$) (Figure 2).

Blood sample biomarker results

The TP-I levels were significantly higher in the ACL group animals compared to the other two groups ($p<0.001$). TP-I levels were found to be similar in HG and TACL groups. This difference was statistically insignificant ($p>0.05$) (Figure 2).

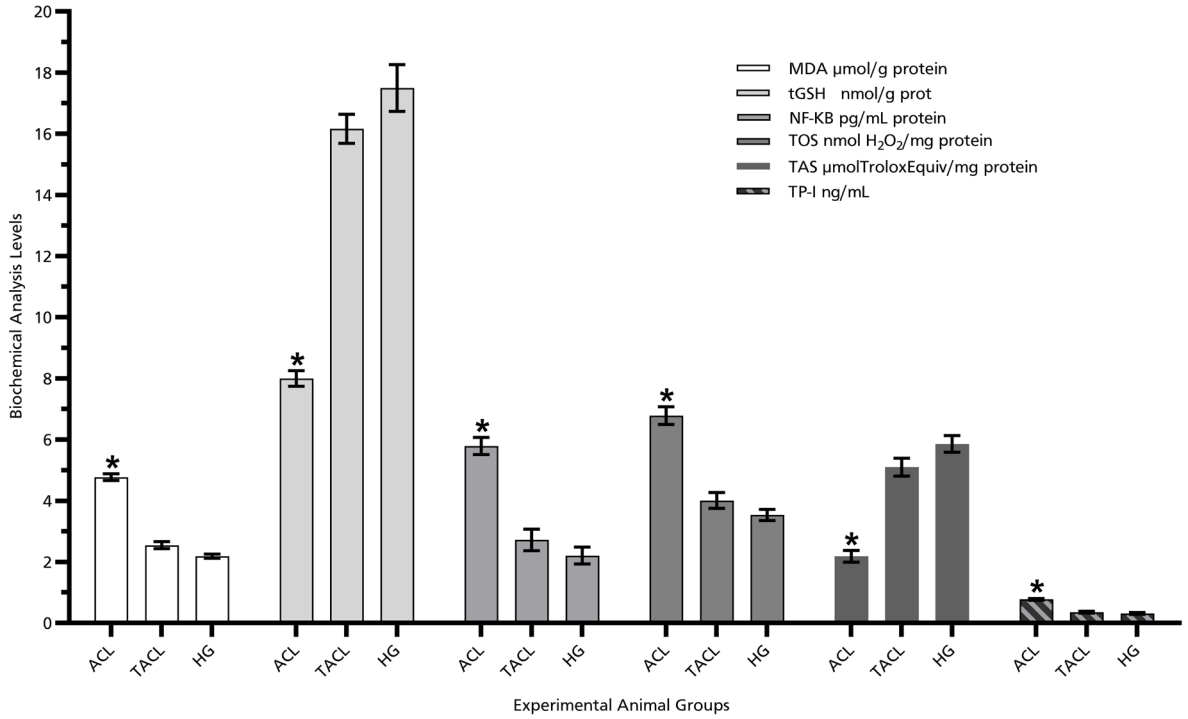

Figure 2 – Oxidative status in heart tissue and troponin-I levels in blood serum of the experimental groups. Erzurum, Turkey, 2021.
Note: *$p<0.001$ according to ACL group. MDA: Malondialdehyde; tGSH: Total Glutathione; NF-KB: Nuclear Factor Kappa-B; TOS: Total Oxidant Status; and TAS: Total Antioxidant Status levels in the heart tissue and Troponin-I (TP-I) in the blood serum of study groups (n=6). Acrylamide (ACL) group compared to Healthy Group (HG) and Acrylamide+Taxifolin (TACL) groups.

Histopathological results

Under microscopic examination, normal endocardial, myocardial, and epicardial histological structure layers were observed in the heart tissue of HG. Acrylamide-alone administration caused myocardial and endocardial degeneration, inflammatory cell infiltration, dilated and congested coronary vessels in the ACL group (Figure 3A). Additionally, in the ACL group, loss of myofibrillar striation, substantial hemorrhage, and edema in the necrotic areas was observed (Figure 3B). Contrary to the ACL group, in the heart tissue of the TACL group animals, a decrease in the inflammatory cell infiltrate, minimal vascular congestion, and noticeably reduced hemorrhage were observed (Figure 3C). Taxifolin supplementation maintained the integrity of all heart layers and vessels.

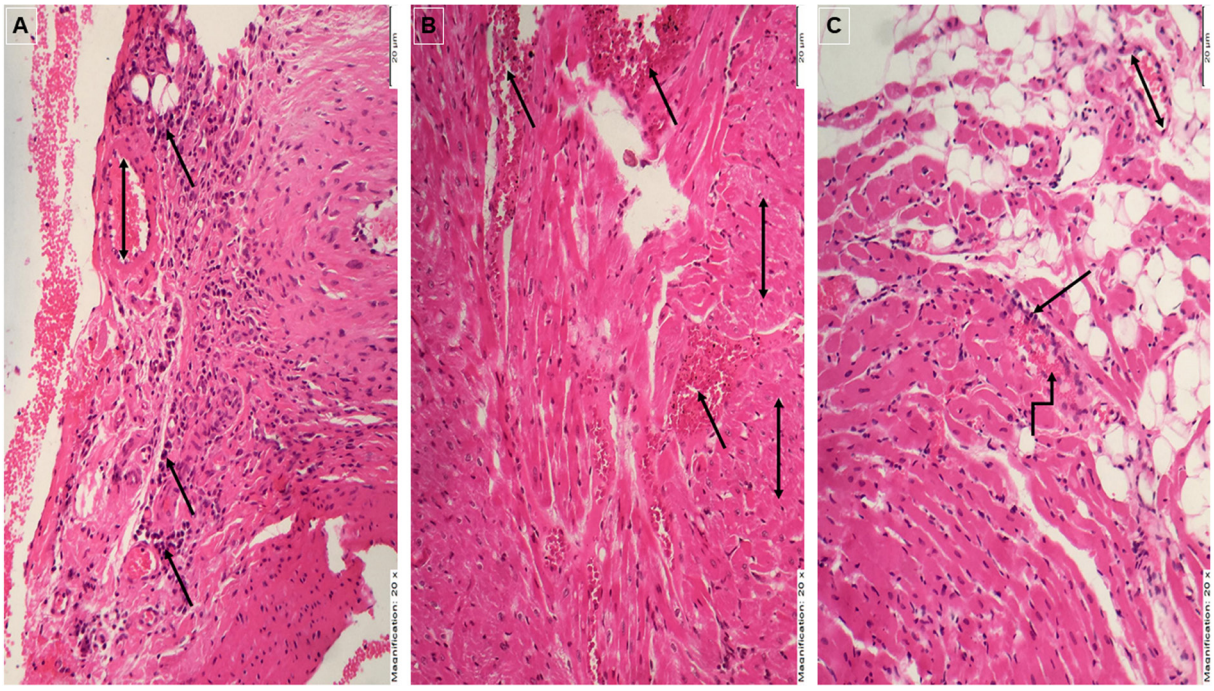

Figure 3 – Histopathological results of the experimental groups. Erzurum, Turkey, 2021.
Note: A: Substantial inflammatory cell infiltration (arrow) and vascular congestion (double arrow) in the heart tissue of the Acrylamide (ACL) group (H&E x 200). B: Hemorrhage and edema (arrow), myocardial degeneration, and loss of myofibrillar striation (double arrow) in the heart tissue of the ACL group (H&E 200). C: The decrease in the inflammatory cell infiltrate (arrow), vascular congestion (double arrow), and hemorrhage (zigzag arrow) were detected in the heart tissue of the Acrylamide+Taxifolin (TACL) group (H&E x 200).

DISCUSSION

We conducted this study to evaluate the taxifolin effects on acrylamide-induced oxidative heart damage. Numerous published studies have shown that acrylamide exposure and subsequent tissue accumulation may trigger oxidative stress on many organs due to the consumption of highly processed foods rich in carbohydrates [23,24]. According to the results of our study, acrylamide-alone exposure significantly decreased body weight, food and water intake until the end of the second month in the ACL group. However, in the TACL group, the bodyweight increase rate, food and water intake were recorded to be similar to the HG, despite the exposure to acrylamide. Taxifolin treatment steadily increased all three parameters by the end of the first and second months. Acrylamide-related body weight loss and decrease in water and food intake may be associated with alterations in thirst and hunger regulation centers in the hypothalamus and may also be related to the significant gut oxidative stress due to a decrease of antioxidant levels [25,26]. Previous studies have shown that acrylamide-induced cytotoxicity is mediated through mitochondrial dysfunction and oxidative stress [27]. The inflammatory process due to acrylamide's long-extent exposure may be responsible for so-called cardiac cachexia, which is well defined in patients suffering from long-term heart failure [28]. Besides the known association between increased NF-ĸB levels and the inflammatory process, this parameter seems to be a useful indicator for bodyweight alteration due to acrylamide exposure. The statistical evidence that the NF-ĸB levels of the TACL group were found to be close to those of the HG supports the anti-inflammatory and antioxidant effects of taxifolin on acrylamide-induced cardiotoxicity. A recently published paper has shown a preventive effect of dietary taxifolin via NF-ĸB signaling, enhancing intestinal barrier, and modulating gut microbiota [29].

Our experimental results showed that tissue MDA levels, the parameter for toxic damage, were significantly increased in the ACL group. However, the detection of TACL group MDA levels close to HG suggests the inhibitory effect of taxifolin on oxidative damage. Tang Z. *et al.*, consistently with our study, demonstrated the cardioprotective effects of taxifolin treatment by lowering MDA heart tissue levels in the rat ischemia-reperfusion model [30].

Total Glutathione (tGSH) is an endogenous antioxidant that plays an important role in the detoxification of ROS products; hence, in excessive detoxification capacity, the level of tGSH may decrease, suggesting the overproduction of ROS [15,31]. In this study, tGSH levels decreased significantly in the ACL group. However, in the TACL group, antioxidant levels close to the HG suggest that taxifolin has a protective effect on oxidative damage. Li *et al.*, have shown a scavenging effect of taxifolin on hydroxyl radicals, which is defined as one of the strongest toxic ROS [32].

As oxidative stress increases, accordingly, a decrease in TAS levels and an increase in TOS levels are expected [33]. Our results showed that acrylamide exposure significantly increased TOS levels and decreased TAS levels in an ACL group. However, the TOS and TAS levels of the TACL group were found to be close to the HG, suggesting the inhibitory effect of taxifolin on oxidative damage. Recently Kushwah *et al.* demonstrated that the protective effect of flavonoids is more beneficial with high-dose treatment compared to the low-dose [26]. In this term, to avoid inappropriate cooking techniques, increasing the intake of dietary antioxidants can reduce the harmful effects of acrylamide. The underlying mechanism of the protective effects of flavonoids is attributed to the ROS scavenging effect, maintaining the integrity of the cell membrane. Moreover, taxifolin may promote cell survival by regulating signal pathways in heart tissue [34]. Excessive ROS formation causes myocardial membrane damage resulting in myocardial cell leakage and subsequently, cardiac biomarkers get released into the circulation [35]. TP-I is a sensitive biomarker that is widely used for myocardial infarction confirmation [36]. Our study also showed that acrylamide administration increased TP-I levels in the blood serum of rats, whereas taxifolin treatment significantly reduced TP-I levels. These data suggest that taxifolin may protect cell membrane integrity by preventing cardiac biomarker leakage into circulation. In addition to increasing oxidative stress, acrylamide administration also stimulates apoptosis, which can explain myocardial degeneration and inflammation in heart tissue [10]. The histopathological examination showed that taxifolin treatment ameliorated acrylamide-induced cardiac damage in rats. In the ACL group animals, histopathological changes like myocardial degeneration, inflammatory cell infiltration, vascular congestion, and edema were observed prominently. However, in the TACL group, histopathologic signs were similar to the HG. Taxifolin treatment reduced cardiac destruction signs induced by acrylamide and provided cell integrity.

Functional studies are needed to confirm if the biochemical and histopathological changes correlate with cardiac function.

CONCLUSION

Acrylamide exposure substantially induced oxidative stress-related damage in rat heart tissue. Oxidative parameters and cardiac biomarkers might be favorable indicators in the identification of acrylamide-induced cardiotoxicity. Taxifolin was able to ameliorate the toxic consequences of acrylamide, both biochemically and histopathologically, probably due to its antioxidant properties. According to our study results, in order to reverse the effects of acrylamide, a food-based toxin, consuming foods rich in flavonoids such as taxifolin may be beneficial to prevent the risk of cardiovascular diseases.

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CONTRIBUTORS

MS COSGUN was responsible for the designed the methodology, critically revised it for important intellectual content, and worked on the manuscript's final approval. R COSKUN was assisted in drafting and writing the article. AI CELİK was responsible for the made a substantial contribution to the interpretation and analys of data, and to the final review.

REFERENCES

1. Mousavi Khaneghah A, Fakhri Y, Nematollahi A, Seilani F, Vasseghian Y. The concentration of acrylamide in different food products: a global systematic review, meta-analysis, and meta-regression. Food Rev Int. 2020:1-19. https://doi.org/10.1080/87559129.2020.1791175
2. Maan AA, Anjum MA, Khan MKI, Nazir A, Saeed F, Afzaal M, *et al.* Acrylamide formation and different mitigation strategies during food processing: a review. Food Rev Int 2020:1-18. https://doi.org/10.1080/87559129.2020.1719505
3. Iriondo-DeHond A, Elizondo AS, Iriondo-DeHond M, Ríos MB, Mufari R, Mendiola JA, *et al.* Assessment of healthy and harmful maillard reaction products in a novel coffee cascara beverage: melanoidins and acrylamide. Foods. 2020;9(5):620. https://doi.org/10.3390/foods9050620
4. Yoosefian M, Pakpour A, Zahedi M. Carboxylated single-walled carbon nanotubes as a semiconductor for adsorption of acrylamide in mainstream cigarette smoke. Physica E. 2020;124:114299. https://doi.org/10.1016/j.physe.2020.114299
5. Pelucchi C, Rosato V, Bracci P, L-D, Neale R, Lucenteforte E, *et al.* Dietary acrylamide and the risk of pancreatic cancer in the International Pancreatic Cancer Case: Control Consortium (PanC4). Ann Oncol. 2017;28(2):408-14. https://doi.org/10.1093/annonc/mdw618
6. Guo J, Cao X, Hu X, Li S, Wang J. The anti-apoptotic, antioxidant and anti-inflammatory effects of curcumin on acrylamide-induced neurotoxicity in rats. BMC Pharmacol Toxicol. 2020;21(1):1-10. https://doi.org/10.1186/s40360-020-00440-3
7. Atabati H, Abouhamzeh B, Abdollahifar M-A, Javadinia SS, GharibianBajestanie S, Atamaleki A, *et al.* The association between high oral intake of acrylamide and risk of breast cancer: an updated systematic review and meta-analysis. Trends Food Sci Tech. 2020;100:155-63. https://doi.org/10.1016/j.tifs.2020.04.006
8. Sadat Yousefsani B, Akbarizadeh N, Pourahmad J. The antioxidant and neuroprotective effects of Zolpidem on acrylamide-induced neurotoxicity using Wistar rat primary neuronal cortical culture. Toxicol Rep. 2020;7:233-40. https://doi.org/10.1016/j.toxrep.2020.01.010
9. Huang M, Jiao J, Wang J, Xia Z, Zhang Y. Characterization of acrylamide-induced oxidative stress and cardiovascular toxicity in zebrafish embryos. J Hazard Mater. 2018;347:451-60. https://doi.org/10.1016/j.jhazmat.2018.01.016
10. Foroutanfar A, Mehri S, Kamyar M, Tandisehpanah Z, Hosseinzadeh H. Protective effect of punicalagin, the main polyphenol compound of pomegranate, against acrylamide-induced neurotoxicity and hepatotoxicity in rats. Phytother Res. 2020;34(12):3262-72. https://doi.org/10.1002/ptr.6774
11. Oppedisano F, Macrì R, Gliozzi M, Musolino V, Carresi C, Maiuolo J, *et al.* The anti-inflammatory and antioxidant properties of n-3 PUFAs: their role in cardiovascular protection. Biomedicines. 2020;8(9):306. https://doi.org/10.3390/biomedicines8090306
12. Kalinina I, Potoroko I, Sonawane SH. Sonochemical encapsulation of taxifolin into cyclodextrine for improving its bioavailability and bioactivity for food. In Sonawane SH, Bhanvase BA, Sivakumar M, editors. Encapsulation of active molecules and their delivery system. New York: Elsevier; 2020. p. 85-102.

13. Bedir F, Kocatürk H, Yapanoğlu T, Gürsul C, Arslan R, Mammadov R, *et al.* Protective effect of taxifolin against prooxidant and proinflammatory kidney damage associated with acrylamide in rats. Biomed Pharmacother. 2021;139:111660. https://doi.org/10.1016/j.biopha.2021.111660

14. Salaritabar A, Darvishi B, Hadjiakhoondi F, Manayi A, Sureda A, Nabavi SF, *et al.* Therapeutic potential of flavonoids in inflammatory bowel disease: a comprehensive review. World J Gastroenterol. 2017;23(28):5097-5114. https://doi.org/10.3748/wjg.v23.i28.5097

15. Ahiskali I, Pinar CL, Kiki M, Cankaya M, Kunak CS, Altuner D. Effect of taxifolin on methanol-induced oxidative and inflammatory optic nerve damage in rats. Cutan Ocul Toxicol. 2019;38(4):384-89. https://doi.org/10.1080/15569527.2019.1637348

16. Chen X, Gu N, Xue C, Li BR. Plant flavonoid taxifolin inhibits the growth, migration and invasion of human osteosarcoma cells. Mol Med Rep. 2018;17(2):3239-45. https://doi.org/10.3892/mmr.2017.8271

17. Terekhov RP, Selivanova IA, Tyukavkina NA, Ilyasov IR, Zhevlakova AK, Dzuban AV, *et al.* Assembling the puzzle of taxifolin polymorphism. Molecules. 2020;25(22):5437. https://doi.org/10.3390/molecules25225437

18. Alpan AL, Kızıldağ A, Özdede M, Karakan NC, Özmen Ö. The effects of taxifolin on alveolar bone in experimental periodontitis in rats. Arch Oral Biol. 2020;117:104823. https://doi.org/10.1016/j.archoralbio.2020.104823

19. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351-8. https://doi.org/10.1016/0003-2697(79)90738-3

20. Sedlak J, Lindsay RH. Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal Biochem. 1968;25:192-205. https://doi.org/10.1016/0003-2697(68)90092-4

21. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin biochem. 2005;38(12):1103-11. https://doi.org/10.1016/j.clinbiochem.2005.08.008

22. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem. 2004;37(2):112-9. https://doi.org/10.1016/j.clinbiochem.2003.11.015

23. Ibrahim MA, Ibrahem MD. Acrylamide-induced hematotoxicity, oxidative stress, and DNA damage in liver, kidney, and brain of catfish (Clarias gariepinus). Environ Toxicol. 2020;35(2):300-8. https://doi.org/10.1002/tox.22863

24. Abdel-Daim MM, Abo El-Ela FI, Alshahrani FK, Bin-Jumah M, Al-Zharani M, Almutairi B, *et al.* Protective effects of thymoquinone against acrylamide-induced liver, kidney and brain oxidative damage in rats. Environ Sci Pollut Res Int. 2020;27(30):37709-17. https://doi.org/10.1007/s11356-020-09516-3

25. Mårtensson J, Jain A, Meister A. Glutathione is required for intestinal function. Proc Natl Acad Sci . 1990;87(5):1715-9. https://doi.org/10.1073/pnas.87.5.1715

26. Kushwah AS, KALIA TS. Quercetin attenuates oxidative stress, inflammation and cardiac dysfunction in acrylamide-induced cardiotoxicity. Acta Pol Pharm. 2020;77(2):343-52. https://doi.org/10.32383/appdr/110094

27. Yousef MI, El-Demerdash FM. Acrylamide-induced oxidative stress and biochemical perturbations in rats. Toxicology. 2006;219(1-3):133-41. https://doi.org/10.1016/j.tox.2005.11.008

28. Valentova M, Anker SD, von Haehling S. Cardiac cachexia revisited: the role of wasting in heart failure. Heart Fail Clin. 2020;16(1):61-9. https://doi.org/10.1016/j.hfc.2019.08.006

29. Hou J, Hu M, Zhang L, Gao Y, Ma L, Yan X, *et al.* Dietary taxifolin potently protects against dextran sulfate sodium-induced colitis via NF-κB signaling, enhancing ıntestinal barrier and modulating gut microbiota. Front Immunol. 2020;11:3915. https://doi.org/10.3389/fimmu.2020.631809

30. Tang Z, Yang C, Zuo B, Zhang Y, Wu G, Wang Y, *et al.* Taxifolin protects rat against myocardial ischemia/reperfusion injury by modulating the mitochondrial apoptosis pathway. PeerJ. 2019;7:e6383. https://doi.org/10.7717/peerj.6383

31. Unver E, Tosun M, Olmez H, Kuzucu M, Cimen FK, Suleyman Z. The effect of taxifolin on cisplatin-induced pulmonary damage in rats: a biochemical and histopathological evaluation. Mediators Inflamm. 2019;2019:1-7. https://doi.org/10.1155/2019/3740867

32. Li X, Xie H, Jiang Q, Wei G, Lin L, Li C, *et al.* The mechanism of (+) taxifolin's protective antioxidant effect for OH-treated bone marrow-derived mesenchymal stem cells. Cell Mol Biol Lett. 2017;22(1):1-11. https://doi.org/10.1186/s11658-017-0066-9

33. Marković J, Stošić M, Kojić D, Matavulj M. Effects of acrylamide on oxidant/antioxidant parameters and CYP2E1 expression in rat pancreatic endocrine cells. Acta Histochem. 2018;120(2):73-83. https://doi.org/10.1016/j.acthis.2017.12.001

34. Zakaria N, Khalil SR, Awad A, Khairy GM. Quercetin reverses altered energy metabolism in the heart of rats receiving adriamycin chemotherapy. Cardiovasc Toxicol. 2018;18(2):109-19. https://doi.org/10.1007/s12012-017-9420-4

35. Mair J, Lindahl B, Hammarsten O, Müller C, Giannitsis E, Huber K, *et al.* How is cardiac troponin released from injured myocardium? Eur Heart J Acute Cardiovasc Care. 2018;7(6):553-60. https://doi.org/10.1177/2048872617748553

36. Sarkisian L, Saaby L, Poulsen TS, Gerke O, Jangaard N, Hosbond S, *et al.* Clinical characteristics and outcomes of patients with myocardial infarction, myocardial injury, and nonelevated troponins. Am J Med. 2016;129(4):e5-e21. https://doi.org/10.1016/j.amjmed.2015.11.006

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