Peganum harmala enhanced GLP-1 and restored insulin signaling to alleviate AlCl 3-induced Alzheimer-like pathology model

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Abstract

Peganum harmala (P. harmala) is a folk medicinal herb used in the Sinai Peninsula (Egypt) as a remedy for central disorders. The main constituents, harmine and harmaline, have displayed therapeutic efficacy against Alzheimer's disease (AD); however, the P. harmala potential on sensitizing central insulin to combat AD remains to be clarified. An AD-like rat model was induced by aluminum chloride (AlCl3; 50 mg/kg/day for six consecutive weeks; i.p), whereas a methanolic standardized P. harmala seed extract (187.5 mg/kg; p.o) was given to AD rats starting 2 weeks post AlCl3 exposure. Two additional groups of rats were administered either the vehicle to serve as the normal control or the vehicle + P. harmala seed extract to serve as the P. harmala control group. P. harmala enhanced cognition appraised by Y-maze and Morris water maze tests and improved histopathological structures altered by AlCl3. Additionally, it heightened the hippocampal contents of glucagon-like peptide (GLP)-1 and insulin, but abated insulin receptor substrate-1 phosphorylation at serine 307 (pS307-IRS-1). Besides, P. harmala increased phosphorylated Akt at serine 473 (pS473-Akt) and glucose transporter type (GLUT)4. The extract also curtailed the hippocampal content of beta amyloid (Aб)42, glycogen synthase (GSK)-3б and phosphorylated tau. It also enhanced Nrf2, while reduced lipid peroxides and replenished glutathione. In conclusion, combating insulin resistance by P. harmala is a novel machinery in attenuating the insidious progression of AD by enhancing both insulin and GLP-1 trajectories in the hippocampus favoring GLUT4 production.

Scientific Reports 2021, June