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The effects of natural phenolic compounds including naringenin, hesperetin, and isoflavone as well as a non phenolic compound, lipoic acid, in affecting hepatic fatty acid metabolism were examined in mice and rats. In the first experiment, mice were fed experiment diets containing either 1% naringenin, 1% hesperetin, 2% soy isoflavone or 1% lipoic acid for 21 d. Diets containing naringenin and lipoic acid increased the activity and gene expression of various enzymes involved in fatty acid oxidation except for one occasion. The increase was greater in the latter than in the former. A diet containing a soy isoflavone preparation containing 47% isoflavones mainly as glucoside also increased some of the parameters of fatty acid oxidation. Hesperetin did not affect any of the parameters for hepatic fatty acid oxidation. Lipoic acid strongly decreased the activity and mRNA of various lipogenic enzymes. However, other compounds were rather irrelevant in affecting parameters of lipogenesis. Naringenin, isoflavone and lipoic acid, but not hesperetin reduced serum concentrations of triacylglycerol, cholesterol and phospholipid except for one occasion. In the second trial, to confirm the strong influence of lipoic acid on hepatic fatty acid metabolism, rats were fed experiment diets containing different amounts (0, 0.1, 0.25 and 0.5%) of lipoic acid for 21 d. Lipoic acid dose-dependently decreased the activity and mRNA levels of hepatic lipogenic enzymes accompanying great decreases in the serum concentrations of triacylglycerol, cholesterol, phospholipid, free fatty acid and glucose. However, lipoic acid-dependent increase in hepatic fatty acid oxidation observed in mice was not necessarily confirmed in rats indicating species difference of the physiological activity of this compound in affecting hepatic fatty acid metabolism. Alteration of hepatic fatty acid metabolism may account for the hypolipidemic propensities of naringenin, isoflavone and lipoic acid in mice and rats.