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Possible Protective Effect of Syringic Acid and Fisetin on Thioacetamide-Induced Liver Fibrosis in Rats

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Abstract

Liver fibrosis is a prevalent chronic condition that develops because of persistent hepatic damage. This study investigated the role of syringic acid and fisetin in reversing the progress of thioacetamide (TAA)-induced liver fibrosis in rats compared to standard drug silymarin and possible mechanisms driving that activity. TAA (200 mg/kg, i.p.) twice weekly, for six weeks was used to induce liver fibrosis in rats with concurrent administration of syringic acid (50 and 100 mg/kg/day), fisetin (50 and 100 mg/kg/day) or silymarin (50 mg/kg/day) via oral gavage. Syringic acid and fisetin effectively alleviated TAA-induced hepatic injury via a reduction in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin as well as increasing albumin and total protein levels. Furthermore, syringic acid and fisetin relieved oxidative stress in liver via reducing malondialdehyde (MDA) and restoring reduced glutathione (GSH) levels. Syringic acid and fisetin also attenuated inflammatory injury by suppressing tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Additionally, syringic acid and fisetin improved liver fibrosis by diminishing hepatic levels of transforming growth factor-β1 (TGF-β1), collagen I, tissue inhibitor of metalloproteinase-1 (TIMP-1) and hepatic immune-expression of α-smooth muscle actin (α-SMA), while elevating matrix metalloproteinase-9 (MMP-9) hepatic content. Moreover, syringic acid and fisetin markedly inhibited wnt3a gene expression, which was accompanied by decreased β-catenin and increased GSK-3β levels, as well as lowering cyclin D1 hepatic immune-expression and slowing the progression of histologic hepatic fibroplasia. In conclusion, syringic acid and fisetin stimulated fibrosis regression and showed better activity over silymarin by inhibiting extracellular matrix (ECM) accumulation and enhancing its degradation, via inhibiting hepatic stellate cells (HSCs) activation and proliferation through suppression of the Wnt/β-catenin pathway, modulating TIMP-1 and MMP-9 besides their antioxidant and anti-inflammatory effects. Therefore, syringic acid and fisetin appear to be promising therapeutic options for hepatic fibrosis.

Key words: Liver fibrosis, Thioacetamide, Rats, Syringic acid, Fisetin, Wnt/β-catenin.

Dedicated to

My parents

My husband

My daughters

Who

Shared the responsibility of bringing me up to be grateful

and

To all those who taught me

Acknowledgement

*In the name of **ALLAH** (SWT) the Almighty who taught man about matter that he does not know and prayers and peace be upon our Holy Prophet **Muhammad** (SAW) and his good followers till the Day of Judgment.*

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