World Academy of Science, Engineering and Technology
International Journal of Health and Medical Engineering
Vol:16, No:11, 2022

Repositioning Sodium Valproate for Amelioration of Bleomycin-induced Scleroderma: The Role of Oxidative Stress, Transforming Growth Factor Beta-1, and the Mammalian Target of Rapamycin

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Abstract : Scleroderma is one of the connective tissue disorders characterized by skin and systemic fibrosis. Its pathogenesis involves multiple interrelated processes of autoimmunity, vasculopathy, inflammation, and oxidative stress. This study was a trial to explore the possible ameliorative effects of sodium valproate on an experimental model of skin fibrosis induced by bleomycin. Forty male BALB/c mice were divided into four equal groups as follows: control group; bleomycin group; bleomycin + sodium valproate group, and sodium valproate group. Mice were assessed for their body weight every four days throughout the whole study. Skin tissues were used to evaluate the oxidative stress parameters, transforming growth factor beta 1 (TGF-β1), tumor necrosis factor alpha (TNF-α), interleukin 15, and mammalian target of rapamycin (mTOR). Skin fibrosis was evaluated by measuring dermal thickness and staining the skin tissues with Masson trichrome stain. Also, the skin tissues were immunostained with alpha smooth muscle actin (α-SMA). Administration of sodium valproate to bleomycin-treated mice resulted in the restoration of the body weight with a significant decrease in the dermal thickness, amelioration of oxidative stress, suppression of TGF-β1 and mTOR expression, and significant reduction of the percentage of α-SMA immunostaining and the proinflammatory cytokine levels compared to mice treated with bleomycin alone. In conclusion, sodium valproate has an antifibrotic effect on skin fibrosis which may represent a beneficial therapeutic modality for the management of scleroderma.

Keywords : scleroderma, bleomycin, sodium valproate, skin fibrosis
Conference Title : ICCED 2022 : International Conference on Clinical and Experimental Dermatology
Conference Location : Jeddah, Saudi Arabia
Conference Dates : November 14-15, 2022