Arbutin abrogates cisplatin-induced hepatotoxicity via upregulating Nrf2/HO-1, and suppressing NF-κB/TNF-α and caspase-3/Bax signaling in rats

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Introduction

Cisplatin (CP) is a potent anticancer agent widely employed in chemotherapy. However, CP exerts non-targeted toxicity on healthy organs, including the liver (Jiang et al, 2023; Famurewa et al, 2020).

CP side effect toxicity is related to activation of oxidative inflammation and apoptotic signaling (El Shaffei et al, 2021; Huang et al, 2021).

Arbutin is a natural compound with antioxidant and anti-inflammatory actions.

Therefore, the study explored whether arbutin could prevent CP-induced liver toxicity.
Methodology

- Arbutin, os
- Cisplatin, ip day 15 only

Rats

Rat feed

Treatment period = 15 days

Sacrifice on day 18

Serum: ALT, AST, ALP
Liver: SOD, CAT, GSH, MDA
Gene expression: TNF-α, IL-1β, IL-6, NF-κB, Nrf2, HO-1, Bax, Bcl2, caspase-3
Results

Fig. 1: Effect of arbutin on liver enzymes in CP-injected rats.*Sig against control group; #Sig against CP group; &Sig against ARB50 + CP group; p < 0.05

Fig. 2: Effect of arbutin on liver oxidative stress markers in CP-injected rats

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Fig. 3: Effect of arbutin on hepatic Nrf2 and HO-1 gene expressions in CP-injected rats.
*Significant against control group; #Significant against CP group; p < 0.05
Fig. 4: Effect of arbutin on NF-κB & cytokines in CP-injected rats. P<0.05

Fig. 5: Effect of arbutin on apoptotic markers in CP-injected rats. P<0.05
Cisplatin (10 mg/kg, ip) 

Oxidative stress 

\[ \text{O}_2^{-} \]

\[ \text{OH}^{-} \]

ALT/AST/ALP 
Liver injury 

MDA↑↓ 
SOD, CAT, GSH↓↑ 

Arbutin 
Stimulates 

Nrf2, HO-1↑↓ 

NF-κB 

Bax 

Bcl-2↓↑ 

Cytochrome C 

Caspase-9/3↑↓ 

Apoptosis induction 

IL-1β, IL-6, TNF-α 

Gene expression 

Pro-inflammatory cytokines 

Nucleus 

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Conclusions

These findings suggest that CP induces liver toxicity via oxidative stress-mediated inflammation and apoptosis.

Arbutin is a potential protective adjuvant against CP-induced hepatotoxicity via inhibition of hepatic oxidative stress, inflammation, and apoptosis.

However, there is an unmet need for clinical studies to verify our findings in this study.


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