Thesis Title Stimulatory effect of Curcuma xanthorrhiza (Roxb.) on bile secretion

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ABSTRACT

As a household remedy for treatment of postpartum uterine bleeding and a tonic, Curcuma xanthorrhiza has been widely utilized in Southeast Asian countries and some part of Thailand. Even so, there has not been a systematic study on its pharmacological activity. The experiments thereby were designed to investigate the activities of various extracts of C.xanthorrhiza in stimulating bile secretion and their effect on biliary constituents after the administration through different routes. The investigations were performed in male Wistar rats and were pursued in 5 steps. Firstly, dried ground C.xanthorrhiza was extracted, which resulted in four extracted components consisting of hexane, ethyl acetate (EtOAc), butanol (BuOH) and aqueous extract,respectively.Secondly,toxicity studies of EtOAc extract were tested. Thirdly, study on the potency of various extracts of C.xanthorrhiza on bile secretion was pursued, being followed by the fourth step, the investigation on dose response effect of EtOAc extract in stimulating bile flow rate, and the fifth,the studies on effect of the drug in different routes.

The EtOAc extract was found to have low toxic effect. The LD_{50} value in Swiss albino male mice was estimated to be 5.2 g (i.p.) and 12 g/kg (i.g.) whereas the LD_{50} of DMSO (the solvent) was 14 g/kg (i.p.). The investigation on the potency of the four extracts on bile secretion after the intraduodenal administration demonstrated that the BuOH extract was the most potent choleresis. It increased the bile flow rate (BFR) from the base line control of 100% to 179.28±14.28% at 60 min after the injection. Cx-EtOAc (171.53±4.33%), hexane (148.28±11.67%) and aqueous extracts (120.43±5.43%) had lower potency, respectively. After the administration of EtOAc extract at various concentrations, the choleresis was found to be a dose dependent effect. The maximal dose was 1 g/kg. In addition,the concentration of bile salt was found to be reduced during choleretic period. On the analysis of the biliary constituents, both BuOH and EtOAc extracts markedly lowered the concentration of bile salt, but not the output. The partially purified fraction of EtOAc extract (10%(400 mg/kg) Cx-R-EA-44-5)also gave the similar pattern of response. On the contrary, DMSO tended to increase bile salt concentration but the overall output of bile salt was not significantly changed ($P>0.05$). Hexane and aqueous extracts slightly decreased the concentration of bile salt. Therefore, the active choleretic constituent was likely to be concentrated in butanol and ethyl acetate extracts.

For other biliary constituents,both BuOH and EtoAC extracts (1 g/kg) as well as EtOAc fraction No.5 (400 mg/kg) immediately increased biliary bilirubin secretion after the injection and it did not correspond to DMSO action. This

indicated that the stimulating effects on BFR and bilirubin secretion were of independent process. Furthermore, the solvent (DMSO) was also found to increase cholesterol, but not calcium concentration, and to mask the effect of C.xanthorrhiza either as the extract or the fraction. Because of the much higher hypercholeresis of the drug than that of DMSO, the outputs of bilirubin, cholesterol and calcium were markedly elevated. To minimize the DMSO effect,EtOAc extract (400 mg/kg) was suspended in 0.1% methylcellulose. It did not affect the bile salt though it extremely increased the concentration and output of bilirubin, cholesterol together with calcium. Presumably this is the actual effect of C.xanthorrhiza on bile secretion.

To investigate the possible mechanism of the drug action, 0.1 ml of 0.5% butanol fraction (20 mg/kg) was intravenously injected, the bile and blood samples were simultaneously collected. In spite of the injection via femoral vein, the effect of C.xanthorrhiza was delayed. It is possible that the intraduodenal injection of the drug provides a direct contact of the drug to the intestinal mucosal cell to secrete gut hormone after a more immediate response was observed. Alternately, the action of the drug by different routes might be exerted through different pathways. However, whatever routes of administrations used, the BFR together with the output of bilirubin and cholesterol was elevated while plasma cholesterol was reduced. The drug thereby might be beneficial for treatment of hyperbilirubinemia and hypercholesteremia.