Abstract

Background: *Pterocarpus marsupium* (PM), *Eugenia jambolana* (EJ) and *Gymnemma sylvestre* (GS) belonging to the family Fabaceae, Myrtaceae and Asclepiadaceae respectively are the common plants used in the traditional system of Ayurvedic medicine for the treatment of type 2 diabetes (T2D). A growing body of evidence shows that pharmacological agents used for the treatment of T2D such as dipeptidyl peptidase-4 (DPP-4) inhibitors have become valuable candidates as disease modifying agents in the treatment of Alzheimer’s disease (AD). The present study investigates the neuroprotective roles of PM and EJ as DPP-4 inhibitors in streptozotocin (STZ) induced AD.

Materials and methods: DPP-4 inhibition was evaluated by *in vitro* inhibitory assay, and enzyme kinetics (dissociation) was calculated using one-phase exponential decay equation. Male Wistar rats were intracerebroventricularly administered with STZ to induce AD. Individually, PM heartwood extract and EJ seed extract was administered at a dose of 200 and 400 mg/kg for 30 days following three months of STZ injection. Cognitive assessment was performed on radial arm maze and hole-board during the course of treatment. Following 30 days treatment with the extracts, animals were sacrificed and brains were extracted for the evaluation of biochemical parameters including glucagon-like peptide-1 (GLP-1), amyloid beta 42 (Aβ42), total tau, hyperphosphorylated tau (p-tau) and inflammatory markers.

Results: *In vitro* evaluation shows PM and EJ inhibit DPP-4 potently with IC$_{50}$ of 273.73 ± 2.96 and 278.94 ± 6.73 µg/mL, respectively, compared to GS (773.22 ± 9.21 µg/mL). PM, EJ, and GS exhibit long duration of action with enzyme inhibitory half-lives of 462.3, 317.2 and 153.8 min, respectively. *In vivo* evaluation of PM and EJ extracts in STZ model of AD reveal a time-dependent improvement in cognitive skills and a dose-
dependent attenuation of Aβ42, total tau, p-tau and neuro-inflammation with an increase in GLP-1 levels in the hippocampus at the end of 30 days treatment.

Conclusions: These robust therapeutic effects of PM and EJ, demonstrate a unique mechanism in Aβ, tau clearance, and reverses the cognitive deficits observed in AD. Our finding suggests that PM and EJ are the potential cognitive enhancers against STZ induced AD by DPP-4 inhibitory action and their neuroprotective action attributed through increase in active GLP-1 levels.