Nicorandil ameliorated doxorubicin-induced nephrotoxicity; this study aimed to show and explain the mechanism of this protection. A precise method was elucidated to study the effect of nicorandil on doxorubicininduced nephrotoxicity in rats depending on the critical inflammation pathway TLR4/MAPK P38/NFκ-B. Adult male rats were subdivided into four groups. The 1st group was normal control, the 2nd group received nicorandil (3 mg/kg; p.o., for 4 weeks), the 3rd group received doxorubicin (2.6 mg/kg, i.p., twice per week for 4 weeks), and the fourth group was combination of doxorubicin and nicorandil for 4 weeks. Nephrotoxicity was assessed by biochemical tests through measuring Kidney function biomarkers such as serum levels of urea, creatinine, albumin and total protein] besides renal kidney injury molecule-1 (KIM-1) and cystatin C], oxidative stress parameters such as [renal tissue malondialdehyde (MDA), reduced glutathione (GSH), SOD, catalase and nrf-2], mediators of inflammation such as [Toll like receptor 4 (TLR-4), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), p38 MAPK, Interleukin 1 beta (IL-1 β), and Tumor necrosis factor alpha (TNF-α)] and markers of apoptosis [BAX and Bcl-2 in renal tissue]. Finally, our data weresupported by histopathology examination. Nicorandil pretreatment resulted in a significant decrease in nephrotoxicity biomarkers, oxidative stress markers, inflammatory mediators and prevented apoptosis through decreasing BAX and increasing Bcl-2 in renal tissues. Nicorandil prevented all the histological alterations caused by doxorubicin. Nicorandil is a promising antidote against doxorubicin-induced nephrotoxicity by neutralizing all toxicity mechanisms caused by doxorubicin through normalizing inflammatory cascade of TLR4/MAPK P38/NFκ-B.

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