

## Hepatoprotective effects of antioxidants in chronic hepatitis C

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### Abstract

We have read with interest the paper published in issue 2, volume 16 of *World Journal of Gastroenterology* 2010 by Nakamura *et al*, demonstrating that the antioxidant resveratrol (RVT) enhances hepatitis C virus (HCV) replication, consequently, they conclude that RVT is not a suitable antioxidant therapy for HCV chronic infection. The data raise some concern regarding the use of complementary and alternative medicine since the most frequent supplements taken by these patients are antioxidants or agents that may be beneficial for different chronic liver diseases. A recent study by Vidali *et al* on oxidative stress and steatosis in the progression of chronic hepatitis C concludes that oxidative stress and insulin resistance contribute to steatosis, thus accelerating the progression of fibrosis. We are particularly interested in investigating how the oxidative and nitrosative stress mechanisms are involved in the pathogenesis of different chronic liver diseases.

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**Key words:** Antioxidant; Chronic hepatitis C; Resveratrol; S-adenosyl-methionine; Nitric oxide; N-acetyl-cysteine

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### TO THE EDITOR

We read with interest the paper by Nakamura *et al*<sup>[1]</sup> demonstrating that the antioxidant resveratrol (RVT) enhances the hepatitis C virus (HCV) replication, consequently, they conclude that RVT is not a suitable antioxidant therapy for HCV chronic infection. The data raise some concern regarding the use of complementary and alternative medicine since the most frequent supplements taken by these patients are antioxidants or agents that may be beneficial for different chronic liver diseases. A recent study by Vidali *et al*<sup>[2]</sup> on oxidative stress and steatosis in the progression of chronic hepatitis C (CHC) concludes that oxidative stress and insulin resistance contribute to steatosis, thus accelerating the progression of fibrosis. They speculate that therapeutic regimens including anti-oxidant agents could be of clinical relevance in CHC patients infected with genotype non-3, according to their own results<sup>[2]</sup>. There is evidence that antioxidant therapies may ameliorate the necro-inflammatory activity in CHC patients<sup>[3]</sup>.

We are particularly interested in investigating how the oxidative and nitrosative stress mechanisms are involved in the pathogenesis of different chronic liver diseases<sup>[4]</sup>. Based on this rationale, we would like to support the hypothesis that antioxidant compounds might be proven beneficial for acute and chronic liver diseases. According to ours and other author experience, nitric oxide (NO)

has deleterious consequences in the presence of reactive oxygen species, since peroxynitrites are formed. NO participates in the pathophysiology of viral (chronic hepatitis B and CHC) and autoimmune (primary biliary cirrhosis and autoimmune hepatitis) liver diseases<sup>[5,6]</sup>, as well as in acute liver allograft rejection<sup>[7]</sup>. Moreover, NO contributes to liver ischemia-reperfusion injury and inhibition of inducible nitric oxide synthase (iNOS) shows beneficial effects<sup>[8]</sup>. Consistently, we found that N-acetyl-cysteine (NAC) modulates the expression of iNOS in human hepatocytes stimulated by proinflammatory cytokines<sup>[9]</sup>. The effect occurs by blocking the activation of the iNOS promoter, and is associated with modulation of NF- $\kappa$ B activity, a central transcription factor for induction of iNOS expression. The biological phenomenon might well be the basis of the therapeutic effects of NAC on chronic liver diseases different from those caused by acetaminophen intoxication.

Further insights into the hepatoprotective mechanisms of antioxidants might be learnt by analysing the glutathione precursor S-adenosyl-methionine (SAME) actions. Administration of SAME to patients with alcoholic liver cirrhosis showed beneficial effects<sup>[10]</sup>. Its possible mechanisms of action include: (1) acting as a methyl donor compound and contributing to restoration of mitochondrial glutathione content, which is necessary to counterbalance the oxidant environment in cirrhotic liver, and (2) attenuating the hepatic production of NO, through the modulation of nitric oxide synthase-2. SAME exerts these effects by accelerating re-synthesis of inhibitor  $\kappa$ B alpha and blunting the activation of nuclear factor  $\kappa$ B, thereby reducing the transactivation of NO synthase-2 promoter<sup>[11]</sup>.

Taking all these data together, abundant evidence suggests that antioxidants can effectively attenuate the oxidative and nitrosative stress in liver injury, ultimately improving inflammation and fibrosis progression. It is worth testing these drugs in future clinical trials including CHC patients, mainly those who present negative predictive factors of sustained virological response to standard antiviral regimens. However, controversies raise from the results of the study by Nakamura *et al*<sup>[1]</sup> promoting the possible need of investigations on the effects of different antioxidants on HCV replication before its use as a supplement in treatment of CHC patients.

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