**Structural requirements of silibinin from *Silybum marianum* that favourably shift fatty acids from triglycerides towards phospholipids in liver**

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Silibinin is considered as major active component of *Silybum marianum* (milk thistle) extracts and is traditionally used for the treatment of degenerative liver damage and as unique therapy for intoxication with *Amanita phalloides*. However, the molecular mechanisms of silibinin remained enigmatic. Membrane-stabilizing properties of silibinin, modulation of the function of membrane proteins as well as effects on metabolism have been discussed since decades. Here we show that silibinin does not only decrease triglycerides and lipid droplets – which are both increased in the pathology of non-alcoholic liver disease – but significantly increases the cellular content of major phospholipid classes in human hepatocellular carcinoma cells *in vitro* as well as in murine liver *in vivo*. Our data suggests that silibinin directly redistributes fatty acids from triglycerides to phospholipids, rather than engaging *de novo* fatty acid and phospholipid biosynthesis. Independent mechanisms seem to be responsible for the modulation of triglyceride and phospholipid metabolism by silibinin. SAR studies show that the configuration at the 1,4-benzodioxane ring of silibinin A is essential for the decrease in triglycerides, while for phospholipid accumulation, the saturated 2,3-bond of the flavanonol moiety is additionally required. The enrichment of hepatic phospholipids and expansion of intracellular membranes is associated with an increased expression of ER-localized metabolizing enzymes and elevated biotransformation capacity of mouse liver. Taken together, we provide insights into the liver-protective mechanisms of silibinin, which might rely on a favourable redistribution of fatty acids within intracellular lipids, and dissect the contribution of structural features.