contain phytoestrogen physalin and withanolides, toward ventricular TNF-α level and fibrosis in ovariectomized rats. **METHODS** Wistar rats divided into six groups (K1: normal; K2: 5 weeks ovariectomy (OVX); K3: 9 weeks ovariectomy (OVX), K4, K5, and K5: 9 weeks OVX+4 weeks ceplukan leaf's methanolic extract dose 500, 1500, and 2500 $mg \cdot kg^{-1}$, respectively. TNF-α level measured with ELISA method. Fibrosis measured as blue color percentage in Masson's Trichrome staining. **RESULTS** This study showed that prolonged hypoestrogen increase ventricular fibrosis ($P<0.05$). Ceplukan leaf treatment also resulted in a decreased ventricular fibrosis and TNF-α level in dose dependent manner compared with those of without treatment group ($P<0.05$). Furthermore, the TNF-α level normalized in rat treated with 2500 $mg \cdot kg^{-1}$ *Physalis minima* L ($P<0.05$). Reduction of fibrosis positively correlated with TNF-α level ($P<0.05$, $r= 0.873$). **CONCLUSION** Methanolic extract of ceplukan leaf decrease ventricular fibrosis through inhibition of ventricular TNF-α in ovariectomized rats. Duration of hypoestrogen increase ventricular fibrosis.

Key words: *Physalis minima L*; ventricular; TNF-α; fibrosis

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Cucurbitacin E induces apoptosis and attenuates activation of hepatic stellate cells via PI_3K/Akt-AMPK-mTOR signaling pathway

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Abstract: **OBJECTIVE** Hepatic fibrosis is a wound-healing response for injury. Activated hepatic stellate cells (HSCs) are the preferred targets of anti-hepatic fibrotic therapies. cucurbitacin E (CuE) is, one well-known natural compound derived from traditional Chinese medicine, used in Asian countries for the prevention and treatment of hepatic disease. Therefore, the present study elucidated the mechanism of CuE on inducing apoptosis and attenuating hepatic fibrosis towards activated HSCs. **METHODS** The murine HSC (t-HSC/Cl-6) cell line were incubated in 96-well plates and treated with TNF-α and CuE at various concentrations and indicated times. Cell viability was assessed with MTT assay. Another, t-HSC/Cl-6 were incubated in 6-well plates and also treated with TNF-α, CuE, AICAR or metformin for the indicated time and concentration. Cell protein and mRNA were prepared using kit and relevant signaling were detected by Western blotting and RT-PCR. **RESULTS** CuE inhibited cell proliferation of activated HSC/T-6 cells in concentration- and time-dependent manner. CuE triggered the activation of caspase-3, cleaved the PARP, ration of bcl-2/bax, and cytochrom c protein in a time- and concentration-dependent manner. CuE decreased p-Erk/MAPK without effects on p-p38 and p-JNK. CuE inhibited the protein and mRNA expressions of α-SMA, TIMP-1 and collagen Ⅰ in activated HSC-T6. CuE broadly blocked p-PI3K, p-Akt, p-mTOR and p-p70S6K expressions. CuE significantly increased phosphorylated AMPK expression as well as AICAR and metoformin. And metformin showed significantly higher activation of AMPK than AICAR. Ability of CuE on activation of AMPK was between AICAR and metformin. It's also found that CuE significantly decreased p-mTOR as well as AICAR and metformin. **CONCLUSION** CuE could modulate HSC survival and activation as a potential anti-fibrotic agent for liver fibrosis treatment. The findings demonstrate that CuE induced HSC apoptosis via ERK/MAPK and PI_3K/Akt-AMPK-mTOR signaling.

Key words: cucurbitacin E; hepatic fibrosis; PI_3K/Akt; mTOR; AMPK

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