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In silico investigation of binding properties of steroids molecules interacting with Androgen receptor

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Abstract

Prostate cancer (PC) is one of the most prevalent cancers in male worldwide. Androgen receptor (AR) is an essential protein receptor of cells in the prostate gland to induce uncontrolled proliferation. The AR, a member of the steroid hormone nuclear receptor superfamily, plays a key role in regulating gene expression in a variety of tissues including the prostate. Thus, AR is one of the primary targets in the development of new chemotherapeutic for treatments mainly of prostate cancers. In addition, AR is considered as a potential drug target for breast cancers, ovarian cancers and pancreatic cancers. Chemoprevention of cancers by using natural products is well accepted clinical practice nowadays. Natural products such as plant sterols show remarkable anticancer activity, besides other activities. Such seven steroidal alkaloids of plant origin were selected form "Sri Lankan flora" information system (https://science.cmb.ac.lk/tools/slflora/) to investigate the potency to develop cytotoxic drugs for treating multidrug resistant cancer. In this study, seven natural steroid molecules which are structurally similar analogues of natural androgens such as testosterone and dihydrotestosterone (DHT), were chosen as lead molecules targeting AR as a therapeutic receptor. The hydroxyflutamide (HFT) was selected as the synthetic drug candidate for the comparison. The molecular docking simulation results show that two of the selected natural steroids have the close binding energies to both DHT and HFT. Moreover, molecular interaction analysis revealed that these two steroids, chonemorphine and stigmasterol interact with the active site residue R752 of AR in the similar manner to DHT and HFT. The approximate binding energy of the ligand with the receptor is given by the grid score as a summation of electrostatics and van der Waals energies. The best grid scores of the reference ligands, dihydrotestosterone and hydroxyflutamide were −24.1 kJ mol^{-1} and -27.7 kJ mol^{-1} respectively. However, chonemorphine shows -26.5 kJ mol^{-1} of closer grid score to the reference ligands. Further, the stigmasterol also shows a closer grid score of -30.6 kJ mol^{-1}. According to the results, the approximate binding energy of both chonemorphine and stigmasterol are more compatible with the binding energy of hydroxyflutamide and DHT. Furthermore, Chonemorphine and stigmasterol are steroidal alkaloids that have already been identified as potential medicinal agents for various diseases in folk medicines. Therefore, this study shows that chonemorphine and stigmasterol could be used as lead molecules to develop novel drug(s) in multidisciplinary manner for PC patients eliminating side effects.

Keywords: *Molecular docking, steroids, nuclear receptors, cancers, molecular dynamics*

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