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Marantodes pumilum Var Alata (Kacip Fatimah) Ameliorates Derangement in RANK/RANKL/OPG Pathway and Reduces Inflammation and Oxidative Stress in the Bone of Estrogen-Deficient Female Rats with Type-2 Diabetes

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M. pumilum has been claimed to protect the bone against the adverse effect of estrogen deficiency. Additionally, it also exhibits anti-diabetic activity. In view of these, this study aims to identify the mechanisms underlying the bone protective effect of *M. pumilum* in the presence of both estrogen deficiency and diabetes mellitus (DM). Ovariectomized, diabetic female rats were given *M. pumilum* leave aqueous extract (MPLA) (50 and 100 mg/kg/day), estrogen, glibenclamide and estrogen plus glibenclamide for 28 consecutive days. At the end of the treatment, fasting blood glucose (FBG), serum insulin, Ca^{2+}, PO^{3-} and bone alkaline phosphatase (BALP) levels were measured. Rats were sacrificed and femur bones were harvested for determination of expression level and distribution of RANK, RANKL, OPG and oxidative stress and inflammatory proteins by molecular biological techniques. 100 mg/kg/day MPLA treatment decreased the FBG and BALP levels but increased the serum insulin, Ca^{2+} and PO^{3-} levels in estrogen deficient, diabetic rats. Expression and distribution of RANKL, NF-κB p65, IKKβ, IL-6, IL-1β and Keap-1 decreased however expression and distribution of RANK, OPG, BMP-2, Type-1 collagen, Runx2, TRAF6, Nrf2, NQO-1, HO-1, SOD and CAT increased in the bone of estrogen deficient, diabetic rats which received 100 mg/kg/day MPLA with greater effects than estrogen-only, glibenclamide-only and estrogen plus glibenclamide treatments. MPLA helps to overcome the adverse effect of estrogen deficiency and DM on the bone and thus this herb could potentially be used for the treatment and prevention of osteoporosis in postmenopausal women with diabetes.

Keywords: Bone, Diabetes mellitus, Estrogen deficiency, *M. pumilum*, Rank/rankl/opg

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