

Joint Event

4th EUROPEAN BIOPHARMA CONGRESS

&

6th International Conference and Exhibition on PHARMACOLOGY AND ETHNOPHARMACOLOGY

November 09-11, 2017 Vienna, Austria

***Sarcopoterium spinosum*: An antidiabetic medicinal plant with a novel mechanism of action**

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Sarcopoterium spinosum (*S. spinosum*) is an abundant plant in Israel, used by Bedouin traditional medicine for the treatment of diabetes. In our previous studies the glucose lowering properties of this herb were validated *in vitro* and *in-vivo*. The goal of this study is to clarify the mechanisms of action mediating the effects of *S. spinosum* on glucose uptake. *S. spinosum* facilitates glucose uptake by a unique mechanism, different from that induced by either insulin or metformin; *S. spinosum* increased glucose uptake by 3T3-L1 adipocytes in a mechanism involving Glut4 translocation, independent of AMPK or PI3K activity. Akt activation is required to induce *S. spinosum*-dependent glucose uptake, however its mechanism of activation is still unclear; while neither ser473 nor thr308 were phosphorylated by *S. spinosum*, translocation of Akt from cytoplasm to membrane and nucleus was detected. In addition, substrates of Akt were phosphorylated by the extract. The hypothesis that *S. spinosum* utilizes a different set of proteins to induce glucose uptake was supported by results demonstrating that differentiating adipocytes respond differently to insulin and *S. spinosum*; while insulin gradually enhanced glucose uptake from the 11th day of differentiation, *S. spinosum* increased glucose uptake from the 8th day of differentiation. In addition, *S. spinosum* and insulin had additive effect on glucose uptake in fully differentiated adipocytes. Phosphoproteomics of serine/threonine residues phosphorylated by *S. spinosum* followed by bioinformatic analysis indicate for the activation of insulin-receptor pathway. We conclude that active ingredients in *S. spinosum* activate insulin signaling by a unique mechanism. Clarifying this mechanism of action may lead to the development of new agents for the treatment of diabetes.

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