Theoretical and experimental studies on the activity and development of anti-cancer agents

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Abstract: Cancer is one of the leading causes of mortality worldwide. Chemotherapeutic drugs target not only tumor cells but also normal cells. Targeted therapies (TT) directly recognize specific molecules involved in tumorigenesis resulting in lower toxicity. DNA topoisomerase IIα (TopoIIα) as shown in Figure (A) is up-regulated in cancer cells, making it an important target for TT. Mansonones (M) can be divided into four groups including MC, ME, MG, and MH. However, the poor solubility of M is the main problem for further pharmaceutical applications. Beta-cyclodextrin (βCD) as shown in Figure (B) has been extensively used to enhance the solubility of many hydrophobic molecules. In the present study, molecular modeling tools were used to screen and predict the inhibitory activity of the potent M against TopoIIα as well as to investigate the dynamics behavior and stability of M/βCDs complexes. The docking results showed that all series of MG preferentially bind to ATPase domain of TopoIIα. Among 18 derivatives, MG14 analog exhibited the highest binding affinity toward TopoIIα. Additionally, ME and MH could form inclusion complexes well and mostly positioned nearby secondary rim of βCDs. The ME and MH/2,6-DHPβCD inclusion complexes had the highest stability rather than methylated-βCD and βCD. Accordingly, this βCD derivative was the most suitable for inclusion complex formation.

Keywords: Topoisomerase IIα; Beta-cyclodextrin; Mansonones