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## Hypolipidemic effects of dietary 7-oxo-24, 25-dihydrolanosterol\*

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Cholesterol is an important constituent of lipids and biosynthesized from acetate *via* mevalonic acid, squalene, and lanosterol. There are some regulatory steps in the cholesterol biosynthesis. Although HMG-CoA reductase is considered to be the major rate-limiting enzyme in the sterol biosynthetic pathway, conversion of lanosterol to C-27 sterol is also a natural regulatory step in a number of different tissues. It has been proposed that lanosterol metabolism may play a role in the regulation of HMG-CoA reductase. In human serum, lanosterol significantly correlated with changes in cholesterol synthesis. These facts suggest that the inhibition of lanosterol metabolism could lead to a regulation of cholesterol level *in vivo*.

Recently, we reported the effects of lanosterol analogs, cholesterol analogs, oxygenated lanosterol derivatives, and oxygenated cholesterol derivatives on cholesterol biosynthesis from lanosterol. From these studies, it was clarified that both the side chain and skeleton structures of steroids are important in exhibiting their inhibitory effects. Of the tested compounds, 7-oxo-24,25-dihydrolanosterol (7-oxo-DHL) has been shown to be a potent inhibitor of cholesterol biosynthesis from lanosterol in rat hepatic subcellular fraction.

In this paper, we have comparatively examined the hypolipidemic activities of both 7-oxo-DHL and clofibrate (CF), which has been widely used as an effective hypolipidemic drug for many years. Further, the effects of 7-oxo-DHL in rats fed with 3% cholesterol in a diet were examined.

7-Oxo-DHL, an inhibitor of cholesterol biosynthesis from lanosterol *in vitro*, lowered the serum total-cholesterol and triglyceride at a level of 0.1% in a diet on male Wistar rats. This effect was slightly lower than that of CF which was examined as a reference. Further, the reduction in serum total-cholesterol levels were associated with slight reduction in the levels of high density lipoprotein (HDL) cholesterol, resulting in a decrease in the atherogenic index. The rate of decreasing of liver total-cholesterol by 7-oxo-DHL was more higher than that of CF soon after taking off diet. Although CF produced a marked increase of liver size, no significant increase was observed in the rats fed with 7-oxo-DHL.

Generally speaking, three main cholesterol-lowering mechanisms are known, that is; inhibition of intestinal absorption, inhibition of biosynthesis, and enhancement of catabolism of cholesterol. Since 7-oxo-DHL is clearly demonstrated as an inhibitor of cholesterol biosynthesis from lanosterol, the inhibition of hepatic cholesterol synthesis

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is thought to be the main effect by 7-oxo-DHL feeding.

Significant reduction of cholesterol in the liver and a concomitant decrease of the total-cholesterol and triglyceride in the serum provide a strong evidence that 7-oxo-DHL primarily inhibits biosynthesis of cholesterol in the liver and secondarily may interfere with the transport of triglyceride from liver as lipoproteins (chyromicron, VLDL) due to the shortage of a constituent, cholesterol. The data presented in this report suggest that 7-oxo-DHL acts as an inhibitor in the branched pathway for the biosynthesis of cholesterol in the animals which were given through dietary administration of the agent and therefore will appear to be an interesting cholesterol-lowering agent.