Article 7

Targeting SIRT1, NLRP3 inflammasome, and Nrf2 signaling with chrysin alleviates the iron-triggered hepatotoxicity in rats

Abstract:

Blood transfusion-requiring diseases such as sickle cell anemia and thalassemia are characterized by an imbalance between iron intake and excretion, resulting in an iron overload (IOL) disorder. Hepatotoxicity is prevalent under the IOL disorder because of the associated hepatocellular redox and inflammatory perturbation. The current work was devoted to investigate the potential protection against the IOL-associated hepatotoxicity using chrysin, a naturally-occurring flavone. IOL model was created in male Wistar rats by intraperitoneal injection of 100 mg/kg elemental iron subdivided on five equal injections; one injection was applied every other day over ten days. Chrysin was administered in a daily dose of 50 mg/kg over the ten-day iron treatment period. On day eleven, blood and liver samples were collected and subjected to histopathological, biochemical, and molecular investigations. Chrysin suppressed the IOL-induced hepatocellular damage as revealed by decreased serum activity of the intracellular liver enzymes and improved liver histological picture. Oxidative damage biomarkers, and pro-inflammatory cytokines were significantly suppressed. Mechanistically, the levels of the redox and inflammation-controlling proteins SIRT1 and PPARγ were efficiently up-regulated. The liver iron load, NLRP3 inflammasome activation, and NF-κB acetylation and nuclear shift were significantly suppressed in the ironintoxicated rats. Equally important, the level of the antioxidant protein Nrf2 and its target HO-1 were upregulated. In addition, chrysin significantly ameliorated the IOL-induced apoptosis as indicated by reduction in caspase-3 activity and modulation of BAX and Bcl2 protein abundance. Together, these findings highlight the alleviating activity of chrysin against the IOL-associated hepatotoxicity and shed light on the role of SIRT1, NLRP3 inflammasome, and Nrf2 signaling as potential contributing molecular mechanisms.

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