Induction And Inhibition Potential of Lupeol, Betulin And Cubebin In Rat Liver Microsomes

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CYP450 is a group of drug metabolizing enzymes responsible for metabolism of over 70% xenobiotics. Numerous phytoconstituents are known to induce or inhibit CYPs, resulting either in failure of therapy or toxicity of the co-administered drugs. Thus, it is crucial to screen phytoconstituents having potential therapeutic applications for their interactions with CYPs. Lupeol and betulin are the phytosterols possessing number of therapeutic activities like anti-microbial, anti-cancer. Cubebin is a lignan compound with antiprotozoal and anti-inflammatory activity.

The objective of the present study was to investigate the interaction of these phytoconstituents with CYP450 enzymes.

For induction study, Lupeol (20 mg/kg), Betulin (50 mg/kg) and cubebin (5 mg/kg) were dosed intraperitoneally for 14 days in male wistar rats. On day 15th rats were sacrificed, livers were isolated and microsomes were prepared by calcium aggregation method. β-naphthoflavone (CYP1A2), phenobarbitone (CYP2C9) and dexamethasone (CYP3A4) were the enzyme specific standard inducers used. The treated liver microsomes were subjected to phenacetin-O-deethylase (CYP1A2), tolbutamide hydroxylase (CYP2C9) and midazolam hydroxylase (CYP3A4) assays to determine their catalytic activities by respective HPLC methods. Inhibition potential of these phytoconstituents was determined at different concentrations using the above mentioned assays. IC₅₀ values were determined.

None of the three phytoconstituents exhibited any significant induction of CYP450. The IC₅₀ values for inhibition assays were found to be more than 50 µM for lupeol and betulin, and 0.50 µM (CYP3A4), 6.74 µM (CYP2C9), 1.0 µM (CYP1A2) for cubebin. Hence, lupeol and betulin did not inhibit any CYP isoforms whereas cubebin strongly inhibited CYP1A2, CYP2C9 and CYP3A4.

Keywords: Cytochrome P450, lupeol, betulin, cubebin, Induction inhibition interaction.