# Rosmarinic acid attenuates hepatic fibrogenesis via suppression of hepatic stellate cell activation/proliferation and induction of apoptosis.

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**Abstract**

Objective: To investigate the antifibrotic role of rosmarinic acid (RA), a natural polyphenolic
compound, on HSCs activation/proliferation and apoptosis in vitro and in vivo.
Methods: The impact of RA on stellate cell line (HSC-T6) proliferation, activation and
apoptosis was assessed along with its safety on primary hepatocytes. In vivo, rats were
divided into: (i) normal; (ii) thioacetamide (TAA)-intoxicated rats for 12 weeks; (iii) TAA + silymarin or (iv) TAA + RA. At the end of experiment, liver functions, oxidative
stress, inflammatory and profibrogenic markers, tissue inhibitor metalloproteinases type-1
(TIMP-1) and hydroxyproline (HP) levels were evaluated. Additionally, liver histopathology
and immunohistochemical examinations of alpha-smooth muscle actin (a-SMA), caspase-3 and proliferation cellular nuclear antigen (PCNA) were determined.
Results: RA exhibited anti-proliferative effects on cultured HSCs in a time and concentration
dependent manner showing an IC50 of 276 mg/mL and 171 mg/mL for 24 h and 48 h, respectively, with morphological reversion of activated stellate cell morphology to
quiescent form. It significantly improved ALT, AST, oxidative stress markers and reduced TIMP-1, HP levels, inflammatory markers and fibrosis score (S1 vs S4). Furthermore, reduction in a-SMA plus elevation in caspase-3 expressions of HSCs in vitro and in vivo associated with an inhibition in proliferation of damaged hepatocytes
were recorded.
Conclusions: RA impeded the progression of liver fibrosis through inhibition of HSCs
activation/proliferation and induction of apoptosis with preservation of hepatic architecture.

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