

Chemoprevention of HBV-related hepatocellular carcinoma by the combined product of resveratrol and silymarin in transgenic mice

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ABSTRACT

Background: Patients with chronic hepatitis B virus (HBV) infection are at a high risk to develop hepatocellular carcinoma (HCC). Recently, metabolic syndrome has been found to carry a risk for HCC development. Considering the limitation of chemotherapeutic drugs for HCCs, the development of chemopreventive agents for high risk chronic HBV carriers is urgently demanded. In this study, we used combined silymarin and resveratrol extract which have been shown to exhibit biologic effects on activating peroxisome proliferator activated receptors (PPAR) and inhibiting mTOR signaling in a transgenic mice model harboring HBV viral oncoproteins.

Methods: The transgenic mice model harboring HBx and pre-S2 mutant constructs which develop HCC was adopted. First, we *in vitro* tested the ideal combination dosages of the silymarin and resveratrol product, and then we fed the natural product to the transgenic mice. The chemopreventive effects on preventing the development of HCC were evaluated.

Results: MTT assay showed an enhanced effect of the combined silymarin and resveratrol product on the reduction of cell proliferation in two hepatoma cell lines, Huh-7 and Hep G2. *In vitro* reporter assay and Western blot analyses revealed that the combined product could activate PPAR/PGC-1 α signaling and inhibit mTOR expression. *In vivo*, the combined products could significantly ameliorate fatty liver and reduce HCCs in transgenic mice harboring HBV oncoproteins.

Conclusions: The combined silymarin and resveratrol product exhibits a synergistic effect on the reduction of HCC development in transgenic mice model and may represent a potential agent for the prevention of HCC in high risk chronic HBV carriers.

Key words: HBV, HCC, Transgenic mice, Chemoprevention