Summary

Diabetes mellitus, a global pandemic, can be holistically managed with the use of polyherbal formulations which is an accessible form of treatment in developing countries due to fewer side effects, economical and easily available. Commercial polyherbal formulation lacks systematic based scientific study, thus it is suspected to be associated with many contaminations and related toxicities, one of which is considered to be elemental health hazards. Additionally in recent times focus has been driven on mechanistic evaluation of herbal formulation for their action against molecular and cellular targets such as their effect on glucose movement, PPARɣ, PTP1B, DPP-IV, fructose-bisphosphate etc. Therefore, the present study is designed to assess six selected antidiabetic polyherbal formulations (BG, DB, DT, MA,MH and SN) from the Indian market for their element contents, health risk assessment, effect on movement of glucose and inhibitory potential against DPP-IV and PPARγ. Concentrations of 35 essential and non-essential trace-elements were quantified by Handheld X-ray spectrophotometer and health risk assessment was calculated by estimated daily intake (EDI) and total hazard quotient (THQ). Followed by investigation on mechanism of their claimed hypoglycemic effects on glucose adsorption, diffusion, amylolysis kinetics and transport across the yeast cells using *in-vitro* techniques. *In-silico* molecular mode of assessment was incorporated and the inhibitory potential of six bioactive compounds identified by LC-MS/MS of MA was assessed against DPP-IV and PPARγ. The pharmacokinetic properties were analysed using Swiss ADME server followed by toxicology prediction with ProTox ii server.

Elements were found to be in vast range of concentration in the tested APH. Among the 35 elements analyzed, Ca (23100±0.033ppm) and K (14800 ±0.021 ppm) in “MH” and Zn (15600±0.025 ppm) in “DB” were found to be the highest. The lowest concentrations of Rb and Nb (3±2 ppm) were observed in the formulation “MH” and “SN” respectively. THQ of all the elements was calculated to be less than unity except for Rb in the formulation "MA". Rb is rarely associated with toxicities as it is rapidly excreted in sweat and urine. V, Co, Ni, Cu, As, Se, Y, Ag, Sn, Sb, Ba, W, and Hg were absent in all the APH.

Data obtained revealed that the adsorption of glucose increased dose dependently (5mM - 100mM), highest glucose binding capacity was observed in MA (84.48±1.02 mM and 71.14±1.09mM) at 100mM concentration for hydro-alcoholic and aqueous extracts respectively. Rate of glucose uptake into yeast cells was linear (5mM - 25 mM) for all the tested extracts, whereas glucose diffusion was directly proportional to the time (30 - 180 min).

Highest GRDI was calculated to be in MA i.e., 27.87% and 21.74% at 30 min which reduced to 14.39% and 13.81% at 180 min for hydro-alcoholic and aqueous extracts respectively.

In-silico investigation using ADMET and ProTox server revealed drug like properties and low toxicity levels of all the tested compounds. Amongst the tested compounds, 6-Hydroxyluteolin (-8.9 against DPP-IV and PPARγ) and Glycyrrhetaldehyde (DPP-IV: -9.7 and PPARγ: -8.5) have exhibited better binding affinity compared to positive control. Therefore, the above compounds were further considered for molecular dynamic simulation which has showed stability of the docked complexes.

Therefore, the current study indicated the presence of essential elements some of which are important for the management of diabetes and hence can be considered safe for use. Further, it can be concluded that the above two compounds i.e., 6-Hydroxyluteolin and Glycyrrhetaldehyde in MA act as DPP-IV inhibitor and antagonist of PPARγ and might be considered as one of the possible molecular mechanisms in the management of DM.

Signature of PI/Guide

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