

ASBTRACT

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Title of Thesis: Characterization of flubendazol reduction in human *in vitro*

Flubendazole (FLU) is an anthelmintic of the benzimidazole type used as a treatment or prophylaxis of helminthoses in livestock and wild animals. FLU is also registered for the treatment of parasitic diseases caused by intestinal nematodes in humans. Its mechanism of action lies in its specific binding to tubulin, which disrupts the structure and function of microtubules for the therapy of parasitosis in humans. The advantage of this drug is also the low systemic toxicity. That is why the anticancer activity of FLU is now under study.

The aim of this rigorous work was to characterize the reduction of FLU in human liver subcellular fractions as this information is still lacking in available literature. Stereospecificity, subcellular localization, preference of coenzymes, enzyme kinetics of FLU reduction, and activity of enzymes involved in FLU reduction were studied in this project.

Measurement results have shown that FLU is predominantly reduced in cytosol and nicotinamide adenine dinucleotide phosphate reduced (NADPH) coenzyme is preferred. FLU reduction in human is strictly stereospecific because FLU was reduced only to (+)-FLUR enantiomer. In the study of the enzyme kinetics of FLU reduction in the cytosol, kinetic parameters values, apparent maximum velocity (V'_{max}) and apparent Michaelis constant (K'_m) were determined. Both were higher for NADPH coenzyme. It was further found that carbonyl reductase 1 (CBR1) and 11 β -hydroxysteroid dehydrogenase 1 (11 β -HSD1) were involved in the reduction of FLU in the cytosol and in the microsomes, respectively.