### Title

Coumarin: an alternative candidate for the treatment of non-alcoholic steatohepatitis?




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## *Invited Commentary*

# Coumarin: an alternative candidate for the treatment of non-alcoholic steatohepatitis?

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Non-alcoholic fatty liver disease (NAFLD) often manifests as the liver component of obesity, diabetes and the metabolic syndrome, and ranges from fat accumulation to steatohepatitis, and sometimes to fibrosis/cirrhosis. The high prevalence (5–20 % in the general population) of this disorder accounts for an increased incidence of end-stage liver disease and hepatocellular carcinoma in many parts of the world. The initiation of non-alcoholic steatohepatitis (NASH) from the fatty liver, and its progression may be attributed to many factors, such as oxidant stress, alcoholic exposure or drug toxicity, significant insulin resistance, as well as other factors that cause insult to the liver. Although many hypotheses are emerging regarding how the fatty liver progresses to NASH, 'the second hit' is the primary hypothesis that aids in our understanding of this progression along the continuum to NASH, fibrosis and cirrhosis. Growing evidence indicates that insulin resistance plays a pivotal role in enhancing fatty accumulation and lipotoxicity in the liver during the initiation and progression of NASH, especially in those with the metabolic syndrome. While extensive research efforts have been made to understand the molecular mechanisms underlying each pathological pathway, therapeutic strategies, such as lifestyle changes, limiting energy intake, dietary changes and/or increasing exercise, often yield limited efficacy or have a low compliance[1]. However, there have been some positive benefits in the use of insulin sensitisers, such as pioglitazone, or vitamin E, a potent antioxidant[2].

The diverse profile of factors that promotes the initiation and accelerates the progression of NASH determines that the therapeutic strategy may need to vary between individual patients. The proven efficacy with vitamin E highlights the rationale for the use of other antioxidants and food supplements from natural sources, including hypoenergetic food recipes[3], *n*-3 PUFA[4], L-carnitine[5], pentoxifylline[6] and coffee[7], among others. These have been shown to have some positive effects to various extents, including improving indicators of liver function, insulin resistance and blood lipid profiles, as well as steatosis, inflammation and ballooning, and have even led to the resolution of steatohepatitis in liver histology. However, none of them has been proven to be effective in blocking the progression of hepatic fibrosis to cirrhosis histologically[8].

Coumarin is an extract from the tonka bean, vanilla grass or sweet woodruff with a sweet smell. It is used as an aroma enhancer in tobacco and alcoholic beverages. This phenolic compound exists in many plant foods, such as citrus fruits, tomatoes, green tea and many vegetables. Coumarin has been reported to be protective against the hepatotoxicity of D-galactosamine plus lipopolysaccharide[9], has inhibited papilloma formation in the skin and has antioxidant effects in diabetic rats[10]. Additional studies have shown that coumarin may be beneficial in lowering serum lipid levels and body weight. Thus, it could be potentially useful in improving fatty liver in NAFLD. In the *British Journal of Nutrition*, Um *et al.*[11] report that the addition of 0·05 % coumarin in a high-fat diet (HFD) for 8 weeks significantly reduced body weight, body fat, adipocyte size and the blood lipid profile. It also minimised liver fatty acid synthase and malic enzyme activity, and decreased liver TAG content and thiobarbituric acid-reactive substance levels, as well as serum insulin and leptin levels. Moreover, the liver protein and mRNA levels of lipogenic genes, such as sterol regulatory element-binding protein 1 (*SREBP-1*), CCAAT enhancer binding protein α (*C/EBPα*), *PPARγ*, acetyl-CoA carboxylase 1 (*ACC1*) and fatty acid synthase (*FAS*), were markedly decreased in the group fed the HFD plus coumarin compared with the group fed the HFD alone. Therefore, the findings of this study demonstrate that coumarin decreases fat accumulation in the body and the liver, and improves insulin resistance and the adipokine profile. These effects may be attributed to the antioxidant effects of coumarin, and to its ability to inhibit lipogenic nuclear factors, hence suppressing hepatic lipogenesis. However, further studies are needed to delineate how coumarin down-regulates these lipogenic nuclear factors or enzymes at the molecular level, and whether the anti-lipogenic effect of coumarin is through its inhibitory effects on inflammation, adipokines or something else. Nevertheless, the study has provided convincing evidence demonstrating the beneficial effects of coumarin on the major pathological disturbances in the development of NASH, and indicates its potential for clinical application in obesity, type 2 diabetes, the metabolic syndrome and NAFLD. In this context, this publication points to the need for further preclinical studies. At the same time, it is necessary to better define the pharmacological, pharmaco-metabolic parameters and safety profile of the agent, because a large dose of coumarin intake as a dietary supplement (100–500 mg/kg body weight daily) resulted in hepatocellular vacuolar degeneration, apoptosis, bile duct

British Journal of Nutrition

hyperplasia, cholangio-fibrosis and even cholangiocarcinoma in mice[12]. For this reason, the European Commission (European Directive 88/388/EEC, Annex II) restricted coumarin as a direct food additive to 2 mg/kg food per d, while allowing higher levels for alcoholic beverages, caramel, chewing gum and certain 'traditional foods'. Therefore, the safety of coumarin as a supplementary remedy for a long-term use is a concern. Based on the data from the study by Um *et al.*[11], each mouse consumed a 3·1 g diet daily, which contained 1·55 mg coumarin (0·05 %) for a mouse with a body weight ranging from 25 to 35 g. This amount translates to 44–62 mg/kg per d, which far exceeds the upper limit of the acceptable dose range for human use. At this amount, coumarin may impose significant adverse effects during long-term use in mice[13]. It is also notable that there is a vast variation in the toxicity of coumarin between species, that the metabolic pathways of coumarin metabolism in humans seem to generate fewer toxic metabolites in contrast to rodents and that most hepatotoxicity reported with its human use may be idiosyncratic[13].

Given the fact that nutritional factors contribute to the initiation and development of NASH and that healthy diets and energy control are the major components in the management of patients with obesity, diabetes, the metabolic syndrome, hyperlipidaemia, hypertension, etc., the use of natural food supplements or extracts, such as coumarin, may have a high patient acceptance and compliance, once they are proven to be effective, safe and affordable. Obviously, more translational studies remain to define the clinical aspects of coumarin use, and it is too early to foresee whether coumarin will be a supplementary remedy for the routine care of NASH. Nevertheless, it is conceivable that coumarin may be beneficial for a selected patient population, such as NASH with insulin resistance.

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British Journal of Nutrition