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Unveiling the mechanism of selected steroids targeting G6PD in gastric cancer through computational approaches

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Gastric cancer ranks as the fifth leading cause of cancer globally, posing a significant challenge despite extensive research and funding efforts. Medicinal chemists continue to face difficulties in developing practical and durable therapies, particularly due to the heightened reliance of cancer cells on Glucose-6-Phosphate Dehydrogenase (G6PD)-mediated NADPH production compared to normal cells. This study investigates the pharmacokinetics and molecular targets of selected steroids as potential anti-gastric cancer agents. The results demonstrate that these steroids likely induce apoptosis by modulating key signalling pathways, with G6PD inhibition increasing reactive oxygen species and activating caspase-3, while regulating cell survival and proliferation through targets such as ATP1A1 and NOTCH1. Molecular docking analyses with the protein 7E6I reveal that CPD5 exhibits greater stability and better localisation within the 7E6I binding pocket than DHEA. Molecular dynamics simulations over 100 ns further confirm a consistent binding mode, highlighting CPD5's effective inhibition of the protein 7E6I. MMGBSA reveals binding free energies of –5.13 kcal/mol (CPD5-7E6I) *versus* –14.38 kcal/mol (DHEA-7E6I). DFT highlights CPD5's reactivity exceeding DHEA's. ADMET profiling confirms CPD5's non-toxicity, stability, and high absorption. Thus, CPD5 represents a viable candidate for gastric cancer therapy *via* 7E6I inhibition.

Keywords: DFT, *In silico* study, G6PD, Gastric cancer, Molecular target, Steroids