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Original Article

Antioxidative Effects of Umbelliprenin Against Acrylamide-Induced Hepatotoxicity in Mice

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Abstract

Introduction: Acrylamide (ACR) is a well-known hepatotoxicant commonly found in heat-processed carbohydrate-rich foods, which induces oxidative stress (OS) and liver injury in animal models. Umbelliprenin, a prenyloxy coumarin with documented antioxidant and anti-inflammatory properties, has been proposed as a potential hepatoprotective agent. This experimental study investigated the protective effects of umbelliprenin against ACR-induced hepatotoxicity in adult male albino mice.

Methods: Animals were randomly allocated to experimental groups. Mice were divided into control, ACR (50 mg/kg/day, oral), umbelliprenin (12.5 mg/kg/day, i.p.), ACR + umbelliprenin, and paraffin vehicle groups (n=7 per). After 10 days of treatment, serum liver function enzymes (alanine aminotransferase [ALT], aspartate transferase [AST], alkaline phosphatase [ALP], and bilirubin) and OS markers, including malondialdehyde (MDA), total antioxidant capacity (TAC), and glutathione peroxidase (GPx) activity, underwent evaluation. Data were analyzed using SPSS version 26.0.

Results: ACR significantly increased ALT ($P=0.012$), AST ($P=0.008$), ALP ($P=0.003$), bilirubin ($P=0.041$), and MDA ($P=0.018$) while decreasing TAC ($P=0.027$) and GPx activity ($P=0.021$), indicating hepatic oxidative damage. Based on the results, umbelliprenin co-administration mitigated these alterations, restoring ALT (vs. ACR group, $P=0.035$) and bilirubin ($P=0.048$) to near control levels, reducing MDA ($P=0.039$), and partially improving TAC ($P=0.044$) and GPx activities ($P=0.042$).

Conclusion: Umbelliprenin exerts hepatoprotective effects against ACR-induced liver injury by enhancing antioxidant defenses, decreasing lipid peroxidation, and preserving liver function, emphasizing its potential as a natural therapeutic factor for chemically induced hepatotoxicity.

Keywords: Acrylamide, Umbelliprenin, Hepatotoxicity, Oxidative stress, Mice

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Introduction

Acrylamide (ACR) is a known toxic substance that forms in carbohydrate-rich foods through Maillard reactions during frying at high temperatures, leading to repeated chronic and subchronic human exposure through the diet (1). Moreover, ACR has been shown to exert hepatotoxic effects in rodents, characterized by the elevated serum biomarkers of liver injury, such as alanine aminotransferase (ALT) and aspartate transferase (AST), histopathological alterations (e.g., hepatocyte degeneration and inflammatory infiltration), and increased oxidative stress (OS), as evidenced by enhanced lipid peroxidation and disruption of antioxidant defense systems, including glutathione depletion (2, 3). Mechanistically, ACR-induced liver injury is associated with the increased production of reactive oxygen species (ROS), inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress, which all contribute to liver cell injury and apoptosis in animal models (2, 4).

Given the pivotal role of OS and inflammation in ACR-induced hepatotoxicity, bioactive agents with antioxidant and anti-inflammatory properties have attracted much attention as potential hepatoprotective compounds. According to some studies, plant-derived polyphenols and flavonoids can mitigate ACR-induced liver injury through enhancing endogenous antioxidative mechanisms while inhibiting inflammatory cascades (3, 5). These findings suggest that bioactive phytochemicals are promising candidates for attenuating chemical-induced hepatic damage.

Umbelliprenin is a prenyloxy coumarin sesquiterpenoid that is widely distributed in the plants of the Apiaceae family, especially in *Ferula* species and related edible herbs, and has been identified to possess diverse pharmacological activities, including anti-inflammatory, immunomodulatory, anticancer, and antioxidant effects (6, 7). In addition, in vivo studies on mice have demonstrated that umbelliprenin administration modulates immune response by promoting T helper 2-type cytokines (e.g., interleukin-4 and interleukin-10) while reducing pro-inflammatory profiles, indicating its potential anti-inflammatory effects in systemic biological contexts (7). Additionally, in vitro investigations have suggested the inhibitory activity of umbelliprenin against key inflammatory enzymes (e.g., lipoxygenase), which may underlie its anti-inflammatory and analgesic properties (8).

In a recent experimental study, the protective effects

of umbelliprenin against ACR-induced reproductive toxicity were evaluated in male mice (9). The findings revealed that umbelliprenin significantly improved sperm parameters, modulated reproductive hormone levels, and enhanced antioxidant defense mechanisms in testicular tissue following ACR exposure. These results highlight the antioxidative and cytoprotective properties of umbelliprenin in the experimental models of ACR-induced tissue injury and provide a scientific basis for investigating its potential protective effects in other target organs, including the liver.

Despite these promising pharmacological attributes, the effects of umbelliprenin on ACR-induced hepatic injury have not yet been directly elucidated in preclinical models. It is noteworthy that ACR-mediated liver toxicity is primarily driven by oxidative and inflammatory pathways, and umbelliprenin exhibits modulatory effects on inflammation and related biological processes. Accordingly, it is scientifically plausible to hypothesize a hepatoprotective potential of umbelliprenin in the context of ACR-induced hepatotoxicity. This study, therefore, aims to investigate the protective effects of umbelliprenin on ACR-induced liver damage in a mouse model, with a particular focus on key biochemical parameters and OS markers associated with hepatic injury.

Materials and Methods

Animals

Thirty-five adult male albino mice (20–30 g) were obtained from the Animal Laboratory of Islamic Azad University, Shahrekord, Iran. The animals were housed under standard laboratory conditions, including a 12-hour light/dark cycle, controlled temperature (22 ± 2°C), and ad libitum access to standard chow and water. They were acclimatized for 7 days prior to the initiation of the experimental procedures. It should be noted that all these protocols were conducted in accordance with institutional ethical guidelines for the care and use of laboratory animals.

Experimental Design

The mice were randomly assigned to five experimental groups (n = 7 per group), including control, ACR, umbelliprenin, umbelliprenin + ACR, and paraffin (vehicle control) groups. The control group received 0.1 mL of normal saline intraperitoneally (i.p.) once daily for 10 consecutive days, and the ACR group was given ACR orally at a dose of 50 mg/kg/day for 10 days in order to induce OS and liver injury. Furthermore, the umbelliprenin group received umbelliprenin at a dose of 12.5 mg/kg/day (i.p.), dissolved in paraffin, for 10 consecutive days. Likewise, the umbelliprenin + ACR group was given umbelliprenin (12.5 mg/kg/day, i.p.) in combination with ACR (50 mg/kg/day, oral) for 10 consecutive days. Finally, the paraffin (vehicle control) group received 0.1 mL of paraffin intraperitoneally once daily for 10 consecutive days.

Blood Collection and Serum Preparation

At the end of the treatment period, mice were fasted overnight (8–12 hours) and anesthetized with (ketamine/xylazine). Blood samples were collected by cardiac puncture and allowed to clot at room temperature for 20–30 minutes. Then, the samples were centrifuged at 3,000 rpm for 10 minutes at 4°C. Ultimately, the serum was separated, aliquoted, and stored at −80°C until biochemical analysis.

Measurement of Liver Enzyme Activities

Serum ALT, AST, alkaline phosphatase (ALP), and gamma-glutamyl transferase activities were measured using commercial enzyme assay kits (Pars Azmoun, Iran) according to the manufacturer's instructions.

Determination of Oxidative Stress Markers

OS biomarkers in the serum were quantified using standardized commercial colorimetric kits (ZellBio GmbH, Germany) following validated protocols commonly applied in rodent models.

Estimation of Serum Malondialdehyde

Serum MDA levels were assessed using a commercially available colorimetric kit (ZellBio GmbH, Germany) in accordance with the manufacturer's instructions. In brief, serum samples were reacted with thiobarbituric acid (TBA) and incubated in a boiling water bath for the period specified in the kit protocol to allow the formation of the MDA–TBA complex. The reaction mixtures were then allowed to cool to room temperature and centrifuged. Moreover, the absorbance of the resulting supernatant was measured at 532 nm using a microplate reader or spectrophotometer. Finally, MDA concentrations were determined from the standard curve provided with the kit and reported as nmol/mL of serum.

Calculation of Total Antioxidant Capacity

The TAC of the serum samples was evaluated using a colorimetric ferric reducing ability of plasma-based assay kit (ZellBio GmbH, Germany). This method relies on the ability of antioxidants in the serum to reduce ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}), leading to the formation of a colored complex. Next, the absorbance was estimated at 593 nm with a microplate reader. Additionally, TAC values were calculated from a calibration curve constructed using the standards supplied by the manufacturer and expressed as mmol Fe^{2+} equivalents per liter of serum.

Measurement of Glutathione Peroxidase Activity

Serum GPx activity was determined using a kinetic colorimetric assay kit (ZellBio GmbH, Germany) following the manufacturer's protocol. The assay is based on the GPx-catalyzed reduction of hydrogen peroxide in the presence of reduced glutathione, which is coupled to the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to $NADP^+$ by glutathione reductase. The decrease in absorbance at 340 nm was monitored

over time, and GPx activity was computed from the rate of NADPH consumption and expressed as U/L of serum.

Statistical Analysis

All data are expressed as means ± standard error of the mean. Statistical analyses were conducted by SPSS (version 26.0) using one-way analysis of variance, followed by Tukey's multiple comparisons post hoc test. A *P*-value of less than 0.05 was considered statistically significant.

Results

Liver Function Parameters

Alkaline Phosphatase: Serum ALP levels demonstrated a significant difference among the groups ($P=0.001$, Table 1). ACR administration substantially increased ALP compared to the control group (456.98 ± 11.12 U/L vs. 106.46 ± 9.02 U/L, $P=0.003$). Umbelliprenin alone had no considerable effect (123.54 ± 15.87 U/L, $P=0.612$). Based on the result, the co-administration of umbelliprenin with ACR could sharply reduce ALP in comparison to the ACR group (278.98 ± 18.11 U/L, $P=0.028$), but it remained higher than the control ($P=0.037$). Eventually, the paraffin vehicle group showed no remarkable difference from the control (118.98 ± 10.16 U/L, $P=0.734$).

Aspartate Transferase : As regards serum AST levels, there was a marked difference among the groups ($P=0.001$, Table 1). ACR administration could significantly increase AST compared to the control group (371.85 ± 10.43 U/L vs. 166.70 ± 7.92 U/L, $P=0.008$). However, umbelliprenin alone had no considerable effect (158.00 ± 8.35 U/L, $P=0.581$). Although the co-administration of umbelliprenin with ACR substantially decreased AST when compared to the ACR group (218.55 ± 8.43 U/L, $P=0.024$), it remained higher than the control ($P=0.033$). Finally, the paraffin vehicle group demonstrated no significant difference from the control (170.95 ± 9.64 U/L, $P=0.692$).

Alanine Aminotransferase: A marked difference was found among the groups in terms of serum ALT levels ($P=0.001$, Table 1). ACR administration considerably increased ALT in comparison to the control group (180.00 ± 8.51 U/L vs. 89.61 ± 8.26 U/L, $P=0.012$). Nonetheless, umbelliprenin alone displayed no substantial effect (86.31 ± 4.76 U/L, $P=0.754$). The co-administration of umbelliprenin with ACR led to a significant reduction compared to the ACR group (100.00 ± 9.07 U/L, $P=0.018$), reaching a level comparable to the control ($P=0.342$). However, the paraffin vehicle group represented no sharp difference from the control (85.35 ± 4.61 U/L, $P=0.821$).

Bilirubin: Serum bilirubin levels revealed a significant difference among the groups ($P=0.006$, Table 1). ACR administration could substantially increase bilirubin compared to the control group (0.90 ± 0.08 mg/dL vs. 0.50 ± 0.18 mg/dL, $P=0.041$). Although umbelliprenin alone had no remarkable effect (0.55 ± 0.11 mg/dL, $P=0.638$), the co-administration of umbelliprenin with ACR significantly reduced bilirubin compared to the ACR group (0.64 ± 0.04 mg/dL, $P=0.039$), displaying a level comparable to the control ($P=0.287$). Finally, the paraffin vehicle group represented no marked difference from the control (0.54 ± 0.03 mg/dL, $P=0.712$).

Oxidative Stress Markers

Malondialdehyde: Serum MDA levels demonstrated a significant difference among the groups ($P=0.014$, Figure 1). Based on the results, ACR administration substantially increased MDA compared to the control group (19.80 ± 2.11 nmol/mL vs. 12.09 ± 1.11 nmol/mL, $P=0.018$). Umbelliprenin alone had no remarkable effect (11.94 ± 1.09 nmol/mL, $P=0.724$). However, the co-administration of umbelliprenin with ACR significantly reduced MDA when compared to the ACR group (13.31 ± 3.04 nmol/mL, $P=0.039$), reaching a level comparable to the control ($P=0.356$). Ultimately, the paraffin vehicle group showed no marked difference from the control (12.96 ± 2.14 nmol/mL, $P=0.683$).

Total Antioxidant Capacity: A considerable difference was observed among the groups in terms of serum TAC levels ($P=0.009$, Figure 1). ACR administration could substantially decrease TAC in comparison to the control group (3.67 ± 0.39 µmol/L vs. 6.54 ± 1.03 µmol/L, $P=0.027$). Although umbelliprenin alone had no remarkable effect (6.00 ± 0.51 µmol/L, $P=0.458$), the co-administration of umbelliprenin with ACR significantly increased TAC compared to the ACR group (4.73 ± 0.23 µmol/L, $P=0.044$), but it remained slightly lower than the control ($P=0.048$). Finally, the paraffin vehicle group displayed no marked difference from the control (6.75 ± 0.18 µmol/L, $P=0.672$).

Glutathione Peroxidase: There was a significant difference among the groups with regard to serum GPx activity ($P=0.011$, Figure 1). ACR administration sharply decreased GPx compared to the control group (43.29 ± 4.35 U/mL vs. 58.12 ± 4.65 U/mL, $P=0.021$). Umbelliprenin alone had no marked effect (60.81 ± 4.41 U/mL, $P=0.534$). Nonetheless, the co-administration

Table 1. Comparison of Liver Function Parameters Among Different Experimental Groups (Mean ± SD)

	Bil (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)
Control	0.50 ± 0.18[a]	89.61 ± 8.26[a]	166.70 ± 7.92[a]	106.46 ± 9.02[a]
ACR	0.90 ± 0.08[b]	180.00 ± 8.51[b]	371.85 ± 10.43[b]	456.98 ± 11.12[b]
Umbelliprenin	0.55 ± 0.11[a]	86.31 ± 4.76[a]	158.00 ± 8.35[a]	123.54 ± 15.87[a]
ACR + Umbelliprenin	0.64 ± 0.04[a]	100.00 ± 9.07[a]	218.55 ± 8.43[c]	278.98 ± 18.11[c]
Paraffin	0.54 ± 0.03[a]	85.35 ± 4.61[a]	170.95 ± 9.64[a]	118.98 ± 10.16[a]

Note. SD: Standard deviation; Bil: Bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ACR: Acrylamide; ALP: Alkaline phosphatase. The presence of different superscript letters in each column indicates a significant difference between groups ($P<0.05$).

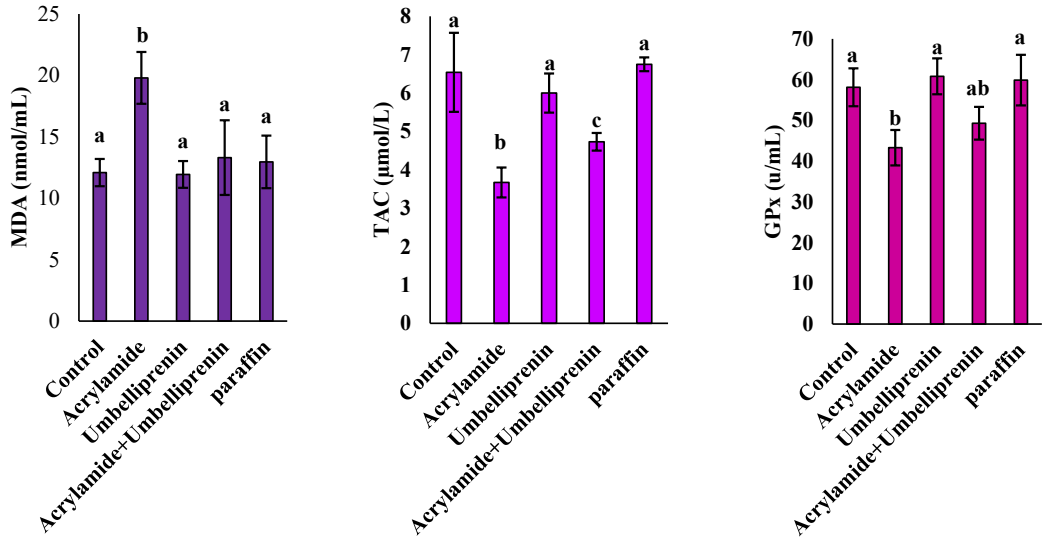

Figure 1. Alterations in MDA, TAC, and GPx Levels Across Experimental Groups
Note. MDA: Malondialdehyde; TAC: Total antioxidant capacity; GPx: Glutathione peroxidase. The presence of at least one common Latin letter indicates no significant difference between the groups ($P > 0.05$)

of umbelliprenin with ACR substantially increased GPx when compared to the ACR group (49.29 ± 4.02 U/mL, $P = 0.042$), representing a level comparable to the control ($P = 0.213$). The paraffin vehicle group demonstrated no considerable difference from the control (59.88 ± 6.21 U/mL, $P = 0.678$).

Discussion

Our findings demonstrated that ACR exposure significantly impairs liver function and increases OS in mice. This was evidenced by decreased activities of endogenous antioxidant enzymes (e.g., GPx and TAC), along with elevated MDA levels, which is consistent with previous reports, highlighting the central role of oxidation and ROS generation in ACR -induced liver injury (3, 5, 10). The increase in liver enzymes, including ALT, AST, and ALP, following ACR exposure likely reflects hepatocyte membrane damage and subsequent leakage of enzymes into the circulation, which conforms to observations in previous studies with flavonoids (11). Elevated bilirubin levels further indicated hepatocyte injury, which is a pattern commonly observed in chemically induced liver toxicity models.

In the group receiving only umbelliprenin, no significant changes were observed in liver function parameters or OS markers compared to controls, representing the absence of intrinsic toxicity under normal physiological conditions. This aligns with broader literature showing that natural flavonoids and prenylated coumarins can support endogenous antioxidant defenses without adverse effects at non-stress doses (6, 7, 12). The results suggest that umbelliprenin may help maintain antioxidant homeostasis under normal conditions.

Importantly, the co-administration of ACR and umbelliprenin substantially improved antioxidant parameters while reducing MDA levels, indicating effective mitigation of OS. Likewise, the co-administration of umbelliprenin resulted in partial hepatoprotection, with ALT and bilirubin returning to levels comparable to those of the control group. However, AST and ALP remained significantly higher than control values, implying incomplete restoration of liver function.

Although TAC did not completely normalize, the improvement demonstrated umbelliprenin's ability to enhance endogenous antioxidant responses, stabilize cellular membranes, and reduce ROS-mediated hepatocellular damage (13, 14). These findings corroborate those of previous studies, reporting that phytochemicals with strong antioxidant properties can modulate hepatic enzyme activities and reduce serum bilirubin in various liver injury models (3, 5).

In line with these observations, a previous in vivo study confirmed that pomegranate peel powder substantially attenuated cadmium-induced toxicity in Japanese quail through the enhancement of endogenous antioxidant defense systems and reduction of OS biomarkers in target tissues (15). The study highlighted the pivotal role of phytochemical-rich natural compounds in modulating toxin-induced oxidative injury, further supporting the present findings regarding the protective capacity of umbelliprenin against chemically induced hepatotoxicity.

Moreover, umbelliprenin likely exerts hepatoprotective effects through multiple complementary mechanisms. Primarily, it may enhance cellular antioxidant capacity, reduce lipid peroxidation, and preserve hepatocyte membrane integrity, thereby modulating liver enzyme activities and bilirubin levels (16, 17). Based on previous studies on umbelliprenin (7, 8, 18), it is possible that anti-inflammatory mechanisms may also contribute to the observed effects and could complement its antioxidative activity; however, this was not directly assessed in the present study, warranting further investigation.

Such multi-pathway effects are in line with the findings of previous studies on the protective roles of polyphenols and flavonoids in OS and liver enzyme dysfunction (1, 2, 4, 19).

In a study by Mahdavi-Yekta et al, antioxidant-enriched nanocomposite systems were shown to reduce chemically induced toxicity by improving oxidative status (20). These findings support the potential role of antioxidant-based strategies in mitigating toxin-induced oxidative damage and are in conformity with the protective mechanisms of umbelliprenin against hepatic injury observed in the present study.

In addition to antioxidant effects, evidence suggests that umbelliprenin possesses anti-inflammatory and immunoregulatory properties, potentially enhancing T helper 2 responses while reducing tissue injury in stress models (7, 8).

The paraffin control group confirmed that the vehicle used for umbelliprenin administration did not induce significant changes in liver parameters or oxidative status, reinforcing the validity of the observed protective effects.

The present study had several limitations. First, liver tissue was not examined histopathologically (e.g., hematoxylin and eosin staining); therefore, structural evidence supporting the hepatoprotective effect remains unavailable. In addition, inflammatory cytokines were not measured, and thus the proposed anti-inflammatory mechanism remains speculative. Accordingly, future studies should address these limitations in order to provide a more comprehensive understanding of the hepatoprotective mechanisms of umbelliprenin.

Conclusion

These findings of this study support the hypothesis that umbelliprenin can substantially attenuate ACR-induced hepatotoxicity. It was revealed that its hepatoprotective profile involves the improvement of antioxidant status, reduction of oxidative products, preservation of liver enzyme function, and engagement of multiple biological pathways, highlighting its potential as a natural agent for preventing chemically induced liver injury. These findings align with accumulating evidence that natural antioxidant compounds can mitigate hepatotoxicity and may have translational potential for applications in OS-related liver disorders.

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Artificial Intelligence Disclosure Statement

During the preparation of this manuscript, the authors employed the ChatGPT service for specific purposes (e.g., language editing and grammatical editing).

Authors' Contribution

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Software: Firoozeh Saghaei
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Validation: Maryam Karimi-Dehkordi
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Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

Ethical considerations in this study included obtaining permission from the Ethics Committee of Islamic Azad University, Shahrekord (ethical No. IR.IAU.SHK.REC.1403.374) and receiving written consent from the participants to participate in the study.

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