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# Amelioration of diet-induced nonalcoholic steatohepatitis in rats by Mn-salen complexes via reduction of oxidative stress

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## Abstract

**Background:** Nonalcoholic steatohepatitis (NASH), a progressive stage of nonalcoholic fatty liver disease (NAFLD), is characterized by steatosis (accumulation of triacylglycerols within hepatocytes) along with inflammation and ballooning degeneration. It has been suggested that oxidative stress may play an important role in the progress of NAFLD to NASH. The aim of present study was to determine whether antioxidant supplementations using EUK-8, EUK-134 and vitamin C could improve the biochemical and histological abnormalities associated with diet-induced NASH in rats.

**Methods:** NASH was induced in male N-Mary rats by feeding a methionine - choline deficient (MCD) diet. The rats were fed either normal chow or MCD diet for 10 weeks. After NASH development, the MCD-fed rats were randomly divided into four groups of six: the NASH group that received MCD diet, the EUK-8 group which was fed MCD diet plus EUK-8, the EUK-134 group which was fed MCD diet plus EUK-134 and the vitamin C group which received MCD diet plus vitamin C. EUK-8, EUK-134 and vitamin C (30 mg/kg body weight/day) were administered by gavage for eight weeks.

**Results:** Treatment of MCD-fed rats with salens reduced the sera aminotransferases, cholesterol, low density lipoprotein contents, the extent of lipid peroxidation and protein carbonylation whereas the HDL-C cholesterol levels were significantly increased. In addition, EUK-8 and EUK-134 improved steatosis, ballooning degeneration and inflammation in liver of MCD-fed rats.

**Conclusion:** Antioxidant (EUK-8, EUK-134 and vitamin C) supplementation reduces NASH-induced biochemical and histological abnormalities, pointing out that antioxidant strategy could be beneficial in treatment of NASH.

**Keywords:** Nonalcoholic fatty liver, superoxide dismutase mimetic, oxidative stress, Mn-salen complexes, methionine and choline deficient diet

## Background

Nonalcoholic fatty liver disease (NAFLD) is regarded as a hepatic manifestation of the metabolic syndrome which is associated with obesity, insulin resistance, dyslipidemia and hypertension [1]. NAFLD encompasses a spectrum of liver abnormalities, including simple steatosis (nonalcoholic fatty liver, NAFL), nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis [2]. NAFLD is defined as hepatic fat accumulation exceeding 5-10% of liver weight, in the absence of excess alcohol consumption or any other liver disease and other causes of steatosis, such as certain toxins and drugs [2,3]. It is estimated that NAFLD affects 20-30% of the general population, 20-30% of which eventually progress into NASH. As a progressive stage of NAFLD, NASH is characterized by steatosis (accumulation of triacylglycerols within hepatocytes) along with inflammation and ballooning degeneration. The pathogenesis of steatosis occurrence and progression of NAFLD into NASH are not fully understood. A “multi-hit” (previously called “two-hit”) hypothesis has been proposed to explain the progression of NAFLD into NASH [4]. It is believed that insulin resistance and/or prolonged over-nutrition

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