（学位第３号様式）

学 位 論 文 要 旨

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題　目	Elucidation of antifibrotic effects for *Osbeckia octandra*: Isolation of main antifibrotic compounds and identification of regulatory molecular pathways （*Osbeckia octandra* の抗線維化効果の解析：主要抗線維化化合物の同定とその調節経路の解明）

The liver is a vital organ responsible for numerous functions in the body, including detoxification, metabolism, and storage of nutrients. Liver diseases encompass a wide range of conditions, such as hepatitis, cirrhosis, fatty liver disease, and liver cancer. These diseases can significantly impact the quality of life for individuals worldwide. Symptoms may include fatigue, jaundice, abdominal pain, and altered mental function. Liver diseases can lead to complications like liver failure, which may require transplantation. The burden of liver diseases is substantial, affecting millions of people globally, causing physical discomfort, reduced productivity, financial strain, and emotional distress, highlighting the need for effective prevention and treatment strategies.

Traditional medicine has long been recognized for its effectiveness in treating hepatic diseases, particularly in Asian countries such as Sri Lanka, Thailand, India, China, and Japan. *O. octandra* has gained prominence in the treatment of liver disorders, including jaundice and viral hepatitis, according to Sri Lankan traditional medical practitioners. Its leaves have become a crucial ingredient in the preparation of herbal porridges (known as Kola kanda) within the Sri Lankan community.

Previous pharmacological studies on *O. octandra* have demonstrated its antioxidant, anti-inflammatory, and anti-cancer properties. In our own bioactivity screening, we have discovered that the water extract of Osbeckia octandra can alleviate liver fibrosis and cirrhosis. Furthermore, several bioactive chemical components have been isolated from this plant. However, the antifibrotic effects of these compounds have yet to be fully elucidated.

To address this gap, we conducted a study to investigate the prophy lactic and therapeutic effects of crude leaf suspension (CLS) and different leaf extracts using a rat model. After identifying possible fraction which contain antifibrosis effect, we isolated and identified three major compounds, namely pedunculagin (PDN), casuarinin (CSU), and gallic acid (GA), using NMR and confirmed their identities through mass spectrometry. Gallic acid (GA) has already been recognized as a hepatoprotective agent based on in vitro and in vivo studies. However, the impact of ellagitannin on liver fibrosis remains largely unexplored. Furthermore, our study marks the first time that PDN and CSU have been isolated from *O. octandra*. Thus, we investigated the therapeutic effects and mechanisms of PDN and CSU in an activated HSC cell line (LX-2) in vitro, as the activation of hepatic stellate cells plays a crucial role in liver fibrosis and is influenced by various signaling pathways.

Our bioassay results indicate that both PDN and CSU exhibit antifibrotic effects, with PDN demonstrating a more pronounced effect compared to GA. Additionally, PDN and CSU effectively reverse fibrosis in activated HSCs by downregulating the TGF-β/SMAD, ER stress, and Wnt/β-catenin signaling pathways. Collectively, these findings suggest that the compounds derived from *O. octandra*, as described in this study, hold considerable therapeutic potential in BLE for combating liver fibrosis.