

## *Citrus auraptene*: A potential multifunctional therapeutic agent for nonalcoholic fatty liver disease

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Dear Editor

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease that encompasses a range of disorders from simple steatosis to cirrhosis and hepatocellular carcinoma. Although the pathophysiology of NAFLD has not been fully clarified, the “two-hit” hypothesis is currently regarded as the most widely accepted etiopathophysiologic model for this disorder. According to this model, hepatic insulin resistance and consequent fat accumulation in hepatocytes represent the first hit (hepatic steatosis), which may predispose to hepatic injury and non-alcoholic steatohepatitis (NASH) in the second hit. Oxidative stress has been proposed as the primary mediator of the second hit.<sup>1</sup> In spite of its high prevalence, there is as yet no proven treatment for NAFLD.

Auraptene (7-geranyloxycoumarin) is the best known and, to the present knowledge, most abundant prenyloxycoumarin in nature.<sup>2</sup> Plants belonging to the *Rutaceae* family are the richest source of auraptene. Auraptene is also among the most common component of *Citrus* spp. fruits. Therefore, species of the genus *Citrus* (such as grapefruit) are frequently used as natural source of auraptene.<sup>2-4</sup> Various interesting pharmacological properties have been reported for this bioactive phytochemical<sup>4,5</sup> such as promising cancer chemopreventive activity (being orally active) –that puts it among the most effective natural chemopreventors ever known–,<sup>6</sup> antioxidant,<sup>7</sup> anti-inflammatory,<sup>8</sup> antimicrobial,<sup>9</sup> an-

tigenotoxic,<sup>10</sup> neuroprotective<sup>11</sup> and immunomodulatory properties.<sup>12</sup>

Herewith, it is hypothesized that auraptene, could exert favorable impacts on both stages of NAFLD pathogenesis through the following mechanisms, and might represent a potential promising agent for the prevention and treatment of the disease.

- I.** As the most abundant adipokine, adiponectin has been reported to possess insulin-sensitizing effects and improve hepatic as well as systemic insulin resistance. Moreover, adiponectin has been found to exert other hepatoprotective effects such as inhibition of TNF- $\alpha$  production and fatty acid synthesis in liver, attenuation of liver inflammation and fibrosis, reduction of hepatic fat accumulation, gluconeogenesis, *de novo* lipogenesis, and enhancement of hepatic fatty acid oxidation. Owing to these beneficial effects, and with respect to some reports on the lower levels of adiponectin in NAFLD and its association with disease severity, there has been recent interest on adiponectin up-regulation as a therapeutic approach against NAFLD.<sup>13</sup> Auraptene has been reported to induce both mRNA expression and protein secretion of adiponectin in adipocytes. Besides, auraptene treatment was associated with an increase in the ratio of high-molecular weight multimers of adiponectin –a subform of adiponectin that is predominantly associated with hepatic insulin-sensitizing effects– to the total amount of adiponectin.<sup>14</sup> Therefore, it is likely that auraptene could ameliorate liver histology through up-regulation of adiponectin.
- II.** There is increasing evidence on the important role of peroxisome proliferator-activated receptors  $\alpha$  (PPAR $\alpha$ ) and  $\gamma$  (PPAR $\gamma$ ) in the development and treatment of NAFLD. PPAR $\alpha$  has been reported to reduce hepatic triglyceride accumulation and increase fatty acid  $\beta$ -oxidation. PPAR $\gamma$  exerts favorable impacts on insulin sensitivity and redu-

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ces fatty acid delivery to the liver. PPAR $\gamma$  is also associated with down-regulation of proinflammatory cytokines such as TNF $\alpha$  and may thereby reduce liver inflammation. Besides, the activity of these PPARs is associated with adiponectin, which has been shown to be up-regulated by PPAR $\gamma$  and capable of PPAR $\alpha$  activation.<sup>14</sup> Interestingly, auraptene has been reported to act as the agonist of PPAR $\alpha$  in hepatocytes and dual agonist of PPAR $\alpha$  and PPAR $\gamma$  in adipocytes.<sup>14,16</sup>

- **III.** Oxidative stress is considered to play a major role in both pathogenesis and progression of NAFLD, being involved as an important contributor in the second stage of the two-hit hypothesis. Auraptene has well-known antioxidant properties and may therefore counteract the oxidative injury and prevent against progression of NAFLD from steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis.
- **IV.** Cytokines are regarded as potential mediators for the second hit of NAFLD leading to a shift from steatosis to NASH and fibrosis. Among cytokines, TNF- $\alpha$  is an important member that has been reported to be associated with hepatic insulin resistance, fat accumulation, apoptosis and necrosis, inflammation and oxidative stress.<sup>17</sup> Auraptene has been reported to possess anti-inflammatory properties and there is evidence that it could modulate the expression and release of TNF- $\alpha$ .<sup>18,19</sup>
- **V.** Excessive accumulation of triglycerides in hepatocytes that leads to hepatic steatosis is the hallmark of NAFLD. A very recent study has reported that auraptene administration normalizes lipid abnormalities in hepatocytes, reduces hepatic triglyceride accumulation and enhances the expression and activity of enzymes involved in  $\beta$ -oxidation.<sup>20</sup>

The aforementioned mechanisms imply that auraptene might serve as a potentially attractive therapeutic agent for NAFLD and NASH, and could exert its beneficial effects via different mechanisms. Moreover, regarding preclinical findings on the safety of auraptene, its wide oral bioavailability, well tolerability, biological activities and presence in citrus fruits (which have been commonly used for a long time),<sup>2,3</sup> this compound appears to exert several other health benefits. However, future experimental and clinical data on the efficacy and safety of auraptene are warranted to verify the present hypothesis on the applicability of this phytochemical as a multi-functional agent for the prevention and treatment of NAFLD.

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