Silybin enhances mitochondrial function and inhibits NFκB activation in murine nonalcoholic fatty liver disease

Francesco Cappello1*, Giovanni Li Volti2*, Federico Salamone3*, Antonella Marino-Gammazza1, Patrizia Cataneo1, Alessandro Pitruzzella1, Luigi Rizzato1, Filippo Macaluso1, Claudia Campanella1, Sabrina David1, Valentina Di Felice1, Vito Marcianò1, Giovanni Peri1, Giovanni Zummo1

1 Department of Experimental Biomedicine and Clinical Neurosciences, Section of Human Anatomy, University of Palermo, Italy
2 Department of Biological Chemistry, Medical Chemistry and Molecular Biology, University of Catania, Italy
3 Department of Internal Medicine, University of Catania, Italy
* These authors contributed equally to the present work

Background & Aims Non Alcoholic Fatty Liver Disease (NAFLD) is a chronic liver disease with possible cirrhotic and tumorigenic evolution. Despite a number of treatment has been proposed for NAFLD, none of these is really satisfying. Silybin, a flavonolignan extracted from milk thistle, showed marked liver protecting action in a variety of liver injury and is used as hepatoprotectant. We aimed to clarify the putative therapeutic significance of silybin and to identify the molecular pathways of silybin-mediated hepatoprotection in a murine model of NAFLD.

Methods We explored the effect of a 4-week daily (20mg/kg i.p.) administration of silybin in 6-week-old db/db mice feeding a methionine-choline deficient (MCD) diet. We examined liver histology, hepatic lipid homeostasis, mitochondrial function, oxidative-nitrosative stress and NFkB activation in silybin-treated mice compared with untreated animals.

Results Silybin markedly decreased serum ALT and liver triglycerides content. Steatosis was less severe in grade and distribution, and lobular inflammation was almost absent in silybin-treated mice. At the molecular level, silybin promoted the gene expression of key enzymes involved in free fatty acids elongation and β-oxidation and completely restores mitochondrial respiratory chain activity. Furthermore, silybin markedly decreased oxidative-nitrosative stress and inhibited NFkB p65 and p50 subunits binding activity.

Conclusions In the current study we showed that silybin displayed a marked anti-steatotic and anti-inflammatory effect in the db/db + MCD murine model of NAFLD. In our opinion, these findings provide the rationale for the use of silybin in the clinical management of patients with NAFLD, which will require well-designed clinical trials.

Key words Liver histology, hepatic lipid homeostasis, mitochondrial function, oxidative-nitrosative stress