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Title: Multimechanistic Antifibrotic Effect of Biochanin A in Rats: Implications of Proinflammatory and Profibrogenic Mediators

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Abstract: Objective: Biochanin A (BCA) is an isoflavone found in red clover and peanuts. Recently, it drew much attention as a promising anticancer and antioxidant. Due to its diversity in pharmacological actions, we were encouraged to investigate its potential as an antifibrotic, elucidating the different molecular mechanisms involved.
Design: Rats were pretreated with BCA, then injected with carbon tetrachloride (CCl4) for 6 weeks. Changes in liver weight and histology were examined and levels of aspartate and alanine aminotransferases, cholesterol, triglycerides, alkaline phosphatase and total bilirubin measured. To assess hepatic efficiency, indocyanine green was injected and its clearance calculated and albumin, total proteins and insulin-like growth factor-1 expression were measured. Cytochrome P4502E1 activity, cytochrome P4501A1 expression, in addition to sulfotransferase1A1 expression were determined to deduce the effect of BCA on hepatic metabolism. As oxidative stress markers, lipid peroxides levels, reduced glutathione, superoxide dismutase and catalase activities, as well as the total antioxidant capacity, were assessed. Nitric oxide, inducible nitric oxide synthase and cyclooxygenase-2 were used as indicators of the inflammatory response. Signaling pathways involving tumor necrosis factor-alpha, nuclear factor-kappa B, transforming growth factor-beta1, matrix metalloproteinase-9 and alpha-smooth muscle actin were investigated accordingly. Extent of fibrosis was examined by Masson's stain and measuring hydroxyproline levels.
Results: BCA pretreatment significantly protected against the chronic damage of CCl4. Liver injury, oxidative stress, inflammation and fibrosis markers decreased, while hepatic efficiency improved.
Conclusion: Our findings suggested that BCA administration protects against fibrotic complications, a property that can be contributed to the multimechanistic approach of the drug.

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