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Effects of Plant Phenolic Compounds on Ethanol-Induced Hepatocyte Damage: A Comparative Study

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ABSTRACT

Background: Previous studies have shown the beneficial effects of phenolic compounds on liver disorders. In the present study, the effects of eight phenolic compounds— chlorogenic acid, curcumin, gallic acid, hesperidin, resveratrol, rosmarinic acid, silibinin, and silymarin—on ethanol-induced cytotoxicity were investigated both individually and in combination.

Methods: The HepG2 liver cell line and primary rat liver-derived cells were cultured in the presence of ethanol (7% v/v) and different concentrations of phenolic compounds. We used different incubation designs, including co-incubation and pre-incubation, and varied incubation times to investigate the effect of these compounds on alcohol-induced cytotoxicity.

Results: Incubation of HepG2 cells and primary liver cells for 4 hours with ethanol significantly decreased their viability ($p < 0.001$). Pre-incubation and co-incubation with concentrations of 3-50 µM of chlorogenic acid, curcumin, gallic acid, resveratrol, rosmarinic acid, silibinin, or silymarin did not restore cell viability. Only hesperidin at 12.5 µM showed a mild but statistically significant ($p < 0.05$) protective effect in HepG2 cells. Binary combinations of curcumin, silibinin, and resveratrol at 12.5 µM did not show additive or synergistic activity against ethanol cytotoxicity after 4 hours. Additionally, combinations of chlorogenic acid, hesperidin, rosmarinic acid, and silymarin did not induce additive or synergistic activities after 6 hours.

Conclusion: The phenolic compounds tested did not exhibit significant cytoprotective effect in the model of ethanol-induced acute toxicity used in the present study. Conducting further research using different study designs—such as chronic toxicity models or lower ethanol concentrations—might yield different results.

Keywords: Alcohol, Curcumin, Ethanol, Liver, Phenolic compounds, Rosmarinic acid.

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Introduction

The liver is essential for metabolizing alcohol and detoxifying harmful substances, making it particularly vulnerable to damage caused by excessive alcohol intake (1). Alcohol consumption is thought to be a contributing factor in nearly 5% of all fatalities worldwide. In the United States, approximately 4.3% of cases involve alcohol-related steatosis. Furthermore, it is estimated that about 26 million people globally suffer from cirrhosis linked to alcohol intake (2). The underlying mechanisms of alcoholic liver disease primarily involve the buildup of acetaldehyde within liver cells, resulting in mitochondrial damage, increased fat accumulation, oxidative stress, and inflammatory reactions. This creates a harmful cycle that exacerbates liver injury by initiating various forms of cell death, such as apoptosis and necrosis (3, 4)

The search for effective protective agents against alcohol-induced liver damage has shifted attention toward natural compounds, particularly those belonging to the class of phenolic compounds, which have garnered interest due to their potent antioxidant and anti-inflammatory properties (5, 6). The group of phenolic compounds includes various phytochemicals, some of which are the focus of the current study, including chlorogenic acid, curcumin, gallic acid, hesperidin, resveratrol, rosmarinic acid, silibinin, and silymarin. The chemical structures of these compounds are shown in Figure 1. They were selected based on the large number of published studies demonstrating their potential to protect hepatocytes against toxins.

Rosmarinic acid, a natural compound found in various herbaceous plants, is renowned for its anti-inflammatory and antioxidant properties (7, 8). Gallic acid, derived from tannins, is recognized for its ability to scavenge free radicals and inhibit lipid peroxidation (9). Curcumin, extracted from turmeric, has shown promise in reducing inflammation and protecting against hepatotoxicity (10, 11). Resveratrol, a polyphenolic compound found in grapes, has been extensively studied for its role in promoting liver health via its antioxidant capacity (12). Silymarin and silibinin, derived from milk thistle, have been used traditionally for liver disorders due to their hepatoprotective effects (13). Chlorogenic acid, commonly found in coffee beans, exhibits significant antioxidant activity (14). Hesperidin, a flavonoid abundant in citrus fruits, has been reported to possess various health benefits, including anti-inflammatory properties (15). Although previous studies have highlighted the potential benefits of these phenolic compounds, their effects may vary depending on the concentration, exposure duration, experimental model, etc. In particular, direct comparative data on these compounds and their combinations under the same ethanol-exposure conditions remain limited.

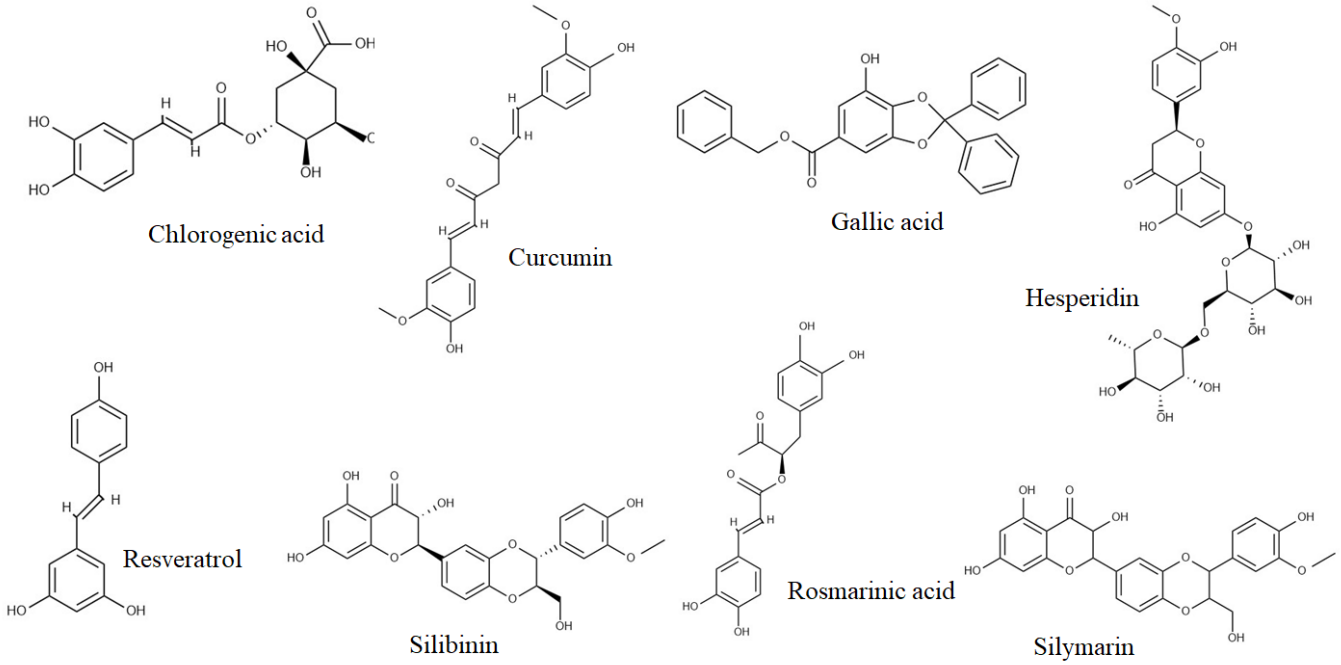

Figure 1. The chemical structure of phenolic compounds used in this study.

The goal of this study was to investigate both the individual and combined effects of these eight phenolic compounds on liver cells subjected to alcohol-induced damage. We aimed to determine which compound provides a better protective effect against ethanol cytotoxicity compared to the others. Furthermore, we hypothesized that certain combinations may yield synergistic effects, enhancing their protective capabilities. Understanding the efficacy of these compounds in this context could pave the way for developing novel therapeutic strategies for preventing and mitigating liver damage associated with alcohol consumption.

Materials and Methods

Materials

Gallic acid, resveratrol, rosmarinic acid, silibinin, silymarin, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma (USA). Chlorogenic acid and hesperidin were obtained from Gol Exir Pars (Iran). Curcumin was sourced from Sami Labs Limited (India). Collagenase type D and fetal bovine serum (FBS) were acquired from Boehringer Mannheim (Germany) and Gibco (USA), respectively. Roswell Park Memorial Institute (RPMI) cell culture medium was provided by Betacell Company (Iran). Penicillin-streptomycin solution was purchased from Capricorn (Germany).

HepG2 Cell Cultivation and Treatment

The human hepatocellular carcinoma HepG2 cells were cultured in 96-well plates at a density of 5,000 cells per well using RPMI medium enriched with 10% FBS and 1% penicillin-streptomycin. The cells were kept in an incubator at 37 °C for 48 hours. Following this incubation period, the cells were exposed to ethanol and varying concentrations of phenolic compounds. Different incubation designs, including co-incubation (simultaneous exposure to phenolic compound and ethanol) and pre-incubation (First incubation with phenolic compound and then with ethanol) were used to investigate the effects of these compounds on alcohol-induced cytotoxicity (Fig. 2). All phenolic compounds were dissolved in dimethyl sulfoxide and diluted in RPMI. At the highest concentration (200 µM) of the compounds, the final concentration of the solvent (vehicle) was less than 1%.

Primary Culture of Rat Liver-Derived Cells

A total of three newborn Wistar rats (less than one week old, weighing 8-14 g) were used for the isolation of liver cells. The animals were obtained from the Animal House of the Faculty of Medicine (Mashhad University of Medical Sciences). Animals were sacrificed by decapitation, and the livers were collected from each animal and immediately placed in sterile phosphate-buffered saline. The tissue samples were cut into small pieces under sterile conditions. After washing with phosphate-buffered saline, the pieces were digested with collagenase type D (2 mg/mL RPMI) for 90 minutes at 37 °C and 5% CO_2. The tissue was then centrifuged at 3,000 rpm for 5 minutes. The supernatant was discarded, and the cell pellets were resuspended in RPMI containing 20% FBS and 1% penicillin-streptomycin, and then placed in T-25 culture flasks. In order to obtain a sufficient quantity of cells for the experiment, the cultures underwent two passages.

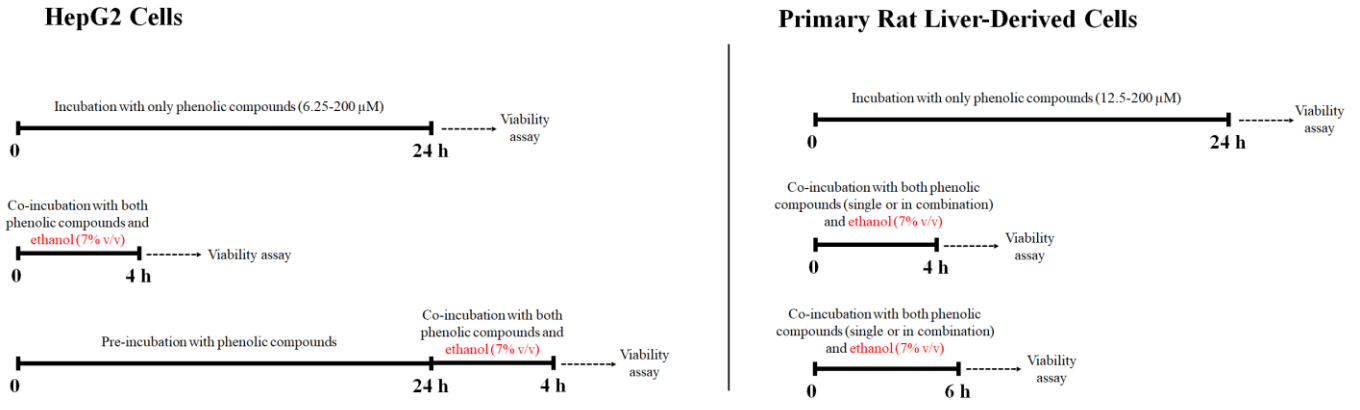

Figure 2. Study design and method of incubating HepG2 cells and primary rat liver-derived cells with phenolic compounds.

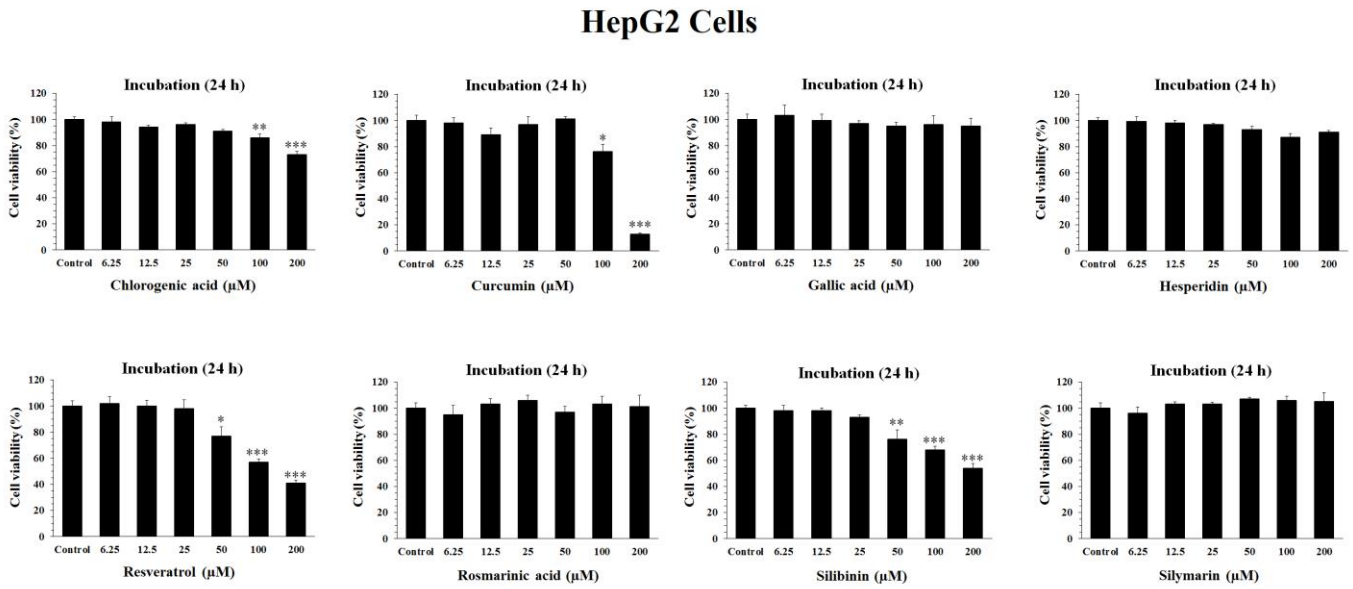

Figure 3. Effects of phenolic compounds on the viability of HepG2 cells. The cells were incubated for 24 h in the presence of each compound. Data are presented as SEM (n = 5). *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$ *vs* control

Cell Viability Assay

Following incubation with ethanol and the phenolic compounds, the culture medium was replaced with a new one containing MTT reagent at a concentration of 0.05% (w/v) (16). The cells were then incubated in a culture incubator for four hours. Subsequently, the medium was discarded, and to dissolve the formazan crystals, 200 µL of dimethyl sulfoxide was added to each well. The optical density for each well was recorded at a wavelength of 570 nm using a Stat FAX – 2100 plate reader from Awareness Technology Inc., USA.

Statistical Analysis

A one-way analysis of variance (ANOVA) was conducted with Tukey's post hoc tests to assess the differences among the treatment groups, with a significance level set at $p < 0.05$. The results are presented as mean ± standard error of the mean (SEM).

Results

Effects of Phenolic Compounds on Viability of HepG2 Cells

First, to ensure that the phenolic compounds under investigation did not have a toxic effect on the HepG2 cells, we treated the cells for 24 hours with these compounds in the absence of ethanol. As shown in Figure 3, gallic acid, hesperidin, rosmarinic acid, and silymarin at concentrations up to 200 µM did not cause any changes in cell viability. Both chlorogenic acid and curcumin, at concentrations of ≥ 100 µM, significantly decreased cell viability ($p < 0.05$). This decrease in viability was observed at concentrations of ≥ 50 µM for resveratrol and silibinin. Since chlorogenic acid, curcumin, resveratrol, and silibinin exhibited cytotoxic effects on their own at 50 µM or higher, concentrations below ≤ 50 µM were selected for the remainder of the study.

Effects of Phenolic Compounds on Ethanol-Induced Cytotoxicity in HepG2 Cells

As shown in Figure 4, incubation of HepG2 cells for 4 hours with ethanol (7% v/v) significantly decreased their viability ($p < 0.001$). Co-incubation with concentrations of 3-50 µM of chlorogenic acid, gallic acid, resveratrol, rosmarinic acid, silibinin, or silymarin did not prevent ethanol-induced cytotoxicity. Only hesperidin at a concentration of 12.5 µM showed a mild but statistically significant ($p < 0.05$) protective effect. Curcumin at a concentration of 50 µM exacerbated the toxic effect of ethanol on the cells ($p < 0.01$).

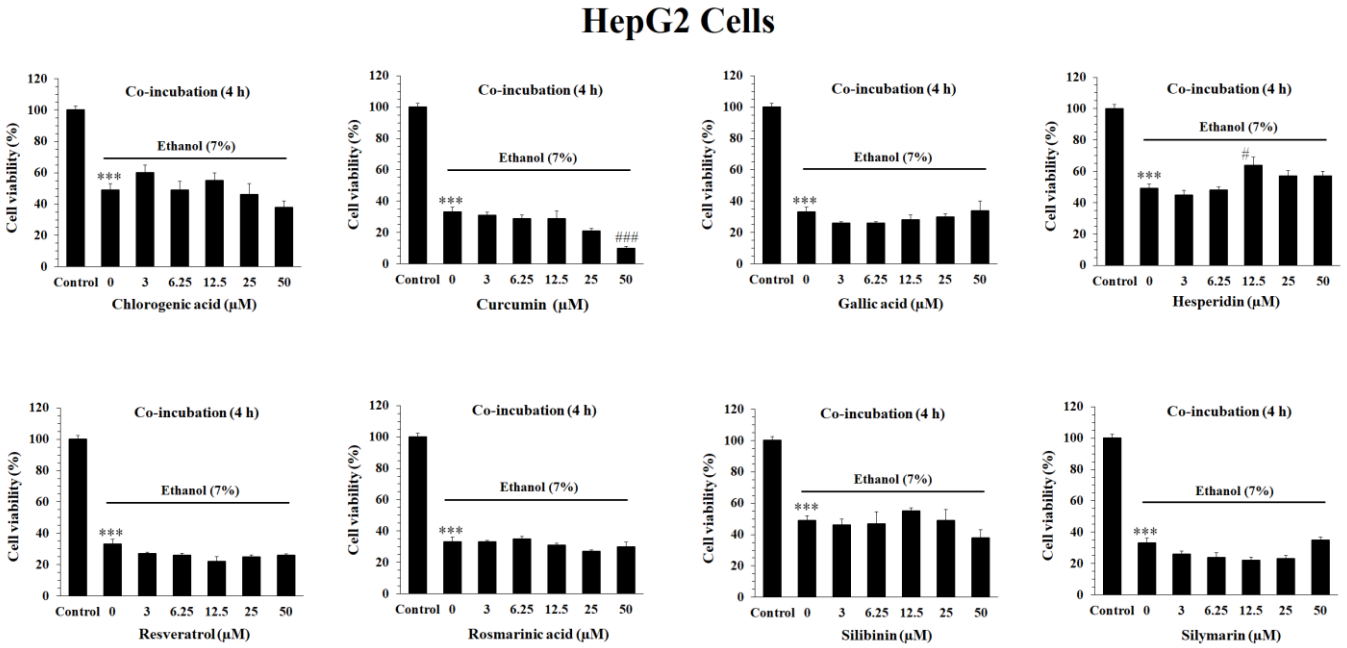

Figure 4. Effects of incubation with phenolic compounds on ethanol-induced cytotoxicity in HepG2 cells. The cells were incubated with the compounds for 4 h in the presence of ethanol (7%, v/v). Data are presented as SEM (n = 5). ***: $p < 0.001$ *vs* control, #: $p < 0.05$, ###: $p < 0.001$ *vs* concentration of 0 µM of the phenolic compound

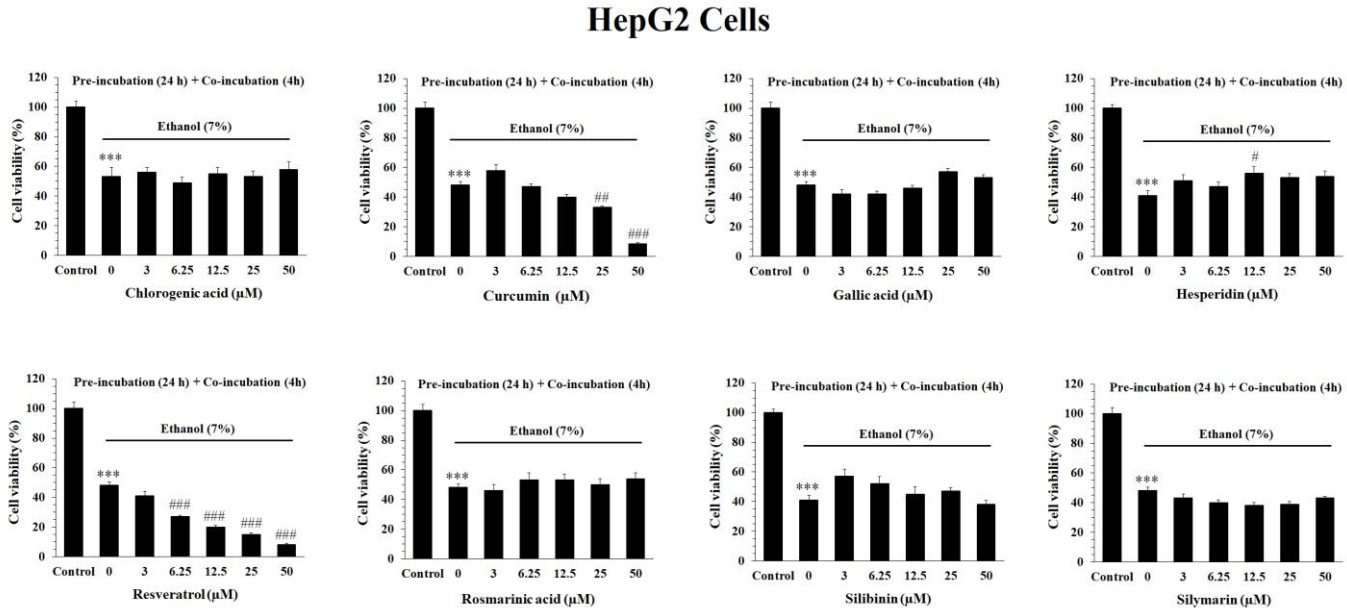

Figure 5. Effects of pre-incubation with phenolic compounds on ethanol-induced cytotoxicity in HepG2 cells. The cells were first pre-incubated with the compounds for 24 h in the absence of ethanol and then incubated for 4 h with both ethanol (7%, v/v) and the phenolic compound. Data are presented as SEM (n = 5). ***: $p < 0.001$ *vs* control, #: $p < 0.05$, ##: $p < 0.01$, ###: $p < 0.001$ *vs* concentration of 0 µM of the phenolic compound

To test whether pre-incubation with phenolic compounds can inhibit ethanol-induced cytotoxicity, the cells were first pre-incubated for 24 hours with these compounds in the absence of ethanol and then incubated with them for 4 hours in the presence of 7% ethanol. As shown in Figure 5, only hesperidin at a concentration of 12.5 µM showed a protective effect ($p < 0.05$). Chlorogenic acid, gallic acid, rosmarinic acid, silibinin, and silymarin did not induce any significant protective activity. Curcumin and resveratrol exacerbated the toxic effect of ethanol at concentrations of ≥ 25 µM and ≥ 6.25 µM, respectively.

Effects of Phenolic Compounds on Primary Rat Liver-Derived Cells

Co-incubation with concentrations of 6.25-50 µM of chlorogenic acid, hesperidin, resveratrol, rosmarinic acid, silibinin, or silymarin had no significant effect on ethanol-induced cytotoxicity (Fig. 6). Similarly, curcumin and gallic acid showed no significant protective effect, with even a concentration of 50 µM exacerbating the toxic effect of ethanol ($p < 0.05$).

To test whether combinations of phenolic compounds can inhibit ethanol-induced cytotoxicity, the primary liver-derived cells were co-incubated with different combinations of these compounds. An exploratory combination experiment was performed using curcumin, silibinin, and resveratrol. These compounds were selected for exploratory testing rather than to evaluate a predefined molecular interaction. As shown in Figures 7A-C, they showed no cytotoxicity at concentrations of ≤ 50 µM. For the combination assay, a concentration of 12.5 µM was selected to ensure the absence of cytotoxicity. None of the tested phenolic mixtures showed evidence of improved protection against ethanol-induced cytotoxicity after the 4-hour co-incubation period (Fig. 7D). Additionally, a second exploratory combination comprising chlorogenic acid, hesperidin, rosmarinic acid, and silymarin was evaluated at a 6 h co-incubation period, with no positive findings (Fig. 8).

Discussion

Excessive intake of alcohol is one of the main contributors to liver injury (2). The decrease in the viability of hepatocytes due to oxidative stress provoked by ethanol-related metabolites (e.g., acetaldehyde) is at the core of the pathophysiology of alcoholic liver disease (3, 4). Phenolic compounds found in plants have potent antioxidant and anti-inflammatory properties (15, 16). Therefore, the goal of this study was to investigate both the individual and combined effects of these compounds on liver cells exposed to alcohol in cell culture conditions.

As expected, ethanol led to a significant reduction in the viability of HepG2 cells and primary liver cells. Pre-incubation and co-incubation with chlorogenic acid, curcumin, gallic acid, resveratrol, rosmarinic acid, silibinin, or silymarin did not restore cell viability. Only hesperidin at 12.5 µM showed a mild but statistically significant protective effect in HepG2 cells. Since HepG2 cells possess cancerous characteristics, we repeated the experiments on primary rat liver-derived cells, which are normal cells. The results obtained from these cells were almost similar to those from HepG2 cells.

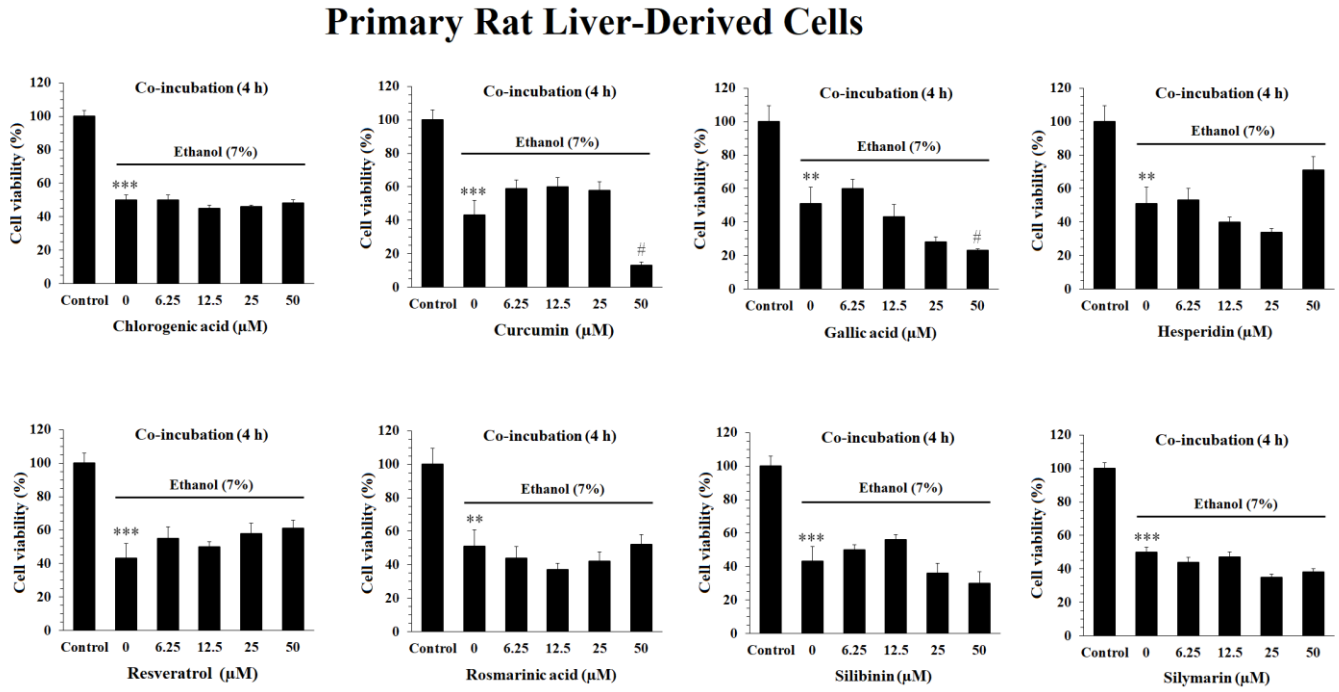

Figure 6. Effects of incubation with phenolic compounds on ethanol-induced cytotoxicity in primary rat liver-derived cells. The cells were incubated with the compounds for 4 h in the presence of ethanol (7%, v/v). Data are presented as SEM ($n = 5$). **: $p < 0.01$, ***: $p < 0.001$ *vs* control, #: $p < 0.01$ *vs* concentration of 0 µM of the phenolic compound

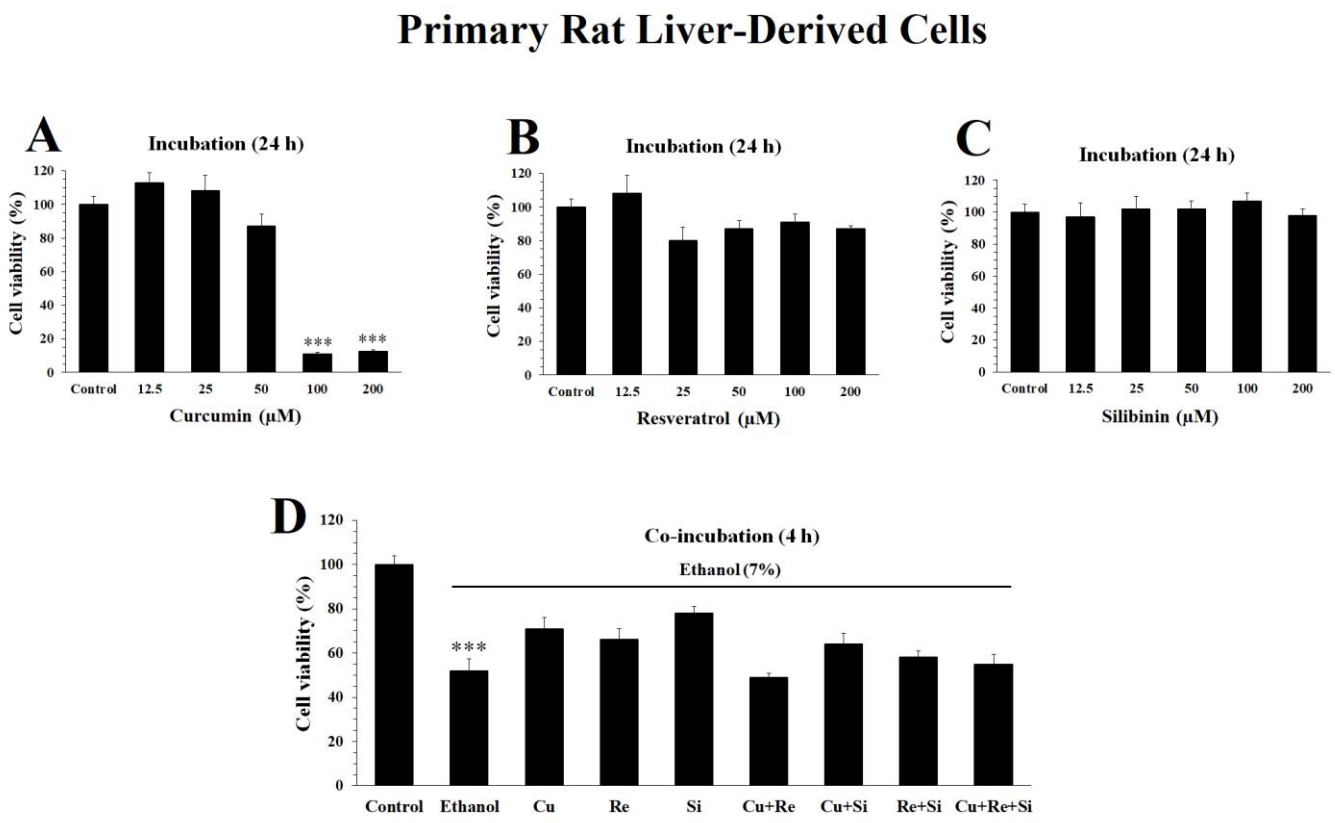

Figure 7. Effects of a mixture of three phenolic compounds on the viability of primary rat liver-derived cells. A-C: Effects of 24 h incubation with curcumin (Cu), resveratrol (Re), and silibinin (Se) on cell viability. D: Effects of 4 h incubation with mixtures of the phenolic compounds on ethanol (7%, v/v)-induced cell death. Data are presented as SEM (n = 5). ***: $p < 0.001$ *vs* control

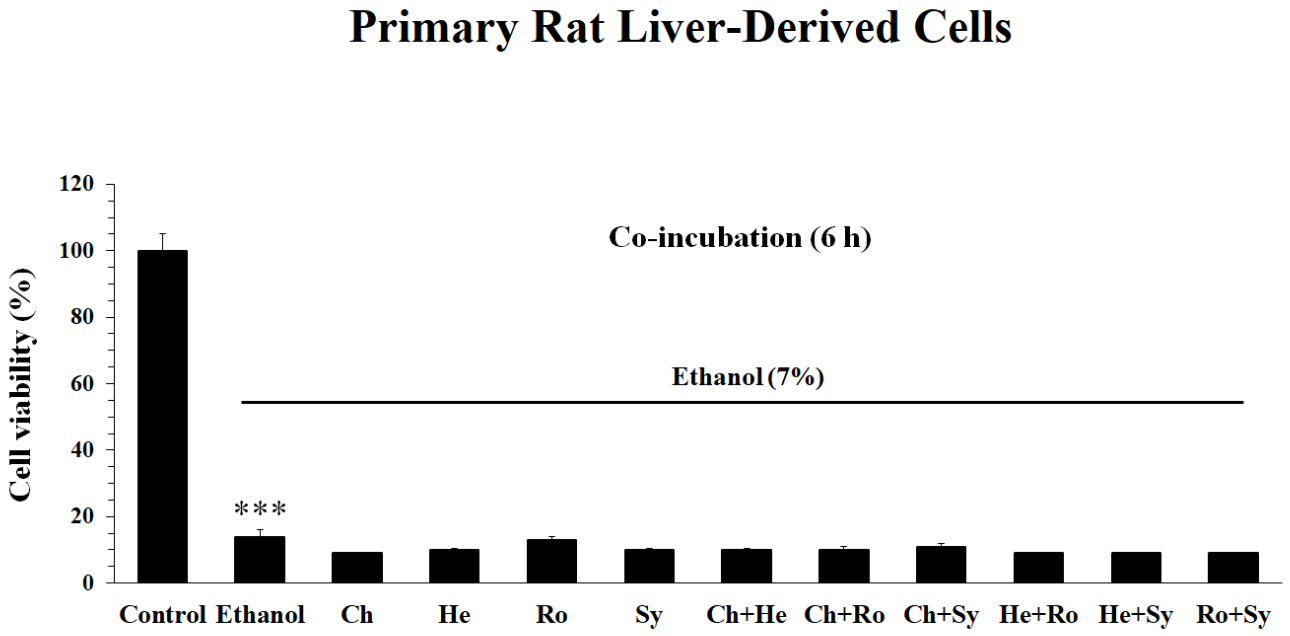

Figure 8. Effects of a mixture of four phenolic compounds on the viability of primary rat liver-derived cells. The cells were incubated with mixtures of chlorogenic acid (Ch), hesperidin (He), rosmarinic acid (Ro), and silymarin (Sy) for 4 h in the presence of ethanol (7%, v/v). Data are presented as SEM (n = 5). ***: $p < 0.001$

Binary combinations of curcumin, silibinin, and resveratrol did not induce additive or synergistic protective activities against ethanol. Additionally, combinations of chlorogenic acid, hesperidin, rosmarinic acid, and silymarin failed to induce such activities. Consequently, under our study conditions, the tested phenolic compounds did not show significant hepatoprotective activity. This contrasts with published studies that reported beneficial effects of these compounds on liver disorders (17-20). For example, the hepatoprotective effects of silymarin, the active component of the plant *Silybum marianum*, have been widely studied concerning several models of liver disorders, including alcohol-induced hepatotoxicity (17). In another study, it has been shown that gallic acid down-regulated the expression of pro-inflammatory cytokines and up-regulated antioxidant gene expression in a rat model of CCl_4-induced hepatic damage (18). Kim et al. observed that chlorogenic acid reduced alcohol-induced steatosis, apoptosis, and fibrosis via inhibiting oxidative stress (19). Wang et al. reported that a combination of curcumin and baicalin (a flavone glycoside) ameliorated alcohol-induced oxidative stress in rat liver through the nuclear factor erythroid 2-related factor (Nrf2)/Hemoxygenase 1 (HO-1) pathway (20). The causes of controversy between these reports and our results may include differences in experimental conditions such as concentrations of the compounds, concentration of ethanol, duration of incubation, endpoints measured, laboratory conditions, cells studied, and other factors.

In our work, the concentrations of phenolic compounds for protection against alcohol were selected based on a preliminary study of their cytotoxicity. As shown in Figure 3, we first examined the effects of these compounds on the cells in the absence of alcohol. The results indicated that some of these compounds were cytotoxic at concentrations exceeding 50 µM; therefore, concentrations of ≤ 50 µM were used for the remainder of the study. There are published studies that support this level of concentration. For example, Bao et al. and Liu et al. investigated the effects of curcumin and resveratrol on ethanol-induced cytotoxicity at concentrations similar to those we used (21, 22).

Numerous studies incubate HepG2 cells with ethanol and use this as a model of liver injury. These studies have employed varying ethanol concentrations and incubation durations (23-25). Given the wide variation in ethanol concentration and its toxicity across published studies, we established an optimal concentration (7%) and exposure duration (4 h) in a preliminary study. However, one of the limitations of our study is that, due to the use of a high ethanol concentration and a short incubation period, we employed only an acute toxicity model. This short period may not capture delayed oxidative, transcriptional, apoptotic, or adaptive responses. Therefore, our results regarding the effects of plant phenolic compounds on ethanol-induced hepatocyte injury apply only to the acute phase. Another limitation is that no reference hepatoprotective agent (e.g., N-acetylcysteine) was included in our study. Furthermore, viability was the primary variable examined, and potential effects on oxidative stress, apoptosis, or other molecular pathways were not directly assessed. Therefore, our study cannot rule out hepatoprotective effects that might be identified using different models or mechanistic outcome markers.

Taken together, the phenolic compounds tested did not exhibit significant cytoprotective effects in the model of ethanol-induced acute toxicity used in the present study. Conducting further research using different study designs—such as chronic toxicity models or lower ethanol concentrations—might yield different results.

Acknowledgment

The data in this article are derived from the MD thesis of one of the authors.

Ethical Considerations

This study was approved by the Research Ethics Committee of Mashhad University of Medical Sciences (Ethics code: IR.MUMS.MEDICAL.REC.1404.209).

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Authors' Contributions

AG proposed the idea of the study, supervised the work, analyzed the data, and wrote the initial draft of the manuscript. HG conducted cell culture and treatment, performed a cell viability

assay, and participated in data analysis. NM contributed to cell culture. FS and LM contributed to the cell viability assay. BRZ, FG, and AH participated in designing the study, advising the experiments, discussing the results, and revising the draft of the manuscript. All authors approved the manuscript and give their consent for publication.

Conflict of interests

The authors affirm that there are no conflicts of interest to disclose.

Data availability

Data will be made available on request from the corresponding author.

Artificial intelligence (AI)-assisted technology

We acknowledge the use of Gemini to revamp the main text of the manuscript.

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