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HDACIs, An alternative therapeutic approach human breast cancer treatment, *in vivo* and *in vitro*

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Breast cancer is the most common cause of cancer and the second most common cause of death in women worldwide. Despite major recent advances in therapy, more effective approaches to the treatment and prevention are necessary. Histone deacetylase inhibitors (HDACIs) provide an alternative therapeutic approach for the treatment of breast cancer. The therapeutic potential of HDACIs stems from their capacity to selectively induce apoptosis in tumor cells. HDACIs show promise as a single anti-cancer drugthat given the range of molecular and biological responses andhave a minimal toxicity to normal cells. In the present study, we investigated and compared the anticancer effects of two structurally distinct HDACIs, Vorinostat (SAHA) and Valproic Acid (VPA) respectively. In addition, we tested the effect of VPA/SAHA as a combination treatment, using T-47Dhuman breast cancer cell line. Anticancer effects of tested drugs were assessed by MTT assay, western blotting analysis of expression levels of p53, β-catenin and cyclin D1. In addition, apoptotic induction and morphological characteristics of T-47D breast cancer cells upon treatment with SAHA, VPA and combined treatment byboth drugs were performed.Furthermore, the antitumor effect of SAHA was investigatedbyimmunohistochemical analysis to detectcyclin Dl expression in tumor tissues of MNU-induced breast carcinoma *in vivo*. *In vivo* model, breast tumor size was decreased and nuclear localization of cyclin D1profoundly was changedupon SAHA treatment. *In vitro*, SAHAshowed a strong inhibitory effect on cyclin D1 expression compared to VPAinT-47D cells. In addition, HDACIs- treated T-47D cancer cells suppressed the expression level of oncogenic β-catenin expression and enhancedtotal p53 expression. Furthermore, SAHA,VPA and VPA/SAHA combined treatments induced morphological changes, apoptosis induction and DNA fragmentations. These results suggest that the combination treatment of SAHA and/or VPA exerts significant antitumor activity and could be a promising therapeutic candidate for human breast cancer treatment.

Biography

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ADMET based screening, molecular docking and dynamics simulation for DNA topoisomerase directed anti-cancerous alkaloids

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Topoisomerases (Topo I and II) have been looked as crucial targets against various types of cancers. In view of the fact that many lead molecules are eliminated during the development process because of poor ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, it is vital for any lead molecules to achieve a long term success as a drug to fulfill the ADMET criteria. In the present paper one hundred anti-cancerous alkaloids were subjected to *in silico* ADMET analyses for investigation of their pharmacokinetic properties. Out of one hundred, only eighteen alkaloids were found to fulfill all the ADMET descriptors which also obeyed Lipinski Rule of Five successfully. All these eighteen alkaloids were found to dock successfully within the active site of both Topo I and II. A comparison of the binding energy and inhibition constant (Ki) of the docked eighteen alkaloids with those of known inhibitors (drugs) of Topo I (topotecan) and Topo II (etoposide) revealed that four alkaloids, namely oliveroline, coptisine, aristolactam and piperine were found to be more potent inhibitors of both Topo I and II while two alkaloids, namely anonaine and liriodenine were found to be more potent inhibitors of Topo II with oliveroline being outstanding. The results of best docked alkaloid, oliveroline, were validated and compared with respective drugs topotecan and etoposide using 10 nanosecond (ns) molecular dynamics (MD) simulation which revealed stabilization of these complexes within 5 ns of simulation with better stability of Topo II complex than that of Topo I.