Effects of cytochrome P450 (CYP) 2D6 inhibitions in *in vivo* toxicity studies of mitragynine.

Zamri Chik
University of Malaya, Malaysia
zamrichik@um.edu.my

Mitragynine, the most abundant active component found in the leaves of *Mitragyna speciosa*, has been proposed to use as pain and opiate withdrawal symptoms reliever. Even though it had been banned in certain countries, however, some people still consume it for different medical indications. In recent years, it has been strongly related to drug abused and several reported death cases. In our study, the effects of CYP2D6 on mitragynine's metabolism and drug-drug interaction (DDI)-induced toxicity were investigated intensively using quinidine, a CYP2D6 inhibitor. The findings showed that co administration of 10 mg/kg quinidine increased the mitragynine elimination half-life and area under the curve significantly using a conventional pharmacokinetic study. The experiment was extended with *in vivo* 14-days toxicity study at highest dose 50 mg/kg of mitragynine. Lethal dose of 300 mg/kg mitragynine alone was identified in the pilot study. Whereas, mortality rate of mitragynine (4 out of 6 rats) at 50 mg/kg was dramatically increased in the presence of quinidine as compared with mitragynine control. Liver markers such as AST and ALT were also significantly elevated at the dose as low as 5 mg/kg with quinidine co-administration. Lastly, histopathological analysis showed inflammatory cell infiltration in both of liver and kidney at highest tested dose. In conclusion, CYP2D6 plays the major role in phase I metabolism of mitragynine and it strongly associated with the DDI-induced mortality, as well as hepatotoxicity. Therefore, concurrent administration of mitragynine and drugs which are inhibitors of the CYP2D6 enzyme would increase fatality among mitragynine consumers or abusers.