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CARDIOVASCULAR DISEASE

In keeping with tradition

For centuries, Chinese herbalists have used extracts from the *Coptis chinensis* (golden thread) plant to treat a range of ailments, from dysentery to infectious diarrhoea. Now, research published in *Nature Medicine* suggests that the active component of this herbal remedy — an alkaloid called berberine — might also be able to lower elevated levels of LDL ('bad') cholesterol in the blood, a major risk factor for heart disease.

Furthermore, it seems that berberine works in a way that is different from the statins, which are the current drug class of choice for treating high cholesterol. Although statins have had tremendous success, some patients fail to respond adequately to treatment, and high doses have been associated with serious side effects. So, a drug with an alternative mode of action that could be used in combination with statins, or even as an alternative therapy, could improve treatment for patients with high cholesterol.

Statins work by blocking the synthesis of cholesterol in liver cells, which signals the cells to activate transcription of the *LDLR* gene. This in turn increases the production of cell-surface LDL receptors (LDLRs), which take up cholesterol from the circulation into cells to compensate for the lower intracellular levels. The overall consequence is that blood LDL cholesterol levels drop.

In cultures of human liver cells, Kong and colleagues showed that berberine also increases the production

of cell-surface LDLRs. However, it exerted its effects independently of intracellular cholesterol levels, and did not stimulate transcription of the *LDLR* gene. Instead, berberine increased the stability of *LDLR* mRNA, thereby increasing the number of LDLRs produced during translation.

The researchers showed that this berberine-mediated stabilization depended on the presence of a small stretch of nucleotides in the 3' untranslated region (UTR) of the *LDLR* mRNA. They also found that activation of ERK (a component of the MAP kinase signalling pathway) was required for berberine to exert its effects. This led them to suggest that activation of the ERK signalling cascade by berberine might stimulate mRNA-binding proteins to interact with specific motifs in the 3' UTR of the *LDLR* mRNA, resulting in mRNA stabilization and enhanced LDLR production.

Next, the effects of berberine on serum cholesterol levels were assessed in 91 patients with high cholesterol, who were treated with either berberine or placebo for 3 months. Berberine was well tolerated, and reduced LDL cholesterol in the bloodstream by 20% without affecting levels of HDL ('good') cholesterol. Subsequent experiments in hamsters verified that increased expression of hepatic LDLRs by berberine was responsible for its ability to reduce levels of LDL cholesterol in the blood.



Not only does berberine seem to act through a distinct pathway to the statins, but preliminary experiments showed that it might even enhance their cholesterol-lowering effects. As a traditional Chinese medicine with a long history of safe use, berberine could therefore be an ideal supplement to statin therapy, reducing the risks associated with higher doses of statins. Further studies of its potency, and its effect in combination with statins, are needed to determine whether this ancient remedy can be developed into a modern-day drug for preventing heart disease.

Clare Ellis

References and links

ORIGINAL RESEARCH PAPER Kong, W. *et al.* Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nature Med.* 7 Nov 2004 (doi:10.1038/nm1135)