

## Summary

### Effect of epigallocatechin gallate

Epigallocatechin gallate (EGCG), the major green tea catechin, has been shown to be protective in various experimental models of liver injury. Since its effect on biliary physiology and liver cholesterol homeostasis has not been thoroughly studied, the present study investigated effect of EGCG on bile flow, bile acid homeostasis and cholesterol metabolism in healthy and ethinylestradiol-treated rats. Compared to controls, EGCG treatment in rats decreased bile flow by 23%. Hepatic paracellular permeability and biliary bile acid excretion were not altered by EGCG administration, but biliary glutathione excretion was reduced by 70%. Accordingly, the main glutathione transporter at the hepatocyte canalicular membrane, multidrug resistance-associated protein 2 (Mrp2), was significantly decreased at the protein level. Interestingly, EGCG markedly enhanced biliary excretion of cholesterol and phospholipids. These changes tightly correlated with increased expression of ATP-binding cassette transporter G5 and G8 (Abcg5/8) and scavenger receptor class B type 1 and with decreased expression of acyl-CoA:cholesterol acyltransferase (Acat2). EGCG administration to rats also doubled plasma bile acid concentrations compared to controls. While protein expression of the main hepatic bile acid transporters was unchanged, the rate-limiting enzyme in the bile acid synthesis, Cyp7a1, was significantly increased by EGCG. Enhanced bile acid synthesis in these animals was also confirmed by a 2-fold increase in plasma marker of Cyp7a1 activity, 7 $\alpha$ -hydroxy-4-cholesten-3-one. In contrast, EGCG markedly downregulated the major bile acid transporters (Asbt and Ost $\alpha$ ) and regulatory molecules (Shp and Fgf15) in the ileum.

When EGCG was coadministered with ethinylestradiol, a potent cholestatic agent, it did not show any additional effect on the induced cholestasis but reduced plasma total cholesterol and VLDL cholesterol. Further, EGCG coadministration in ethinylestradiol-treated rats attenuated liver weight increase and liver cholesterol accumulation, which was linked with the corresponding reduction in Acat2 expression.

This study showed ability of EGCG to raise plasma bile acid concentrations, mainly through Cyp7a1 upregulation, and to decrease bile production through reduction in Mrp2-mediated bile flow. Despite the cholestatic effect, EGCG enhanced biliary cholesterol excretion and attenuated ethinylestradiol-induced liver cholesterol accumulation through Abcg5/8 upregulation and Acat2 reduction, respectively. Collectively, these data significantly contribute to the current knowledge of EGCG effect on bile acid and cholesterol.