

# Taraxerol protects the human hepatic L02 cells from hydrogen peroxide-induced apoptosis

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## Article Info

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## Abstract

Taraxerol is known to exhibit anti-inflammatory and anti-cancer activity. However, cytoprotective effect of taraxerol on hepatocytes has not been reported. In the present study, we investigated the hepatoprotective effect of taraxerol in the human hepatic L02 cells injured by hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). Taraxerol decreased H<sub>2</sub>O<sub>2</sub>-induced cell viability loss and lactate dehydrogenase release. Taraxerol also inhibited H<sub>2</sub>O<sub>2</sub>-induced cell apoptosis. Further, taraxerol attenuated H<sub>2</sub>O<sub>2</sub>-induced increase in cleaved-caspase-3 and cleaved-PARP. H<sub>2</sub>O<sub>2</sub>-activated p38 and JNK were also inhibited by taraxerol. These data suggest that taraxerol could protect the L02 cells against H<sub>2</sub>O<sub>2</sub>-induced apoptosis via suppression of p38 and JNK. Taraxerol may be an effective protective agent against oxidative stress-induced liver injury.

## Introduction

Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) is an important member of the reactive oxygen species (ROS) family of molecules that have been investigated in recent years (Brewer et al., 2015). Low levels of H<sub>2</sub>O<sub>2</sub> are required for many biochemical processes, such as cell differentiation, immunity, antimicrobial infection (Veal and Day, 2011). However, excessive increase of H<sub>2</sub>O<sub>2</sub> can lead to mitochondrial damage, lipid peroxidation, cytokine release, and cell death, which are involved in cancers, diabetes, rheumatism and various neurological disorders (Gough and Cotter, 2011). Liver damage is often accompanied by apoptosis of liver cells (Guicciardi and Gores, 2010). Therefore, anti-oxidants may reverse oxidative stress-induced cell death in liver cells.

Taraxerol is a triterpenoid isolated from many medicinal plants including *Mangifera indica*, *Taraxacum japonicum*, *Achillea millefolium* and *Acrocarpus andfraxinifolius* (Sharma and Zafar, 2015). Taraxerol is also known to exhibit anti-inflammatory and anti-cancer activity (Tsao et al., 2008; Takasaki et al., 1999; Setzer et al., 2000; Jang et al., 2004). We have also reported that taraxerol significantly inhibited LPS-

induced production of pro-inflammatory mediators by preventing the activation of TAK1, Akt and NF-κB (Yao et al., 2013). Taraxerol has an antidiabetic effect. It can be used as a PI3K dependent dual activator of glucose transport and glycogen synthesis and effectively restored dexamethasone-induced desensitization via restoration of PI3K and GLUT4 expression (Sangeetha et al., 2013; Sangeetha et al., 2010). However, cytoprotective effect and its mechanism of taraxerol on hepatocytes are unclear. In this study, we assessed taraxerol on H<sub>2</sub>O<sub>2</sub>-induced apoptotic effect in L02 cells, and determined the activation of caspases-3, PARP, Bcl-2, Bax and MAPK.

## Materials and Methods

### Chemicals

Taraxerol (99% purity analyzed by HPLC), 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma Chemical Co. (USA). Lactate dehydrogenase (LDH) assay kit was obtained from Nanjing Jiancheng Bioengineering Institute (China). The antibodies to Bcl-2, Bax, cleaved-



caspase-3, PARP and polyclonal antibodies to p38, JNK/SAPK, and phospho-specific antibodies against JNK (Thr183/Tyr185), p38, U0126, SB203580, SP600125 were purchased from Cell Signaling Technology (USA). GAPDH antibody was from Bioworld Biotechnology (China).

#### Cell culture and cell treatment

The normal human hepatic cell strain, L02 obtained from Institute of Biochemistry and Cell Biology, the Chinese Academy of Sciences (China), was cultured in Dulbecco's modified Eagle's medium (DMEM) (Hyclone) supplemented with 10% fetal bovine serum (FBS) (Hyclone), 100 U/mL penicillin, and 100 µg/mL streptomycin at 37°C in a 5% CO<sub>2</sub> humidified environment. Taraxerol was dissolved in DMSO to make a stock of 100 mM and further diluted to final concentrations of 20-200 µM with a serum-free culture medium.

#### Cell viability and LDH assay

L02 cells were seeded into 96-well plates (10<sup>5</sup> cells/well) for 12 hours, followed by treatment with various concentrations of H<sub>2</sub>O<sub>2</sub> or taraxerol. Cell viability was determined using MTT assay. The absorbance was measured at 570 nm. The LDH levels in the medium were measured with the use of commercial kits according to the manufacturer's protocols after each treatment. The absorbance at 420 nm was recorded for the calculation of LDH activity under Mutiskan Go (Thermo, INC).

#### Flow cytometric analysis

The extent of apoptosis was measured through annexin V-FITC/PI apoptosis detection kit (Nanjing Keygen Biotech, KGA108) according to the manufacturer's instruction. Cells were washed twice with PBS, gently resuspended in binding buffer and incubated with annexin-V-FITC and PI in the dark for 10 min and detected by flow cytometry (BD Accuri C6). The data

were analyzed using BD Accuri C6 Software.

#### Western blot analysis

Cells were rinsed twice with ice-cold PBS, and lysed with the RIPA lysis buffer for 30 min on ice. Lysates were centrifuged (12,000 × g) at 4°C for 15 min. Total cell lysates were separated by SDS-PAGE and transferred to nitrocellulose membranes or polyvinylidene difluoride membranes. Membranes were blocked for 60 min at room temperature. Membranes were probed with specific primary antibodies overnight at 4°C and subse-quentially incubated with IRDye 800CW secondary antibodies for 1 hour. Membranes were visualized using Odyssey Infrared Imaging Scanner. The fluorescence intensities were analyzed using Image Studio Software (Li-Cor Biosciences) or membranes were incubated with horseradish peroxidase-conjugated secondary antibodies. Band quantifications were performed by ChemiScope 3400 chemiluminescence imaging systems (Clinx Science Instruments, China).

#### Statistical analysis

Results were expressed as mean ± SD from replicate experiments. Statistical analysis was carried out using an unpaired, two-tailed Student's t-test. Significance was defined as p<0.05 or 0.01.

## Results

#### Effect on the cell viability

The effect of H<sub>2</sub>O<sub>2</sub> and taraxerol on the viability of L02 cells was evaluated by the MTT assay. Consistent with our previous report, H<sub>2</sub>O<sub>2</sub> significantly inhibited L02 cell viability (Figure 1A) (Li et al., 2011). However, as shown in Figure 1B, taraxerol alone did not significantly affect the cell viability of L02 cells even at the dose of 200 µM.

#### Effect on H<sub>2</sub>O<sub>2</sub>-induced cell viability and LDH leakage

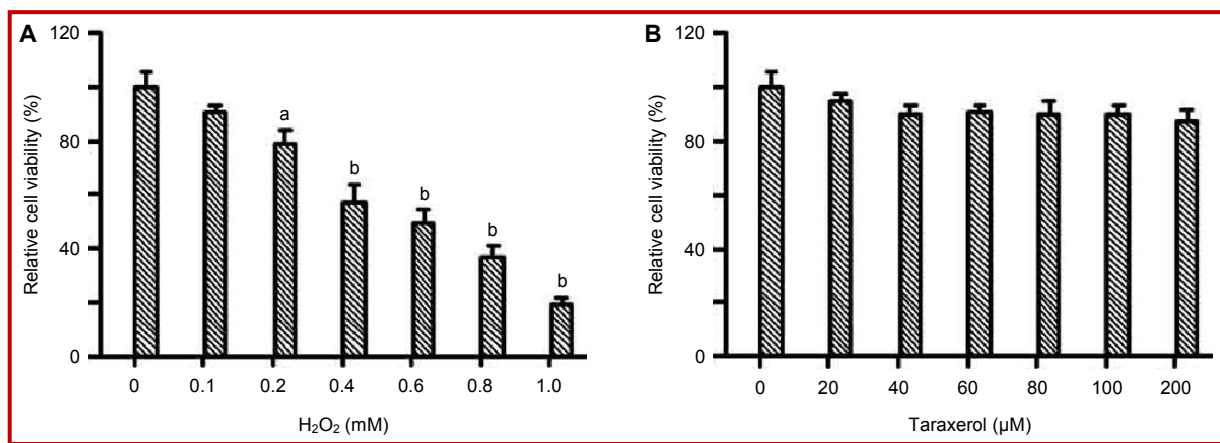


Figure 1: Effects of H<sub>2</sub>O<sub>2</sub> and taraxerol on the cell viability of L02 cells. L02 cells were treated with various concentrations of H<sub>2</sub>O<sub>2</sub> or taraxerol for 12 hours, then measured by MTT analysis. A) Effect of H<sub>2</sub>O<sub>2</sub> on the cell viability of L02 cells. B) Effect of taraxerol on the cell viability of L02 cells. Data are expressed as mean ± SD (n = 6). <sup>a</sup>p<0.05, <sup>b</sup>p<0.01 compared with control

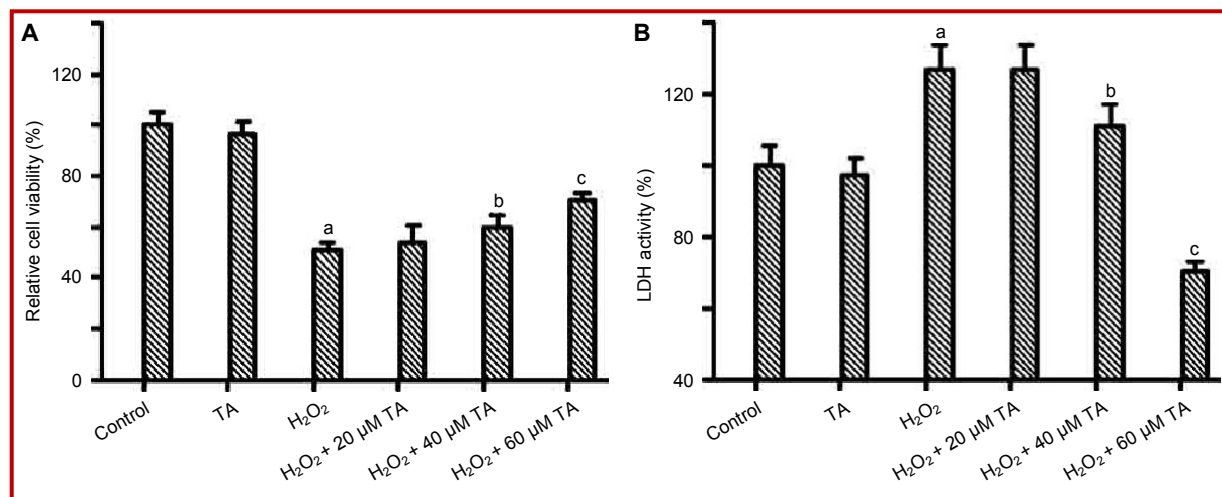


Figure 2: Taraxerol protects L02 cells against H<sub>2</sub>O<sub>2</sub>-induced cell injury. L02 cells were pretreated with or without 40 μM taraxerol for 1 hour, followed by 0.4 mM H<sub>2</sub>O<sub>2</sub> treatment for 12 hours. A) Cell viability was measured by MTT analysis, B) LDH release was measured. TA: taraxerol. Data are expressed as mean ± SD (n = 6); <sup>a</sup>p<0.01 compared with control; <sup>b</sup>p<0.05, <sup>c</sup>p<0.01 compared with the group of H<sub>2</sub>O<sub>2</sub>-treated L02 cells alone

To explore the effect of taraxerol on H<sub>2</sub>O<sub>2</sub>-induced cell viability loss, L02 cells were pretreated with taraxerol at different concentrations for 1 hour, followed by 0.4 mM H<sub>2</sub>O<sub>2</sub> treatment for 12 hours. As shown in Figure 2A, H<sub>2</sub>O<sub>2</sub>-induced loss of cell viability was significantly decreased by taraxerol in a dose-dependent manner. LDH leakage which was frequently used to evaluate the degree of cellular injury was assayed. H<sub>2</sub>O<sub>2</sub> stimulation significantly increased LDH leakage in L02 cells (Figure 2B). Taraxerol prevented H<sub>2</sub>O<sub>2</sub>-induced LDH release.

#### H<sub>2</sub>O<sub>2</sub>-induced apoptosis

We further investigated apoptosis of cells by annexin-V/PI double staining. After being incubated with 40 μM taraxerol for 24 hours, H<sub>2</sub>O<sub>2</sub> could significantly increase in the early and late stages of apoptotic cells (12.1, 40.1%) compared with the control group (1.2, 4.3%) indicating that cells were significantly damaged, while cells treated with taraxerol and H<sub>2</sub>O<sub>2</sub> were significantly lower in the early and late stages of apoptotic cells (4.3, 22.4%) than those in the H<sub>2</sub>O<sub>2</sub>-stimulated group (Figure 3). These results demonstrated that taraxerol protected H<sub>2</sub>O<sub>2</sub>-induced apoptosis in L02 cells.

#### Cleavage of caspase-3 and PARP in H<sub>2</sub>O<sub>2</sub>-injured cells

We examined the expression of cleaved-caspase-3 and PARP. The results showed that the protein of cleaved-caspase-3 and cleaved-PARP were up-regulated in H<sub>2</sub>O<sub>2</sub>-treated L02 cells, showing that the cells were undergoing apoptosis. However, pretreatment with taraxerol inhibited the increase in the two proteins induced by H<sub>2</sub>O<sub>2</sub> (Figure 4). These data are in agreement with the results of annexin-V/PI double staining.

#### Effects on H<sub>2</sub>O<sub>2</sub>-induced Bcl-2 and Bax

As shown in Figure 5, Bcl-2 protein expression was down-regulated while Bax was up-regulation in H<sub>2</sub>O<sub>2</sub>-treated L02 cells. In contrast, taraxerol could inhibit the expression of Bax induced by H<sub>2</sub>O<sub>2</sub>, and increased the expression of Bcl-2. Thus, Bax/Bcl-2 ratio was significantly lower than in H<sub>2</sub>O<sub>2</sub>-treated L02 cells alone.

#### H<sub>2</sub>O<sub>2</sub>-induced activation of p38 and JNK

In our previous study, taraxerol markedly repressed LPS-induced p38, ERK and JNK phosphorylation in RAW264.7 cells (Yao et al., 2013). To verify that MAPKs are involved in the apoptosis, cells were pretreated with 30 μM inhibitors (U0126, an ERK inhibitor; SB203580, a p38 inhibitor or SP600125, a JNK inhibitor) for 1 hour, followed by addition of H<sub>2</sub>O<sub>2</sub>. As shown in Figure 6A, increase in cleaved-caspase-3 and cleaved-PARP were prevented by SB203580 and SP600125, while they were no significant change in the U0126-pretreated cells when compared with H<sub>2</sub>O<sub>2</sub>-treated cells alone, indicating that p38 and JNK are involved in H<sub>2</sub>O<sub>2</sub>-induced cell apoptosis in L02 cells.

We further explored whether taraxerol affected the activation of p38 and JNK induced by H<sub>2</sub>O<sub>2</sub>. Cells were treated with H<sub>2</sub>O<sub>2</sub>, JNK and p38 activation increased, while cells were pretreated with taraxerol and H<sub>2</sub>O<sub>2</sub>, p38 and JNK activation reduced in L02 cells compared with the H<sub>2</sub>O<sub>2</sub>-treated group (Figure 6B).

## Discussion

In the present study, we showed that taraxerol dose-dependently decreased H<sub>2</sub>O<sub>2</sub>-induced cell viability loss and lactate dehydrogenase (LDH) release. Taraxerol inhibited H<sub>2</sub>O<sub>2</sub>-induced cell apoptosis. Further, taraxerol attenuated H<sub>2</sub>O<sub>2</sub>-induced increase in cleaved-caspase-3 and cleaved-PARP. H<sub>2</sub>O<sub>2</sub>-activated p38 and

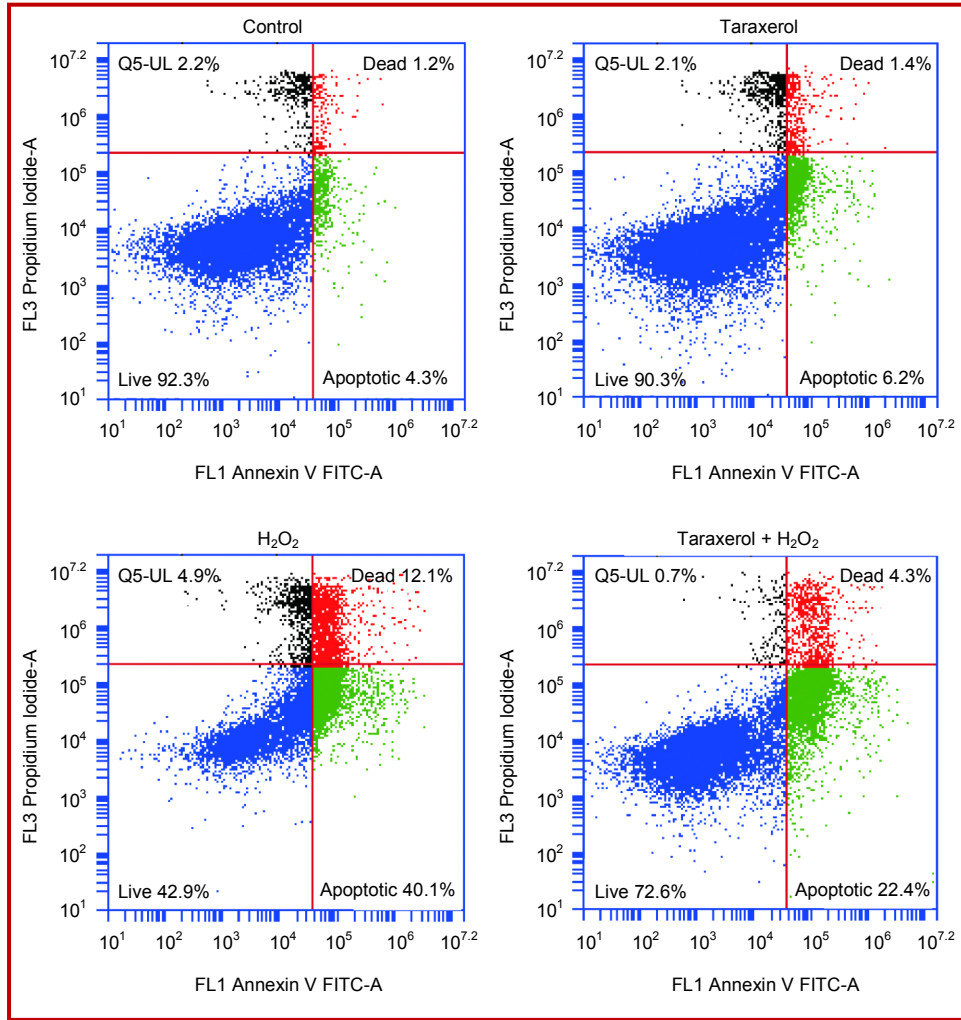


Figure 3: Taraxerol protects L02 cells from H<sub>2</sub>O<sub>2</sub>-induced apoptosis. After treated with taraxerol or H<sub>2</sub>O<sub>2</sub> for 12 hours, L02 cells were dyed with both of annexin-V/FITC and propidine iodide (PI). Flow cytometric analysis was performed with BD Accuri C6 Software

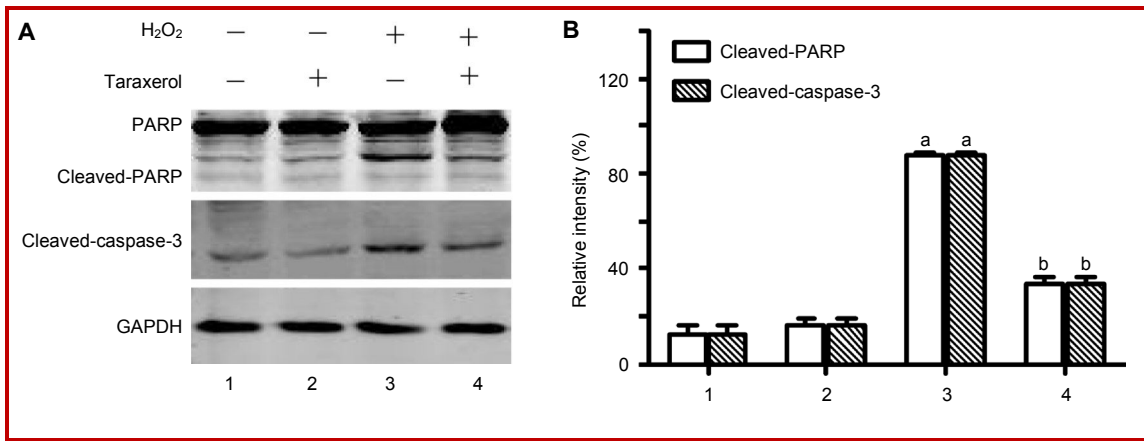


Figure 4: Taraxerol attenuates H<sub>2</sub>O<sub>2</sub>-induced reduction in cleaved-caspase-3 and cleavage of PARP. L02 cells were pretreated with or without 40 μM taraxerol for 1 hour, followed by 0.4 mM H<sub>2</sub>O<sub>2</sub> treatment for 12 hours. A) Then, the expression of cleaved-caspase-3 and PARP was tested by Western blot. GAPDH was used to confirm that equal cell equivalents were loaded. B) Relative intensity of cleaved-caspase-3 and cleaved-PARP in Figure 4A. Data are expressed as mean ± SD (n = 3); <sup>a</sup>p<0.01 compared with control; <sup>b</sup>p<0.01 compared with the group of H<sub>2</sub>O<sub>2</sub>-treated L02 cells alone

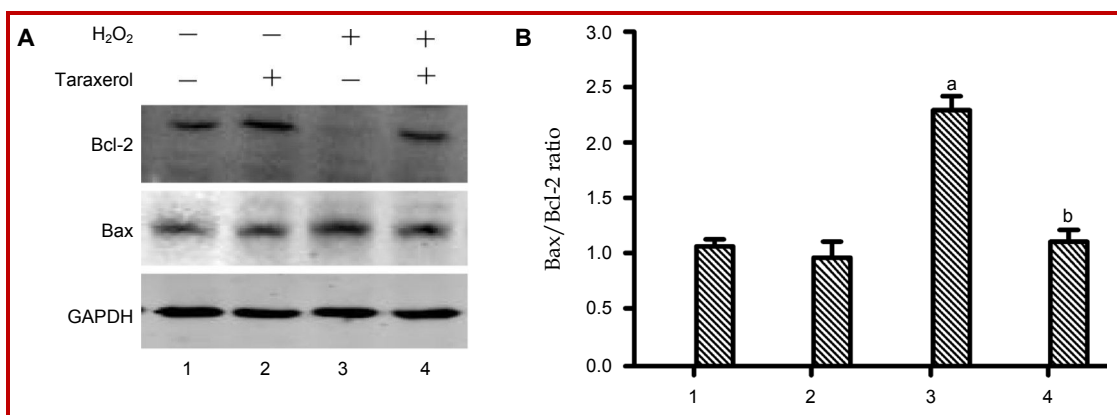


Figure 5: Effects of taraxerol on H<sub>2</sub>O<sub>2</sub>-induced Bcl-2 and Bax. L02 cells were treated with taraxerol or H<sub>2</sub>O<sub>2</sub> for 12 hours, A) Bcl-2 and Bax were tested by Western blotting. GAPDH was used to confirm that equal cell equivalents were loaded. B) The graph shows the ratio of Bax/Bcl-2 in Figure 5A. Data represent the mean ± SD (n = 3); <sup>a</sup>p<0.01 compared with control; <sup>b</sup>p<0.01 compared with the group of H<sub>2</sub>O<sub>2</sub>-treated L02 cells alone

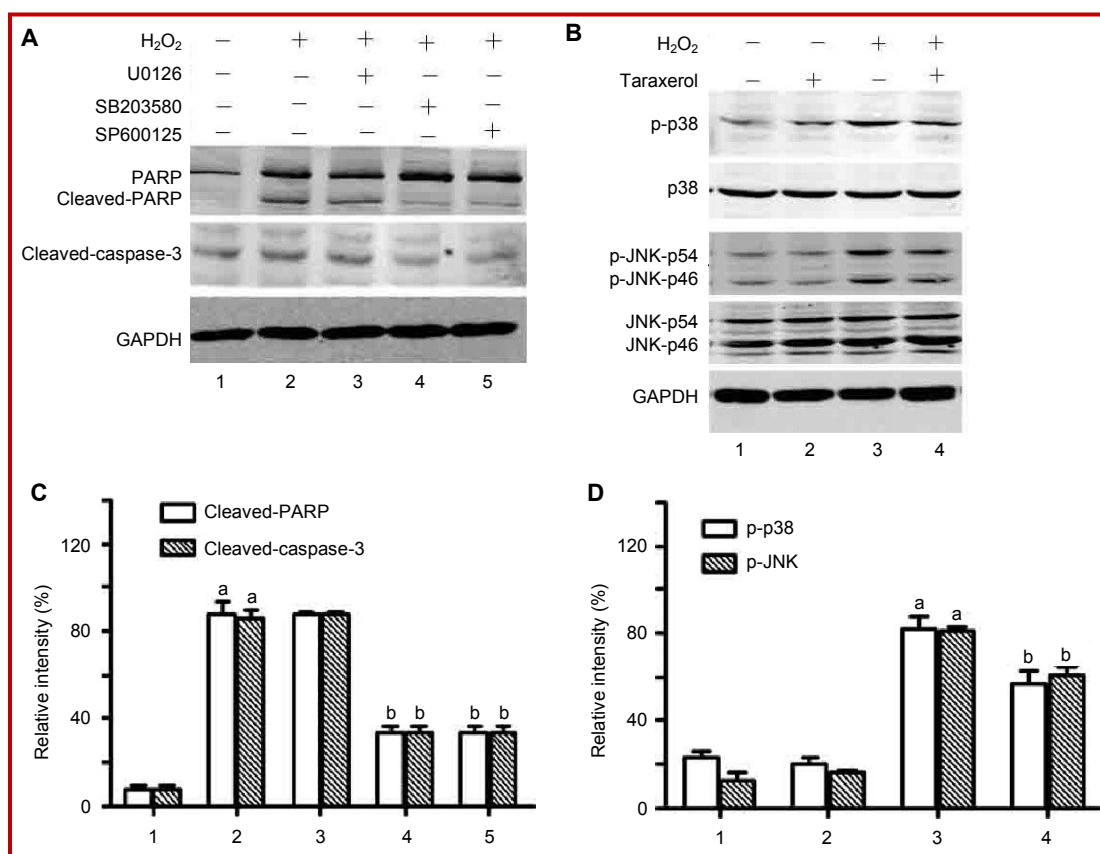


Figure 6: Taraxerol inhibits H<sub>2</sub>O<sub>2</sub>-induced p38 and JNK activation. A) L02 cells were pretreated with 30 μM U0126, SB203580, or SP600125 for 1 hour, followed by 0.4 mM H<sub>2</sub>O<sub>2</sub> for 12 hours. The cell lysates were detected by antibodies of cleaved-caspase-3, and PARP. GAPDH was used to confirm that equal cell equivalents were loaded. B) L02 cells were pretreated with or without 40 μM taraxerol for 1 hour and then exposed to 0.4 mM H<sub>2</sub>O<sub>2</sub> for 30 min. The cell lysates were detected by antibodies of p38, phospho-p38 (Thr180/Tyr182), JNK/SAPK, and phospho-JNK/SAPK (Thr183/Tyr185). P38 and JNK were used for normalization. GAPDH was used to confirm that equal cell equivalents were loaded. C) Relative intensity of cleaved-caspase-3 and cleaved-PARP in Figure 6A. D) Relative intensity of phospho-p38 and phospho-JNK/SAPK in Figure 6B. Data are expressed as mean ± SD (n = 3). <sup>a</sup>p<0.01 compared with control; <sup>b</sup>p<0.01 compared with the group of H<sub>2</sub>O<sub>2</sub>-treated L02 cells alone

JNK were also inhibited by taraxerol. These data suggest that taraxerol could protect L02 cells against H<sub>2</sub>O<sub>2</sub>-induced apoptosis via suppression of p38 and JNK. Taraxerol might potentially be useful in the prevention and treatment of liver diseases.

Bax/Bcl-2 ratio plays an important role in cell apoptosis (Cory and Adams, 2005). Some studies have shown that H<sub>2</sub>O<sub>2</sub>-induced apoptosis is usually related to the ratio of Bax/Bcl-2 (Liu et al., 2013; Huang et al., 2015). In this study, we found that taraxerol significantly inhibited the expression of Bax and promotion of Bcl-2 in L02 cells after H<sub>2</sub>O<sub>2</sub> stimulation, indicating that taraxerol inhibited H<sub>2</sub>O<sub>2</sub>-induced apoptosis which is associated with decreasing the ratio of Bax/Bcl-2.

It is well known that increased ROS production leads to the activation of ERK, JNK, or p38 (McCubrey et al., 2006). ERK signaling promotes cell survival under mild oxidative stress, whereas JNK and p38 can induce apoptosis by involving direct phosphorylation of pro/anti-apoptotic Bcl-2 family members, transactivation of transcription factor AP-1, and stabilization of p53 (Groeger et al., 2009). We showed taraxerol protects L02 cells from H<sub>2</sub>O<sub>2</sub>-induced apoptosis by inhibiting JNK and p38. Our previous study demonstrated that L-theanine could protect L02 cells against H<sub>2</sub>O<sub>2</sub>-induced apoptosis via suppression of p38 (Li et al., 2011). However, propofol protects hepatic L02 cells from H<sub>2</sub>O<sub>2</sub>-induced apoptosis via activation of ERK pathway (Wang et al., 2008). These data support the view that the MAPK pathway in H<sub>2</sub>O<sub>2</sub>-induced apoptosis is complex. Fisetin, a dietary flavonoid induces apoptosis via modulating the MAPK and PI3K/Akt signalling pathways in human osteosarcoma cells (Li et al., 2015).

Furthermore, hesperidin augmented cellular antioxidant defense capacity through the induction of HO-1 via ERK/Nrf2 signaling (Chen et al., 2010). Hyperoside attenuates H<sub>2</sub>O<sub>2</sub>-induced L02 cell damage via MAPK (p38 and ERK)-dependent Keap/Nrf2/ARE signaling pathway (Xing et al., 2011). Thus, whether taraxerol-stimulated cytoprotective effect is involved in MAPK-dependent Keap/Nrf2/ARE signaling pathway remains elusive. On the other hand, Mantzaris reported that iron determines H<sub>2</sub>O<sub>2</sub>-induced apoptotic signaling by sustaining the ASK1/JNK-p38 axis (Mantzaris et al., 2016). Further investigation is needed to identify upstream regulatory proteins such as ASK1 in protective mechanism of taraxerol in H<sub>2</sub>O<sub>2</sub>-induced apoptosis.

## Conclusion

Taraxerol protects human hepatic L02 cells from hydrogen peroxide-induced cell injury including promotion of cell viability, the inhibition of apoptosis and LDH release by the activation of caspases-3 and PARP, down-regulation of Bax/Bcl-2 ratio. It inhibits p38 and JNK

signal pathway activated by H<sub>2</sub>O<sub>2</sub>. Taraxerol may be an effectively protective agent against oxidative stress-induced liver injury.

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## Conflict of Interest

All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work.

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