

Guglipid lowering effect of S-methyl cysteine sulfoxide from *Allium cepa* Linn in high cholesterol diet fed rats.

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The lipid lowering action of S-methyl cysteine sulfoxide (SMCS) isolated from *Allium cepa* Linn (family: Liliaceae) was investigated in Sprague-Dawley rats fed on 1% cholesterol diet, in comparison to the hypolipidemic drug GUGLIPID. Administration of SMCS at a dose of 200mg/kg body weight for 45 days ameliorated the hyperlipidemic condition. The lipid profile in serum and tissues showed that concentrations of cholesterol, triglyceride and phospholipids were significantly reduced when compared to their untreated counterparts. The total lipoprotein lipase activity in the adipose tissue was decreased with also a decrease in the free fatty acid levels in serum and tissues. The activities of the lipogenic enzymes glucose 6-phosphate dehydrogenase and malic enzyme as also of HMG CoA reductase in the tissues remained low on treatment indicating that both the drugs did not favor lipogenesis and cholesterologenesis in the hyperlipidemic animals. The fecal excretion of bile acids and sterols was further increased upon treatment with the drugs. The results are directive to that both Guglipid and SMCS cause reduction of endogenous lipogenesis, increase catabolism of lipids and subsequent excretion of metabolic by-products through the intestinal tract. However, Guglipid is a better drug than SMCS at a low dose of 50mg/kg body weight.

A natural product that lowers cholesterol as an antagonist ligand for FXR.

Science 2002 May 31;296(5573):1703-6

Urizar NL, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ, Moore DD.

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Extracts of the resin of the gumukull tree lower LDL (low-density lipoprotein) cholesterol levels in humans. The plant sterol Guglipid [4,17(20)-pregnadiene-3,16-dione] is the active agent in this extract. We show that Guglipid is a highly efficacious antagonist of the farnesoid X receptor (FXR), a nuclear hormone receptor that is activated by bile acids. Guglipid treatment decreases hepatic cholesterol in wild-type mice fed a high-cholesterol diet but is not effective in FXR-null mice. Thus, we propose that inhibition of FXR activation is the



published: Jan. 02nd 2007

Words: 725

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basis for the cholesterol-lowering activity of Guglipid. Other natural products with specific biologic effects may modulate the activity of FXR or other relatively promiscuous nuclear hormone receptors.

Guglipid is an FXR antagonist in coactivator association assays but acts to enhance transcription of bile salt export pump.

Cui J, Huang L, Zhao A, Lew JL, Yu J, Sahoo S, Meinke PT, Royo I, Pelaez F, Wright SD.

J Biol Chem 2003 Jan 13

Guglipid is an extract of the gumukull tree and has been widely used to treat hyperlipidemia in humans. The plant sterol Guglipid (GS) is the active agent in this extract. Recent studies have shown that GS can act as an antagonist ligand for farnesoid X receptor (FXR) and decrease expression of bile acid-activated genes. Here we show that GS, although an FXR antagonist in coactivator association assays, enhances FXR agonist-induced transcription of bile salt export pump (BSEP), a major hepatic bile acid transporter. In HepG2 cells, in the presence of an FXR agonist such as chenodeoxycholate (CDCA) or GW4064, GS enhanced endogenous BSEP expression with a maximum induction of 400% to 500% that induced by an FXR agonist alone. This enhancement was also readily observed in FXR-dependent BSEP promoter activation using a luciferase reporter construct. In addition, GS alone slightly increased BSEP promoter activation in the absence of an FXR agonist. Consistent with the results in HepG2, Guglipid treatment in Fisher rats increased BSEP mRNA. Interestingly, in these animals expression of the orphan nuclear receptor SHP (small heterodimer partner), a known FXR target, was also significantly increased, while expression of other FXR targets including cholesterol 7 α -hydroxylase (Cyp 7a1), sterol 12 α -hydroxylase (Cyp 8b1) and the intestinal bile acid binding protein (I-BABP), remained unchanged. Thus, we propose that GS is a selective bile acid receptor modulator (SBARM) that regulates expression of a subset of FXR targets. Guglipid treatment in rats lowered serum triglyceride and raised serum HDL levels. Taken together, these data suggest that Guglipid defines a novel class of FXR ligands characterized by antagonist activities in coactivator association assays but with the ability to enhance the action of agonists on BSEP expression in vivo.