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Zedoariae rhizoma and curcumin inhibits platelet-derived growth factor-induced proliferation of human hepatic myofibroblasts

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Abstract

During the course of liver fibrogenesis, hepatic myofibroblast cells (hMF), mostly derived from hepatic stellate cells (HSC), proliferate and synthesize excessive amounts of extracellular matrix (ECM) components. To evaluate the antiproliferative effect of a traditional herbal medicine, *Zedoariae rhizoma* water extracts (ZR) was examined on the growth inhibition of human hMF since proliferation of hMF is known to be central for the development of fibrosis during liver injury, and factors that may limit their growth are potential antifibrotic agents. The aim of this study was to test the effects of ZR on the proliferation and to clarify the molecular mechanisms of ZR inhibition of HSC proliferation in cultured human hMF. The cells were stimulated by platelet-derived growth factor (PDGF)-BB in the presence or absence of ZR. Proliferation was determined by bromodeoxy-uridine (BrdU) incorporation. The mRNA expressions of collagen α1(I) and (IV) were evaluated by a quantitative reverse transcription–polymerase chain reaction (RT-PCR). PDGF-receptor tyrosine phosphorylation was detected using anti-phosphotyrosine antibody. PDGF-receptor radioligand binding assay was performed by [^{125}I]PDGF-BB. ZR inhibited the PDGF-BB-induced cell-proliferation and collagen α1(I) and (IV) mRNA expressions. ZR reduced the autophosphorylation of the PDGF-receptor. ZR blocked PDGF-BB binding to its receptor in a non-competitive manner. Furthermore, the 80% aqueous acetone extract of ZR was also found to show a decreasing effect against the proportion of S phase cells after PDGF stimulation. To clarify the active compounds, the principal constituents of seven sesquiterpenes (curdione, dehydrocurdione, germacrone, curcumenol, isocurcumenol, zedoarondiol and curcumenone) and a diarylheptanoid (curcumin) were examined. Among them, curcumin was found to decrease the proportion of S phase cells after PDGF stimulation at a dose of 30–50 μM. Potent

Abbreviations: ZR, *Zedoariae rhizoma* water extracts; hMK, hepatic myofibroblasts; DMEM, Dulbecco's modified essential medium; BrdU, bromodeoxy-uridine; ECM, extracellular matrix; FBS, fetal bovine serum; HSC, hepatic stellate cells; PDGF, platelet-derived growth factor; MAP, mitogen-activated protein; PI3K, phosphatidylinositol 3-kinase; SMA, smooth muscle actin; MTT, 3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide; PMSF, phenylmethylsulfonyl fluoride; G3PDH, glyceraldehydes-3-phosphate dehydrogenase; PGE2, prostaglandin-2; COX, cyclooxygenase.

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antiproliferative and antifibrogenic effects of ZR toward hMF indicated that ZR might have therapeutic implications in chronic liver disease, indicating a novel role for ZR as a growth inhibitory mediator and pointing out its potential involvement in the negative regulation of liver fibrogenesis. In conclusion, ZR has an inhibitory effect on PDGF-induced proliferation of hMF and the blocking of PDGF-BB binding to its receptor may be the mechanism behind this effect.
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Keywords: *Zedoariae rhizoma*; Cellular proliferation; Hepatic myofibroblasts (hMF); Liver fibrogenesis; Liver fibrosis; Cell signal transduction; Curcumin

1. Introduction

Hepatic fibrosis is characterized by the accumulation of smooth muscle α-actin-positive mesenchymal cells, or myofibroblast (MF) cells, within the expanding fibrous septa or in the perisinusoidal spaces [1]. Hepatic fibrosis is also a major complication of various chronic liver diseases and results from increased production and decreased degradation of extracellular matrix (ECM). Moreover, hepatic fibrosis has been implicated as a contributing factor in the development of hepatocellular carcinoma that commonly occurs in the presence of liver cirrhosis. Therefore, it is thought that inhibition of hepatic fibrosis may contribute to clinical improvement of a patient's prognosis. Hepatic stellate cells (HSC), mesenchymal cells located in the space of Disse, are the primary cells producing the extracellular matrix that contributes to hepatic fibrosis. These cells display a quiescent phenotype in normal liver and acquire myofibroblastic features following acute or chronic liver injury [2,3]. In addition, studies in experimental models of liver fibrosis indicate that portal fibroblasts might also contribute to hepatic MF cells (hMF) [4]. In the course of fibrogenesis, hMF cells proliferate [2] and synthesize most extracellular matrix components [5] that accumulate in fibrotic liver [6], such as interstitial and basement membrane (type IV) collagen. This fibrogenic response is characterized by intense proliferation and accumulation of myofibroblasts that actively synthesize extracellular matrix and proinflammatory cytokines, as demonstrated in experimental models and culture studies [7]. Evidence for heterogeneity in the liver myofibroblast population has been provided recently, and it has been described in rat that two populations of myofibroblasts with fibrogenic potential, hepatic stellate cells and hepatic myofibroblasts, accumulate during chronic liver injury [8,9]. During liver fibrogenesis, HSC are activated and acquire a myofibroblast-like phenotype, which is characterized by increased proliferation and extracellular matrix synthesis [10]. Although the underlying mechanisms are not completely understood, it is widely accepted that inflammatory cytokines, such as platelet-derived growth factor (PDGF), play a critical role in hepatic fibrogenesis. Suppression of HSC proliferation and activation of extracellular matrix biosynthesis have been proposed as therapeutic strategies for the treatment and prevention of the hepatic fibrosis that leads to irreversible liver cirrhosis.

There are detailed descriptions of the clinical experiences and prescriptions of liver fibrosis in traditional Korean medicine. *Zedoariae rhizoma* or *Curcuma zedaria* R (Zingiberaceae) is a medicinal plant and used for treatment of symptoms such as weakness caused by fatigue and weakness after illness [11]. The plant is a perennial herb, which is natively distributed throughout Korea, and has been being at present used as a Korean (Korean name, Bongchul) and Japanese herbal medicine (Japanese name, Gajutsu), which is listed in the Korean Pharmacopoeia II as aromatic stomachic, emmenagogus or for the treatment of 'Ohyul extravasated blood' syndrome caused by blood stagnation. Furthermore, *Z. rhizoma* water extract (ZR) also have been used as an important fragrance and spice in Asian countries. As chemical constituents of this plant, many sesquiterpenes, such as furanogermenone [12], germacrone [13,14] and (+)-germacrone 4,5-epoxide [15–25], have been isolated from *Z. rhizoma*, and these sesquiterpenes have been reported to exhibit antihepatotoxic and anti-ulcer effects [12,15]. With respect to its bioactive constituents of natural medicines and medicinal foodstuffs [15–23], it has been reported that the sesquiterpene constituents from ZR exhibited potent vasorelaxant activity. In addition, absolute stereostructures of carabrane-type sesquiter-

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