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IN SILICO EVALUATION OF AROMATASE INHIBITORY ANTI-BENIGN PROSTATIC HYPERPLASIA POTENTIALS OF SPIROSTAN SAPOGENINS

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ABSTRACT

Inherent oestrogen receptor alpha (ERα) and other nuclear receptor signaling activities of typical aromatase inhibitors (AIs) preclude their clinical use as anti-oestrogenic anti-benign prostatic hyperplasia (anti-BPH) agents. Spirostan sapogenins (SS) constitute a chemical space from which AIs without such deterrents could be sought. This work was aimed at in silico discovery of clinical aromatase inhibitory anti-oestrogenic anti-BPH drug leads. Forty-six SS were docked against an inhibitor conformation of the human placenta aromatase. Nuclear receptor signaling activation tendencies of seven of them showing high docking scores comparable to that of the co-crystalised ligand, exemestane, were determined in a ligand-based webserver screening (Protox-II) and docking against an agonist conformation of the ERα ligand binding domain (ERαLBD). Other toxicity and pharmacokinetic/drug-likeness evaluations were caried out using Protox-II and SwissADME webservers. Stability of aromatase complex with the highest-docking-score SS was explored in a molecular dynamics simulation using Webgro molecular dynamics webserver at a 20 ns simulation time. None of the seven SS activated the nuclear receptor signaling pathways; pharmacokinetic/drug-likeness predictors showed that they would be orally bioavailable; they were not susceptible to drug metabolising cytochrome P450 (CYP) isozymes and two of them demonstrated non-susceptibility to the efflux transport activity of P-glycoprotein (Pgp). Molecular dynamics data analysis revealed the root mean square deviation (RMSD) of 2 Å–3 Å and a radius of gyration of and 22 Å over the 20 ns simulation time. This investigation provides a molecular framework for anti-oestrogenic anti-BPH therapeutic strategy via aromatase inhibition (AI) and unmasks seven SS as potential anti-BPH AIs.

***Keywords*:** Spirostan sapogenins, *In silico* ADMET studies, Benign prostatic hyperplasia, Aromatase inhibitos, *In silico* drug discovery

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