Cisplatin induced liver failure via changes in drug-metabolizing enzymes, redox status, apoptotic and inflammatory markers: mitigating role of ginseng

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Introduction

Cisplatin (CIS) is one of the potent cytotoxic antineoplastics extensively used against various types of solid tumors and is approved by the FDA. The clinical application of cisplatin is obstructed due to its resistance and undesirable pathological impact, prominently nephrotoxicity, hepatotoxicity, gastrointestinal toxicity, uterine toxicity, ototoxicity, and neurotoxicity. Cisplatin hazard toxicity on healthy cells is propagated via induction of ROS, pro-inflammatory cytokines, DNA deterioration, caspase activation, mitochondrial dysfunction, and apoptosis. Therefore, banning cisplatin's toxic effects is one of the important issues within the treatment plan (Gholampour, et al., 2022, Dasari, et al., 2022).

Oxidative stress overproduction with the reduction in the antioxidant defense system is implicated in cisplatin-induced mitochondrial toxicity and liver injury (Dasari et al., 2022). Also, ROS accumulation plays a critical role in generating several types of inflammatory molecules that contribute to cisplatin pathogenesis. Moreover, cisplatin upregulates the expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and apoptotic pathway via the activation of the apoptotic markers (caspase, tumor protein 53, Bax) and the suppression of the anti-apoptotic markers as Bcl-2 (Abd Rashid et al., 2021).

Cytochrome P450 (CYP) system plays a critical role in drug disposition and drug-drug interactions (DDIs). DDIs can affect the blood peak of drugs and their pharmacological effects by regulating the metabolizing enzymes. One of the mechanisms by which cisplatin generates ROS is the destruction of the cytochrome P450 system, which leads to excessive production of ROS and oxidative stress (Zhou, et al., 2022).

Ginseng (GIN) is one of the herbal remedies which has numerous bioactive pharmacological properties, such as antitumor, neuroprotective, cardiovascular-protective, hepatoprotection, antivirus, anti-allergic, antiangiogenetic, antiapoptotic, antidiabetic, antioxidant, hepatoprotective, anti-aging and immunoregulatory effects (Zhou, et al., 2020; Ji, et al., 2022).

Hindering liver damage by cisplatin is our goal in this research. Therefore, the current study was designed to assess the therapeutic capability of ginseng as an antioxidant agent against the hepatoxicity induced by the chemotherapeutic agent' cisplatin. We evaluate specific markers that are responsible for liver injury which include: DMEs, oxidative stress, inflammation, apoptosis, histopathology, and immunohistochemistry.

Materials and Methods

1. Drug metabolizing enzymes

Cytochrome P450, cytochrome b5, NADPH- cytochrome C- reductase, amidopyrine N-demethylase, and aniline 4-hydroxylase

2. . Quantitative real-time PCR (qPCR) of DMEs

CYP1A1, CYP2E1, CYP2D6, and CYP3A4 were estimated in the liver

3. Oxidative stress markers

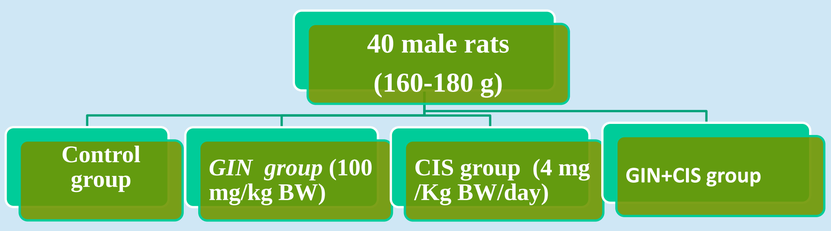
TBARS, NO, SOD, GPX, GST, CAT, GSH, and TAC were measured in liver tissues.

4. Proinflammatory markers & β amyloid by ELISA

The levels of inflammatory molecules (TNF-α, IL-6, TGF-β, NF-κB were evaluated in liver tissues.

5. Apoptosis (Caspase and P53)

5. Histopathological examination and immunohistochemical detection of p53, Bax and Bc1-2



Rats were orally administered their respective doses every day for 90 days.

Results

Table: 1The activities of GST, GPX, CAT, SOD, GR, XO and TAC, and levels of TBARS and GSH in liver tissues of male rats treated with ginseng extract, cisplatin and their combination (means ± SD)

Parameter	Experimental groups			
	Control	Ginseng	Cisplatin	Ginseng + Cisplatin
GST	1.08± 0.032 [a]	1.19 ± 0.039 [a]	0.68 ± 0.034 [c]	0.89 ± 0.033 [b]
GPX	36.7± 1.24 [a]	40.3± 1.34 [a]	25.6± 0.97[b]	31.5± 1.27 [ab]
CAT	70.8 ± 2.77 [a]	77.9 ± 2.42 [a]	36.8 ±1.23 [c]	51.4± 1.23 [b]
SOD	11.61± 0.39[a]	12.80± 0.37[a]	7.34± 0.31[c]	9.83± 0.28[b]
GR	45.1 ± 2.43 [b]	57.3 ± 2.46 [a]	21.6 ± 1.65 [d]	36.3 ± 2.11[c]
XO	32.3 ± 2.12 [c]	25.7 ± 1.67 [d]	49.2 ± 2.88 [a]	41.0 ± 1.92 [b]
TAC	6. 52 ± 0.43b[b]	8.97 ± 0.26[a]	3.81 ± 0.35[d]	4.52 ± 0.34[c]
GSH	5.47 ± 0.16 [a]	5.99 ± 0.15 [a]	2.51±0.09 [b]	4.5± 0.13 [a]
TBARS	21.0± 0.56[c]	19.0±0.63[c]	41.5± 1.88[a]	30.8± 0.98[b]
NO	4.52± 0.16 [c]	3.49± 0.15 [d]	7.67 ± 0.07 [a]	5.48 ± 0.15 [b]

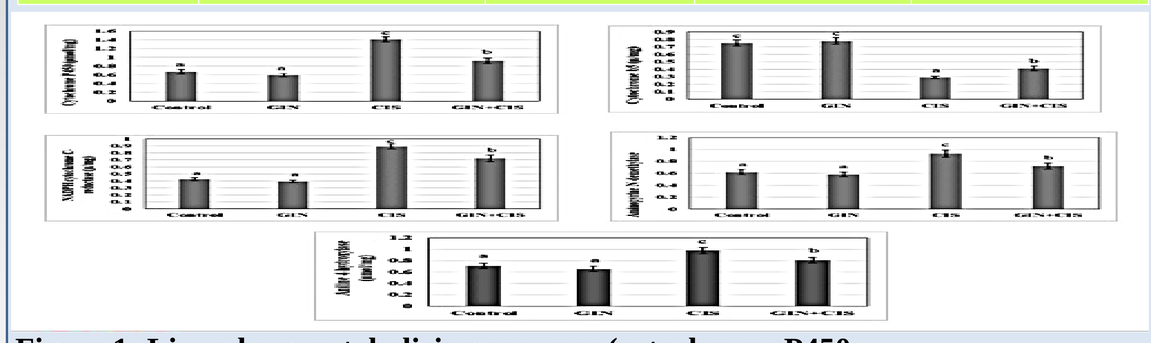


Figure 1: Liver drug metabolizing enzymes (cytochrome P450, nmol cytochrome/mg protein; cytochrome b5, nmol cytochrome/mg protein; NADPH cytochrome C-reductase, □mol cytochrome C reductase/mg protein/min; amidopyrine N-demethylase, □mol/min/mg protein and aniline 4-hydroxylase, □mol/min/mg protein) of male rats treated with ginseng extract, cisplatin and their combination

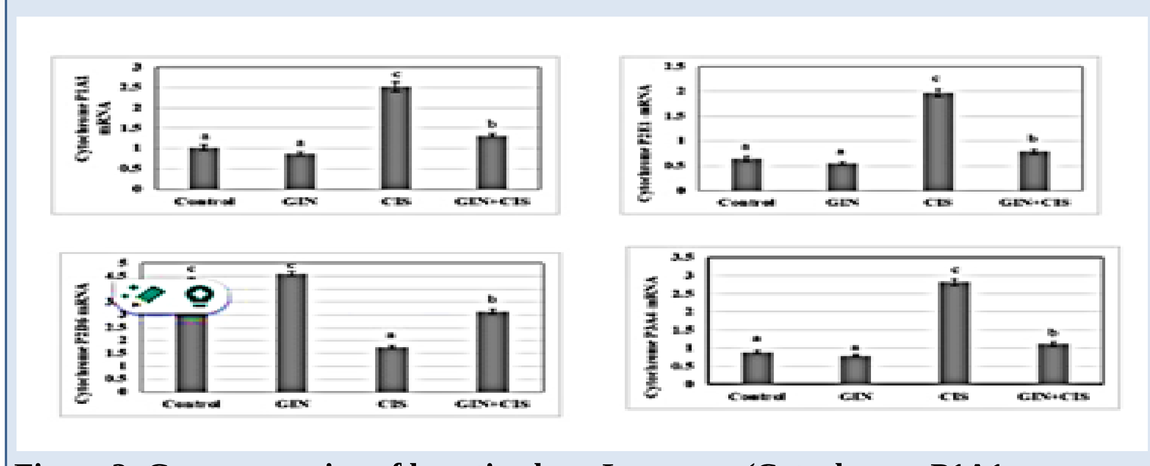


Figure 2: Gene expression of hepatic phase I enzymes (Cytochrome P1A1, Cytochrome P2E1, Cytochrome P2D6 , and Cytochrome P3A4; ng/mg protein) of male rats treated with cisplatin, ginseng, and their combination

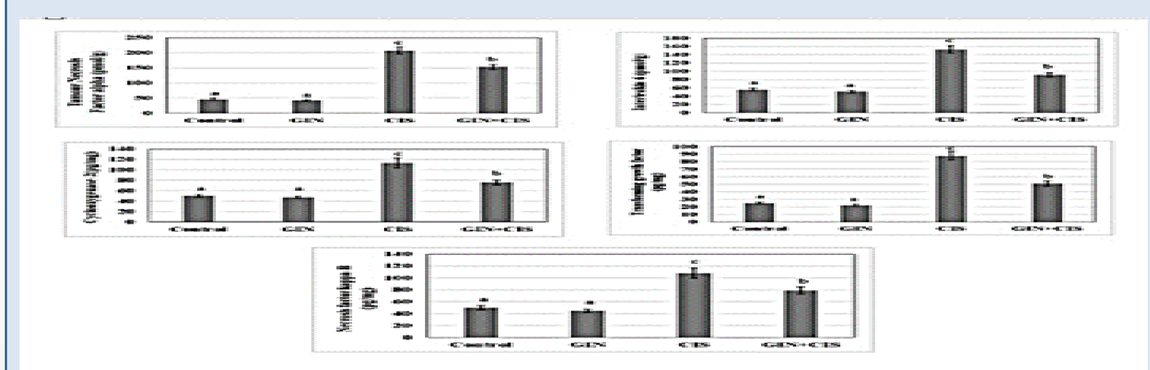


Figure 3: Liver Tumor Necrosis Factor alpha (TNF alpha), Interleukin 6 (IL-6), Cyclooxygenase-2 (COX-2), Transforming Growth Factor (TGF), Necrosis Factor Kappa-B (NF-κB) of male rats treated with ginseng, cisplatin and their combination

Conclusions

The present study concluded that cisplatin causes liver toxicity via changes in liver drug-metabolizing enzymes, disturbance in the activities of hepatic phase I enzymes, increased liver tumor necrosis factor-alpha, interleukin 6, cyclooxygenase-2, transforming growth factor, necrosis factor kappa-B, p53 tumor suppressor protein, and caspase-3, induced oxidative stress, disturbed the activities of liver enzymes, and changes in histological and histochemical picture. Administration of ginseng with cisplatin showed a hepatoprotective effect against cisplatin-induced liver damage. From the obtained results, ginseng could be used as a protective and antioxidant agent to minimize the side effects during the protocol of using cisplatin as a chemotherapeutic drug.

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