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Down Regulation of Smad-2 Transcription and TGF-B1 Signaling in Nano Sized Titanium Dioxide-Induced Liver Injury in Mice by Potent Antioxidants

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Abstract : Although it is known that nano-TiO2 and other nanoparticles can induce liver toxicity, the mechanisms and the molecular pathogenesis are still unclear. The present study investigated some biochemical indices of nano-sized Titanium dioxide (TiO2 NPS) toxicity in mice liver and the ameliorative efficacy of individual and combined doses of idebenone, carnosine and vitamin E. Nano-anatase TiO2 (21 nm) was administered as a total oral dose of 2.2 gm/Kg daily for 2 weeks followed by the afore-mentioned antioxidants daily either individually or in combination for 1month. TiO2-NPS induced a significant elevation in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and hepatic oxidative stress biomarkers [lipid peroxides (LP), and nitric oxide levels (NOX), while it significantly reduced glutathione reductase (GR), reduced glutathione (GSH) and glutathione peroxidase(GPX) levels. Moreover the quantitative RT-PCR analysis showed that nano-anatase TiO2 can significantly alter the mRNA and protein expressions of the fibrotic factors TGF-B1, VEGFand Smad-2. Histopathological examination of hepatic tissue reinforced the previous biochemical results. Our results also implied that inflammatory responses and liver injury may be involved in nano-anatase TiO2-induced liver toxicity Tumor necrosis factor-α (TNF-α) and Interleukin -6 (IL-6) and increased the percent of DNA damage which was assessed by COMET assay in addition to the apoptotic marker Caspase-3. Moreover mRNA gene expression observed by RT-PCR showed a significant overexpression in nuclear factor relation -2 (Nrf2), nuclear factor kappa beta (NF-Kβ) and the apoptotic factor (bax), and a significant down regulation in the antiapoptotic factor (bcl2) level. In conclusion idebenone, carnosine and vitamin E ameliorated the deviated previously mentioned parameters with variable degrees with the most pronounced role in alleviating the hazardous effect of TiO2 NPS toxicity following the combination regimen.

Keywords : Nano-anatase TiO2, TGF-B1, SMAD-2
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