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SIRIPORN TANOMCHART: STUDY ON THE EFFECT OF 2,6-DIHYDROXYACETOPHENONE ON CHOLESTEROL METABOLISM IN HYPERLIPIDEMIC HAMSTERS. THESIS ADVISOR: PRAYAD KOMARATAT, Ph. D., PAWINEE PIYACHATURAWAT, Ph. D., PRAPON WILAIRAT, Ph.D.
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2,6-Dihydroxyacetophenone (2,6-DHA) is an analogue of 2,4,6-trihydroxyacetophenone (THA), aglycone part of naturally occurring glucoside, 4,6-dihydroxy-2-O- (β-D-glucopyranosyl) acetophenone found in *Curcuma comosa* Roxb. (Family *Zingiberaceae*). 2,4,6-THA has been reported to effectively stimulate bile secretion by enhancing bile acid excretion resulting in decreased plasma cholesterol. Attempts have been made in this study to find out the mechanism by which 2,6-dihydroxyacetophenone (DHA) lowers plasma cholesterol in hypercholesterolemic hamsters. Studies were performed in male hamsters induced to become hyperlipidemic by supplementing cholesterol 0.2% body weight (BW) in corn oil for 3 weeks. After plasma cholesterol was elevated to 250-350 mg/dl, a dose of 2,6-DHA (300-800 μ mol/kg body weight) and duration of treatment which could reduce plasma lipids were determined. It was found that the optimum dose of 2,6-DHA which could reduce plasma cholesterol to 46% and plasma triglyceride to 73% of the untreated group was 400 μmol/kg body weight and the suitable duration was 10 days. In order to determine how 2,6-DHA could reduce plasma cholesterol, livers of 2,6-DHA treated and untreated animals were analyzed for free cholesterol, cholesteryl ester and triglyceride contents. Liver microsomes were analyzed for the activity of cholesterol 7α-hydroxylase, and a regulatory enzyme for conversion of cholesterol to bile salt. In feces, bile salt and total cholesterol were determined and in plasma, the distribution of cholesterol in VLDL, LDL and HDL fractions were measured. In the 2,6-DHA treated group, there was no significant difference on liver free cholesterol, cholesteryl ester or triglyceride content when compared with those of the untreated group. This indicated that 2,6-DHA had no effect on cholesterol storage and the key enzyme involved in cholesteryl ester synthesis, was acyl CoA cholesterol acyltransferase. However, in the liver microsome the activity of cholesterol 7α-hydroxylase increased 7-fold in animals fed 2,6-DHA compared to that of untreated animals. In feces of treated animals the bile salt and total cholesterol increased 2- and 6-fold respectively. Moreover, regarding distribution of cholesterol in various fractions of plasma lipoproteins, 2,6-DHA decreased cholesterol in VLDL and LDL but not in HDL fraction.

The results obtained in this study indicate that the hypocholesterolemic effect of 2,6-DHA was on the activation of cholesterol 7α-hydroxylase activity and the excretion of cholesterol and bile salt in feces. The increased fecal excretion of bile salt would up-regulate LDL-receptors leading to a lowering of cholesterol in VLDL and LDL fraction. Accordingly, this compound may have potential for development as a therapeutic agent for treatment of cholestasis, dissolving gallstones and lowering plasma lipid.