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COMMENT

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Oriental Medicine

Comment on "Breviscapine alleviates nonalcoholic steatohepatitis by inhibiting TGF-β-activated kinase 1-dependent signaling"

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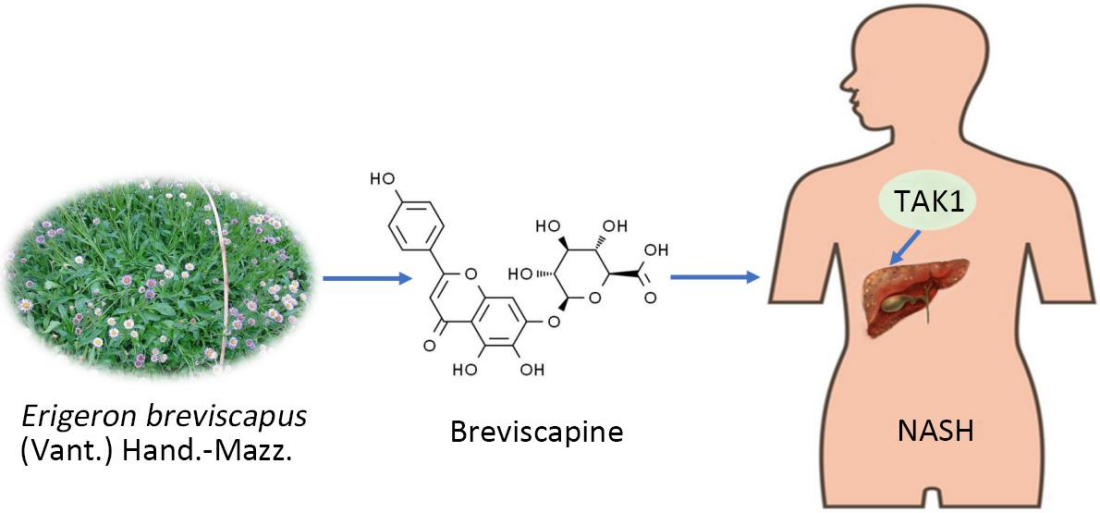

The article by Lan et al. [1], published on 30 October 2021 in *Hepatology*, showed the relationship between the natural flavonoid compound breviscapine and nonalcoholic steatohepatitis (NASH). The researchers demonstrated that breviscapine might be a novel therapeutic candidate for the treatment of NASH. It can be proven that breviscapine prevents metabolic stress-induced NASH progression through direct inhibition of the TGF-β-activated Kinase 1 (TAK1) signaling pathway.

Nonalcoholic fatty liver disease (NAFLD) is a common disease in patients with obesity, and its prevalence is steadily rising [2]. Additionally, NAFLD is the most common cause of liver disease worldwide [3]. The prevalence of NAFLD in most studies is estimated to range from 25% to 45%, and it is increasing at approximately the same rate as that of obesity and diabetes. NASH, the inflammatory subtype of NAFLD [4], has become a major cause of cirrhosis and liver-related death worldwide. NASH is strongly associated with obesity and metabolic syndrome, which causes lipid accumulation in hepatocytes (hepatic steatosis) [5].

As a chronic multi-system disease, NASH leads to a number of complications in other organs, such as chronic kidney disease, type 2 diabetes, and cardiovascular disease [4]. NASH also increases the development of fibrosis, cirrhosis, liver failure, and liver cancer [5]. However, diet and lifestyle changes cannot effectively treat NASH. Therefore, intervention with efficacious drugs is needed to prevent the progression of liver disease.

Breviscapine, as a prescription drug, is a crude extract of several flavonoids from the traditional Chinese herb *Erigeron breviscapus* (Vant.) Hand.-Mazz. The main ingredient is scutellarin (≥ 90%) [6], which can be prepared into various forms including injections, granules, ordinary tablets, dispersible tablets, capsules, mixtures, and drop pills. Breviscapine has strong biological activity and is a common monomeric compound used in clinical practice. It has been formulated into a variety of dosage forms for the treatment of cardiovascular and cerebrovascular diseases, such as atherosclerosis, coronary heart disease, and insufficient cerebral blood supply [7]. At present, more than 10 million patients use breviscapine and related drugs each year in China [8]. To understand its pharmacology or toxicity, the binding mechanism of breviscapine to a model protein, human serum albumin, was probed by fluorescence, circular dichroism, Fourier transform infrared spectroscopy, and electrochemical impedance spectroscopy approaches [9].

Breviscapine has been widely used because of its multiple pharmacological activities, including anti-inflammatory, antioxidative, antiapoptotic, vasorelaxant, antiplatelet, anticoagulation, and myocardial protective activities [10]. Recent studies have suggested that breviscapine protects against CCl_4-induced liver injury by reducing proinflammatory cytokine secretion and oxidative stress [11, 12]. Furthermore, scutellarin, the main component of breviscapine, has been shown to regulate lipid metabolism and may exhibit useful therapeutic effects against NAFLD by reducing oxidative stress [13]. Moreover, recent studies have shown that breviscapine inhibits lipopolysaccharide-induced production of proinflammatory mediators [14] and suppresses NF-κB and NLRP3 inflammasome activation to play a role in anti-inflammatory effects [15]. However, whether breviscapine prevents NASH and its underlying mechanism are not yet clear.

The latest finding from the work of Lan et al. [1] is that breviscapine alleviates NASH by inhibiting TAK1-dependent signaling. TAK1 belongs to the family of mitogen-activated protein kinase kinase kinases (MAP3Ks) and has been defined as a critical upstream

molecule of MAPKs [16, 17]. The authors evaluated the effects of breviscapine on the development of hepatic steatosis, inflammation, and fibrosis in vivo and in vitro under metabolic stress. Their study revealed that breviscapine treatment significantly reduced lipid accumulation, inflammatory cell infiltration, liver injury, and fibrosis in mice fed a high-fat diet, a high-fat/high-cholesterol diet, or a methionine- and choline-deficient diet [1]. In addition, breviscapine attenuated lipid accumulation, inflammation, and lipotoxicity in hepatocytes undergoing metabolic stress [1]. A systematic analysis (RNA sequencing and multiomics analyses) based on RNA sequence data showed that the key mechanism linking the anti-NASH effects of breviscapine was inhibition of TAK1 phosphorylation and the subsequent MAPK signaling cascade to regulate lipid metabolism, suppress inflammation, and reduce liver fibrosis [1]. Breviscapine-mediated hepatoprotection under metabolic stress was abrogated by treatment with the TAK1 inhibitor 5Z-7-oxozeaenol [1]. Molecular docking illustrated that breviscapine directly bound to TAK1 as well [1]. No significant toxic effects or certain adverse reactions were observed after treatment with breviscapine or other breviscapine preparations over a longer period of time. Therefore, to some extent, breviscapine is safe.

Apart from current research, other mechanisms of breviscapine in anti-inflammatory, antioxidative, and myocardial protective activities have been reported by other groups. For example, Li et al. [18] demonstrated that breviscapine may serve as a single drug or a promising adjuvant that can be used in conjunction with other medicine for the treatment of cerebral ischemia/reperfusion-induced injury. In 2017, breviscapine was shown to provide a neuroprotective effect after traumatic brain injury by modulating the Nrf2 signaling pathway [19]. In addition, a team led by Xia et al. [20] found that breviscapine is effective in promoting neurological behavior after traumatic brain injury and that the underlying molecular mechanism may be associated with the suppression of interleukin-6. A study by Guan et al. [21] showed that breviscapine dose-dependently triggered cytotoxicity in prostate cancer cell lines and might be useful in the field of human prostate cancer therapeutics. In addition, breviscapine has been an effective medication for the prevention and treatment of Alzheimer's disease [22]. An extensive meta-analysis was performed to evaluate the effects of breviscapine injection on hypertension in patients with hypertension-induced renal damage [23].

The study by Lan et al. [1] suggests that breviscapine can be used to treat NASH in a number of ways. It was identified as a specific inhibitor of TAK1 and was shown to ameliorate the pathogenesis of NASH through suppression of hepatic lipid accumulation, inflammation, and fibrogenesis. Therefore, the authors' findings will provide new insights supporting the development of therapeutic approaches for NASH. Whether breviscapine will work in humans will depend on the results of clinical trials. We will wait and see!

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Competing interests
The authors declare no conflicts of interest.

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Abbreviations
NASH, nonalcoholic steatohepatitis; TAK1, TGF-β-activated Kinase 1; NAFLD, nonalcoholic fatty liver disease; MAP3Ks, mitogen-activated protein kinase kinase kinases.

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