

# Role of Natural Marine Products in the Treatment of Hepatic Stellate Cell-Related Liver Fibrosis

Ching-Hung Chen<sup>1</sup>, Chang-Hsun Ho<sup>1</sup> and Chan-Yen Kuo<sup>2\*</sup>

<sup>1</sup>Department of Anesthesiology, Show Chwan Memorial Hospital, Changhua, Taiwan

<sup>2</sup>Graduate Institute of Systems Biology and Bioinformatics, National Central University, Chung-li, Taiwan

## Introduction

Activation of Hepatic Stellate Cells (HSCs) is a key event in the development of liver fibrosis. Anti-fibrosis occurs by two pathways—reversion of the stellate cells to a quiescent state or clearance of the cells by apoptosis. Natural marine products have been reported to inhibit tumor growth and inflammation. However, their effect on liver fibrosis is uncertain. In this review, we discuss the role of natural marine products in the treatment of liver fibrosis. We propose that these products can act as novel therapeutic agents for treating hepatic stellate cell-related liver fibrosis.

## Liver fibrosis and HSC activation

Liver fibrosis is a disease that is characterized by severe morbidity and significant mortality [1-3]. Activated Hepatic Stellate Cells (HSCs) are critical for liver fibrosis [4]. During liver fibrosis, activated HSCs induce proliferation, inhibit apoptosis, accumulate Excessive Extracellular Matrix (ECM), and produce pro-inflammatory proteins [5,6]. Therefore, HSCs are an attractive target for anti-fibrotic therapy [7,8]. The anti-fibrotic strategies include decreasing the number of activated HSCs via inhibition of proliferation or induction of apoptosis and inhibiting the excessive deposition of ECM [9]. Thus, suppression of HSC growth and/or induction of HSC apoptosis by natural products are considered as effective options to ameliorate liver fibrosis.

## Natural marine products for treatment of liver fibrosis

Natural marine products have a wide variety of biomedical effects such as anti-tumor, anti-bacterial, anti-fungal, anti-viral, anti-helminthic, anti-protozoan, and anti-allergic effects [10-13]. Several compounds have been isolated from these products, which are important sources of drug discovery [10,14]. However, the pharmacological effects of natural marine products and their underlying mechanisms in the development of HSC-related liver fibrosis are still unclear. Therefore, investigation of HSC activation-dependent liver fibrosis is necessary to understand the importance of inducing apoptosis of HSCs towards treatment of this disease [6,15-18].

## Reactive Oxygen Species (ROS) and HSC activation

It is well documented that ROS is a critical mediator of liver fibrogenesis *in vitro* and *in vivo* [19-22]. Overproduction of ROS causes apoptosis in isolated primary activated HSCs from human and rat [23]. Furthermore, Glutathione (GSH) is a major intracellular antioxidant that plays a significant role in the regulation of cell viability in HSCs [24]. GSH exerts an anti-apoptotic effect by controlling ROS-induced cell death [25]. GSH depletion increases the sensitivity of HSCs to oxidative stress-induced cell death [25,26].

## Signaling pathways in liver fibrosis

Mitogen-Activated Protein Kinases (MAPKs) such as ERK, JNK, p38 kinase, and MAP kinase-1, are important mediators of diverse physiological processes and are critical for induction of oxidative stress response [27-29]. In addition, it is well-known that the MAPK signaling pathway is involved in cell growth and activation in HSCs [30,31]. However, Yu et al. found that continuous generation of H<sub>2</sub>O<sub>2</sub>

caused inhibition of growth of human gingival fibroblasts, which is independent of MAPK activation [32]. The role of the MAPK pathway in the oxidative stress-induced apoptosis of HSCs is unclear. Mao et al. suggested that shikonin-induced Chronic Myelogenous Leukemia (CML) cells undergo apoptosis via the ROS/JNK pathway. In contrast, it has been reported that panaxydol induces apoptosis via the ROS/JNK pathway [33].

## Conclusion

Activated HSCs play important roles in the pathogenesis of liver fibrosis [34]. Growing evidence suggest that induction of HSC apoptosis and inhibition of HSC growth can be effective strategies for treatment and/or prevention of liver fibrosis [6,16-18,35,36]. Furthermore, drug development from natural marine products may serve as additional therapeutic approaches for inhibition of hepatic fibrogenesis via HSC apoptosis.

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\*Corresponding author: Chan-Yen Kuo, Graduate Institute of Systems Biology and Bioinformatics, National Central University, Chung-li, Taiwan, Tel: +886-3-4227151; Fax: +886-3-4226062; E-mail: [cykuo@thu.edu.tw](mailto:cykuo@thu.edu.tw)

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