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Effects of Zizyphus jujube fruit extract on Nrf2 pathway in paracetamol-induced liver injury in rats

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Introduction: Liver diseases represent a major health problem in Egypt. The use of medicinal plants for treating liver diseases have been reported since ancient times. However, the mechanisms underlying the assumed actions of many medicinal plants are not fully understood. We investigated the potential hepatoprotective mechanisms of Zizyphus jujube fruit extract (JFE), focusing on Nrf2 pathway, against paracetamol-induced hepatotoxicity in rats.

Method: Adult male Wistar rats were randomly assigned to 4 groups, 6 rats each. Group 1 received saline (1 ml/day, p.o. for 10 days), group 2 received paracetamol (single dose, 2 g/kg, p.o.), group 3 received JFE (500 mg/kg/day, p.o. for 10 days) followed 1 h later by paracetamol administration (single dose, 2 g/kg, p.o), group 4 received JFE (1000 mg/kg/day, p.o. for 10 days) followed by paracetamol administration. Blood samples and liver tissues were harvested 24 h after paracetamol administration. Activity of serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and serum bilirubin level were measured as indicators of liver function. Liver lysate content of reduced (GSH) and oxidized glutathione (GSSG), malondialdehyde (MDA), nuclear erythroid 2-related factor 2 (Nrf2), hemeoxygenase-1 (HO-1), glutamate cysteine ligase (GCL) were measured as well as glutathione reductase (GR) activity[1]. Preparation of JFE was carried out at National Research Center, Egypt. Data are represented as means ± SE and analysis was carried out using one-way analysis of variance followed by Tukey Kramer multiple comparisons' test.

Results: Both doses of JFE reduced serum ALT, ALP, AST, bilirubin, hepatic MDA level and increased GSH/GSSG indicating significant improvement in liver function and redox status. This beneficial effect is likely secondary to the observed increases in liver content of Nrf2, HO-1, GCL induced by JFE (Table 1).

Conclusion: Pretreatment with JFE exhibited a hepatoprotective effect against paracetamol-induced liver injury in rats via upregulation of Nrf2 and its target proteins HO-1 and GCL.

Reference:

1**.** Goldberg DM. and Spooner RJ (1983). UV method for determination of glutathione reductase activity. In: Bergmeyen HV (ed). Methods of enzymatic analysis 3rd edn. Vertog Chemie: Germany, pp 258-265.

Table·1¶

¤	Gp·1¶ ·(saline,·n=6)¤	Gp·2¶ (paracetamol,· n=6)¤	Gp·3¶ JFE·(500·g/kg,· n=6)¤	Gp·4¶ JFE·(1000· mg/kg,·n=6)¤
ALT·(U/L)¤	70·±2.2¤	130.3±2.8*¤	71·±·0.9#¤	61.5·±1.3*#A¤
AST·(U/L)¤	23.33±0.9¤	124·±2.6*¤	77.5·±0.9*#¤	69.17±1.5*#A¤
ALP·(U/L)¤	48.17·±1.1¤	235.3±18.4*¤	80.67±1.1#¤	81.67±0.9#¤
Bilirubin·(mg/dl)¤	0.34·±0.01¤	1.45·±·0.02*¤	0.38·±0.01#¤	0.36·±0.01#¤
GSH/GSSG¤	104.6·±6.09¤	12.1·±·0.45*¤	52.97·±·0.1*#¤	70.68·±2.83*#A¤
MDA·(nmol/g)¤	155.8±10.58¤	344.9·±34.6*¤	187.6·±15.76#¤	157·±9.8*#¤
GR·activity·(U/L)¤	0.51·±·0.1¤	0.47·±·0.07¤	0.48±0.05¤	0.5·±0.04¤
HO-1·(ng/ml)¤	2.64±·0.03¤	0.66±0.03*¤	1.79±0.06*#¤	2.16·±0.03*#A¤
GCL·(ng/ml)¤	2.59·±·0.03¤	0.67±0.03*¤	1.69±0.05*#¤	1.97·±0.01*#A¤
Nrf2·(pg/ml)¤	29.63+0.46·¤	5.13±0.20*¤	13.00±0.15*#¤	19.13±0.16*#·A¤

*·Significantly·different·from·Gp·1at·p·<·0.05.¶

#·Significantly·different·from·Gp·2·at·p·<·0.05.¶

A·Significantly·different·from·Gp·3·at·p·<·0.05.¶