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A search for molecular and cellular mechanisms of cytotoxicity induced by PLGA-docetaxel nanoparticles and the protective effect of silymarin

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Background and Aims: Docetaxel (DTX) is one of the most widely used drugs in oncology due to its high efficacy against several cancers. However, its current clinical administration, formulated in tween80, causes serious side effects. Polylactide-co-glycolide nanoparticles (PLGA NPs) containing DTX, has been synthesized to overcome this problem; yet there isn't enough study to specify the possible mechanisms of its toxic effects on normal cells.
Methods: Male Sprague–Dawley rats were used in the study. Hepatocytes were obtained by collagenase perfusion and suspended at a density of 106 cells/ml in round-bottomed flasks rotating in a water bath maintained at 37oC, under an atmosphere of 10% O2, 85% N2, and 5% CO2. To avoid either nontoxic or very toxic conditions in this study, we used EC502h concentration for DTX and PLGA-DTX in the isolated hepatocytes.
Results: According to our findings both DTX and PLGA-DTX cytotoxicities were associated with reactive oxygen species (ROS) formation, collapse of mitochondrial membrane potential, activation of caspases cascade and lysosomal membrane leakinessOur findings confirmed that CYP2E1 is directly involved in metabolic activation of both PLGA-DTX and DTX while CYP3A4 acts as a detoxification system. Our findings showed that silymarin can significantly ($p<0.05$) diminish all cytotoxic markers of PLGA loaded docetaxel but not free DTX. These effects must be the result of multi characteristic functions of this herb such, inhibition of hepatic cytochrome P450s (CYPs) and also inhibition of drug resistance protein in cell membrane.
Conclusions: These finding confirmed that cellular mortality of PLGA NPs containing DTX was more than free drug and the mechanisms of cytotoxocity are different between two drugs. It was also shown that the mode of hepatocyte membrane penetration is different between these compounds.

Keywords: PLGA-Docetaxel; Docetaxel; Isolated rat hepatocytes; Oxidative stress; Apoptosis; Silymarin