

## Abstract

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**Title of Thesis:** Ameliorating effects of curcumin on hepcidin, some immunological and oxidative stress parameters induced by diazinon in male rats.

Diazinon (DZN) is the most widely used organophosphorus (OP) insecticides, especially in developing countries. It is used to control the pests of agricultural crops in addition to control livestock pests; however it has deleterious effects on health for both humans and animals. Hepcidin is an iron-regulating peptide hormone, reflecting a likely role of hepcidin in innate immunity; hepcidin is also induced by inflammation. Thirty six male albino rats were classified randomly into six equal groups. Group (G1) was kept as control, G2 and G3 were administrated a low and high dose of DZN as 17.5 and 35 mg/kg b.w. (1/20 and 1/10 LD<sub>50</sub>) respectively, over period of 28 days (5 days/week). G4 received curcumin (CUR) as 200 mg/kg diet. G5 and G6 were administrated high and low dose of DZN, respectively and CUR. The obtained results revealed a significant increase in interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ) as the proinflammatory cytokines, hepcidin and ferritin, decrease in erythropoietin (EPO), hemoglobin concentration (Hb), red blood cells (RBCs), serum iron and its related parameters in G2 and G3 were detected in comparison with untreated control (G1). Moreover, CUR treated groups (G5 and G6) revealed improvement of these parameters in comparison with those of corresponding groups. Significant decline in total protein (TP), total albumin (TAIb), total globulin (TGIb) together with albumin/globulin ratio (A/G) of G2 and G3 than control. Significant increase in liver, kidney and spleen malondialdehyde (MDA), catalase (CAT), nitric oxide (NO) with decrease in total antioxidant capacity (TAC) and glutathione (GSH) levels in G2 and G3 than control. Also, the obtained results revealed that there was a significant increase in liver and kidney function parameters in G2 and G3. As CUR is antioxidant and has anti-inflammatory effect could rebalance the state of hypoproteinemia associated with hypoalbuminemia, and attenuates the oxidative stress. Moreover, upturned in level of liver and kidney function was observed in G5 and G6. The correlation between hepcidin and IL-6, TNF- $\alpha$ , EPO, iron and its related parameters was determined. Histopathological examination revealed degenerative changes in the liver, kidney and spleen tissues in G2

and G3. Meanwhile, CUR alleviates these changes in G5 and G6. In conclusion sub-acute toxicity of DZN induces alteration in some immunological parameters which in turn cause alteration in hepcidin hormone secretion from hepatic cells leading to anemia and CUR administration had a protective effect against these adverse effects of DZN, also alleviate the deleterious biochemical alterations caused by DZN.

**Keywords:** Hepcidin, Diazinon, IL-6, TNF- $\alpha$ , Hematological parameters, protein electrophoresis, oxidative stress, Curcumin.

## List of Abbreviations

<b>A</b>	Absorbance
<b>A/G ratio</b>	Albumin/ globulin ratio
<b>AAP</b>	4-aminophenazone
<b>Ach</b>	Acetylcholine
<b>AChE</b>	Acetyl cholinesterase
<b>Alb</b>	Albumin
<b>ALP</b>	Alkaline phosphatase
<b>ALT</b>	Alanin aminotransferase
<b>AP-1</b>	Activator protein 1
<b>AST</b>	Aspartate aminotransferase
<b>B</b>	Blank
<b>b.w</b>	Body weight
<b>BG</b>	Between Groups
<b>CAT</b>	Catalase
<b>CCl<sub>4</sub></b>	Carbon tetrachloride
<b>CD</b>	Cluster of differentiation
<b>CD4+</b>	T- helper cell
<b>CD8+</b>	T-cytotoxic cell
<b>CNS</b>	Central nervous system
<b>COX-2</b>	Cyclooxygenase
<b>CUR</b>	Curcumin
<b>CV</b>	Central vein
<b>DcytB</b>	Duodenal cytochrome B
<b>DF</b>	Degree of freedom
<b>DHBS</b>	3,5-Dichloro-2-hydroxybenzene sulfonic acid
<b>DMT-1</b>	Divalent metal transporter-1

<b>DNA</b>	Deoxyribonucleic acid
<b>DZN</b>	Diazinon
<b>ELISA</b>	Enzyme-linked immunosorbent assay.
<b>EPO</b>	Erythropoietin
<b>Fe</b>	Iron
<b>FPN</b>	Ferroportin
<b>FPN1</b>	Ferroportin 1
<b>GDF 15</b>	Growth differentiation factor 15
<b>GFAP</b>	Glial Fibrillary Acidic Protein
<b>GOT</b>	Glutamic oxaloacetic transaminase.
<b>GPT</b>	Glutamic pyruvic transaminase.
<b>GSH</b>	Glutathione
<b>GSH-Px</b>	GSH peroxidase
<b>GSSG</b>	Glutathione disulfide
<b>H&amp;E</b>	Hematoxylin and eosin
<b>Hb</b>	Hemoglobin
<b>HCP1</b>	Heme carrier protein 1
<b>HCT</b>	Haematocrit
<b>HEPH</b>	Ferroxidase hephaestin
<b>HMGB1</b>	High mobility group box-1 protein
<b>HO-1</b>	Heme oxygenase 1
<b>Hrs</b>	Hours
<b>HSCs</b>	Hepatic stellate cells
<b>ICAM-1</b>	Intracellular adhesion molecule-1
<b>IFN- <math>\gamma</math></b>	Interferon-gamma
<b>IL</b>	Interleukin
<b>IL-1<math>\beta</math></b>	Interleukin-1 $\beta$
<b>IL-6</b>	Interleukin-6
<b>IMS</b>	Intermediate syndrome

<b>iNOS</b>	Inducible NO synthase
<b>JAK</b>	Janus kinase
<b>LD</b>	Lethal dose
<b>LDH</b>	Lactate dehydrogenase
<b>LPS</b>	Lipopolysaccharide
<b>LYM %</b>	Lymphocyte percent
<b>MAPK</b>	Mitogen-activated protein kinases
<b>MCH</b>	Mean corpuscular Hb
<b>MCHC</b>	Mean corpuscular Hb concentration
<b>MCP-1</b>	Monocyte chemoattractant protein-1
<b>MCV</b>	Mean corpuscular volume
<b>MDA</b>	Malondialdehyde
<b>MDH</b>	Malate dehydrogenase
<b>MHC</b>	Major histocompatibility complex
<b>Min</b>	Minute
<b>mRNA</b>	Messenger ribonucleic acid
<b>NADPH</b>	Nicotinamide adenine dinucleotide phosphate
<b>NF-<math>\kappa</math><math>\beta</math></b>	Nuclear factor kappa beta
<b>NO</b>	Nitric oxide
<b>NOS</b>	Nitric oxide synthase
<b>NRAMP-1</b>	Natural resistance-associated macrophage protein 1
<b>OD</b>	Optical density
<b>OP</b>	Organophosphorus
<b>OPs</b>	organophosphates
<b>PBS</b>	Phosphate buffer saline
<b>PBS-T</b>	PBS-Tween
<b>PCV</b>	Packed cell volume
<b>PLT</b>	Platelet
<b>PMA</b>	Phorbol 12-myristate 13-acetate

<b>PON1</b>	Paraoxonase/arylesterase 1
<b>PR</b>	Precipitating Reagent
<b>PreAlb</b>	Pre Albumin
<b>PV</b>	Portal veins
<b>r</b>	Correlation coefficient
<b>R.T</b>	Room temperature
<b>RBCs</b>	Red blood cells
<b>ROS</b>	Reactive oxygen species
<b>S</b>	Standard
<b>SB</b>	Sample blank
<b>Sec</b>	Seconds
<b>SEM</b>	Standard error of mean
<b>SR</b>	Saturating Reagent
<b>STAT3</b>	Signal transducer and activator of transcription 3
<b>T</b>	Test
<b>TAC</b>	Total antioxidant capacity
<b>TAlb</b>	Total Albumin
<b>TBA</b>	Thiobarbituric acid
<b>TF</b>	Transferrin
<b>TfR1</b>	Transferrin receptor
<b>TGlb</b>	Total globulin
<b>TIBC</b>	Total iron binding capacity
<b>TLR</b>	Toll-like receptors
<b>TLR2</b>	Toll-like receptor 2
<b>TLR4</b>	Toll-like receptor 4
<b>TMB</b>	Tetra methyl benzidine.
<b>TNF-<math>\alpha</math></b>	Tumor Necrosis Factor-alpha
<b>TP</b>	Total protein
<b>TRAIL</b>	TNF-related apoptosis-inducing ligand

<b>TWSGI</b>	Twisted gastrulation I
<b>T<math>\alpha</math></b>	Total alpha
<b>T<math>\beta</math></b>	Total beta
<b>T<math>\gamma</math></b>	Total gamma
<b>UIBC</b>	Unsaturated iron binding capacity
<b>WBCs</b>	White blood cells
<b>WG</b>	Within Groups
<b><math>\alpha</math>1</b>	Alpha 1
<b><math>\alpha</math>2</b>	Alpha 2
<b><math>\alpha</math>2-M</b>	Alpha-2-Macroglobulin
<b><math>\beta</math>1</b>	Beta 1
<b><math>\beta</math>2</b>	Beta 2
<b><math>\gamma</math>1</b>	Gamma 1
<b><math>\gamma</math>2</b>	Gamma 2

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