ABSTRACT

Background: Hepatitis C virus (HCV) infection is a global medical problem. The current standard of care for chronic hepatitis C (CHC) is pegylated interferon plus ribavirin therapy, but this treatment is expensive, has significant side effects and, at best, is only 50% effective. Silymarin, the main active ingredient of milk thistle, is a natural antioxidant that is used by patients with CHC, although its efficacy for decreasing HCV levels or ameliorating CHC remains uncertain. HCV infection is associated with increased hepatic oxidative stress, and one of the antioxidant enzymes which protects cells against this stress is heme oxygenase-1 (HO-1). Methods: We investigated the effects of silymarin on HCV and HO-1 gene expression in wild type Huh-7 cells, as well as two HCV replicon cell lines, CNS3 and 9-13 cells. Results: Silymarin (100 and 200 μM) down-regulated HCV core mRNA (by 20% - 36%) and protein (by 30%-60%) in CNS3 cells. In contrast, silymarin did not decrease HCV NS5A mRNA or protein expression in treated 9-13 cells; in fact, it increased NS5A mRNA levels by two fold. HO-1 mRNA was up-regulated (60%-400%) by silymarin in Huh-7, CNS3 and 9-13 cells. To explore the mechanism by which silymarin up-regulates HO-1 mRNA, we measured the levels of Bach1 and Nrf2 transcription factors. Bach1 and Nrf2 mRNA levels were not affected by silymarin treatment in Huh-7 cells. In CNS3 and 9-13 cells, there was no clear relationship between silymarin-induced changes in Bach1 and Nrf2 and the induction of HO-1 mRNA. Silymarin do not down-regulate HCV core protein through the Jak-Stat pathway. Conclusions: Silymarin significantly down-regulates HCV core mRNA and protein in CNS3 cells. The effect of silymarin to down-regulate HCV core is not related to changes in the Jak-Stat signaling pathway. The levels of the antioxidant enzyme HO-1 are up-regulated by silymarin, but the precise mechanism by which silymarin up-regulates HO-1 mRNA levels in these cell lines remains unknown. These and other recent results suggest that silymarin is of benefit in CHC, although prospective, randomized, controlled-trials are needed to be certain.