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COMPUTER-AIDED DRUG DESIGN WITH KNIME PLATFORM TO DISCOVER DNMT INHIBITORS FROM PHYTOCHEMICALS

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High throughput screening of drug candidates is an expensive and time-consuming process with a high rate of failure. In this regard, computational approaches using quantitative structure-activity relationship (QSAR) are a significant aid, enabling biological activity prediction using theoretically calculated physicochemical properties of candidate molecules. When coupled with machine learning (ML), QSAR approaches to create an ideal platform for discovering potential drug candidates. DNA methyltransferases (DNMTs) are epigenetic target enzymes responsible for adding the methyl group to the fifth position of the DNA base cytosine. Other than a few available drugs, several natural products have been discovered as inhibitors of DNMTs due to their availability and less toxicity. In this study, we combined a QSAR approach with ML using TeachOpenCADD KNIME workflows and applied it to identify plant molecules structurally similar to the active pharmaceuticals of current DNMT inhibitors. KNIME v4.5.2 was used with the KNIME cheminformatics extension. Simplified Molecular Input Line Entry System (SMILES) notations of 295 drug molecules were retrieved from the ChEMBL database, where 27 molecules are known DNMT inhibitor drugs, 229 molecules are phytochemicals, and the rest are used to treat other diseases. FeatMorgan molecular fingerprints were used to prepare the dataset for ML using the RDkit fingerprint. The dataset was cross-validated at 15% by train-to-test ratio. Random forest, Support Vector Machine and Artificial Neural Network were used to train the model to accurately classify DNMT inhibitor medications from candidate phytochemicals with an accuracy of 92.9, 92.2, and 91.9%, respectively. Predicted molecules were filtered with Lipinski's rules of 5 to determine the drug-likeliness. Totally nine phytochemicals were predicted as DNMT inhibitors. These results suggest that the predicted phytochemicals can be studied as potential inhibitors against DNMT. However, further *in-vitro* and *in-vivo* efficacy studies need to be conducted on these phytochemicals.

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Keywords: DNMT inhibitors, KNIME, Machine learning, Phytochemicals