A MACHINE LEARNING APPROACH TO IDENTIFY POTENTIAL TXAS INHIBITORS ON FDA-APPROVED DRUG DATABASE

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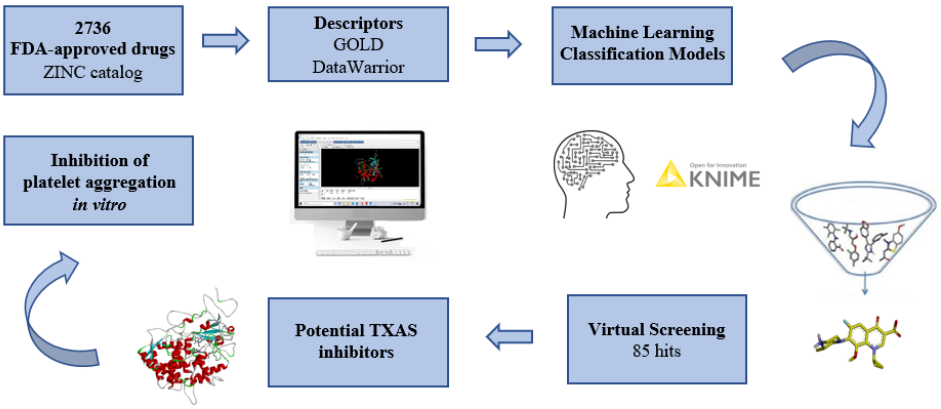
Introduction

Thromboxane A synthase (TXAS) is the enzyme responsible for synthesizing TXA_2, a potent platelet aggregating important in thrombotic events [1]. Virtual screening (VS) using molecular docking is a helpful tool for identifying putative inhibitors for several targets through scoring functions to predict the ligand-protein binding affinity [2]. In this context, machine learning (ML) algorithms enable obtaining classification models to improve the ranking of potential compounds by molecular docking [3,4]. In this work, we present a study to identify potential TXAS inhibitors using a combination of *in silico* and machine learning approaches in the database of FDA-approved drugs.

Material and Methods

This study used a machine learning classification model based on molecular docking and the physicochemical properties of ligands validated in our previous work [5] (Figure 1). We took 2736 FDA-approved drugs from ZINC catalogs (https://zinc.docking.org/) and generated their 3D structures using Open Babel software. We performed a molecular docking study using the ChemPLP function of the GOLD program. The physicochemical descriptors were obtained using the DataWarrior software, and we performed the classification models using the KNIME software (https://www.knime.com/). The datasets were normalized, and descriptors were filtered by linear correlation to be applied in the ML model with the XGBoost algorithm. The ML model was used in the VS of FDA-approved drugs to search for potential TXAS inhibitors. Three drugs were selected for *in vitro* evaluation of inhibition of arachidonic acid (AA)-induced aggregation in human platelet-rich plasma [6].

Figure 1. Machine learning-based virtual screening to identify potential TXAS inhibitors from FDA-approved drugs.

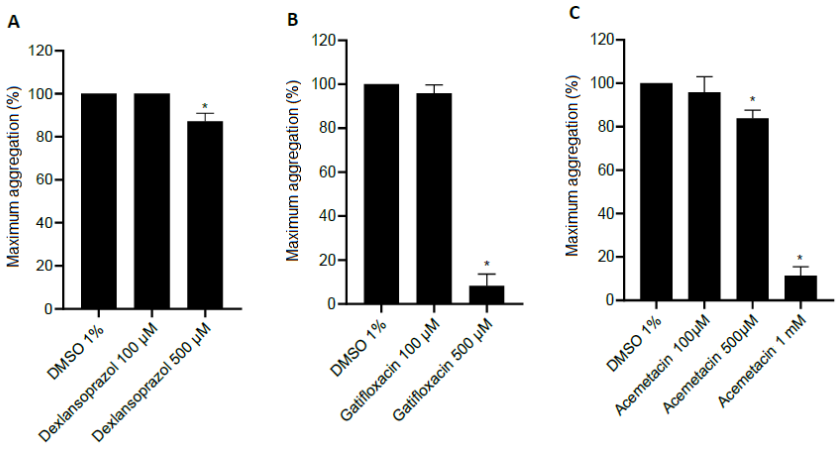


Results and Discussion

The ML classification model predicted 85 drugs from the FDA dataset as TXAS inhibitor. The prediction for all compounds was considered reliable by calculating the applicability domain of the

model in KNIME. The fluoroquinolone-derived antimicrobial gatifloxacin (GFX) showed the best performance with an 86% probability of being a TXAS inhibitor (P=0.86). The drugs selected for *in vitro* platelet aggregation inhibition assay induced by AA were gatifloxacin (GFX, P=0.86), acemetacin (ACM, P=0.65), and dexlansoprazol (DLS, P=0.60). Figure 2 presents the results of antiplatelet activity of these drugs in concentrations of 100 and 500 µM, and also ACM in 1 mM. A significant antiplatelet effect was observed through maximum aggregation values of GFX 500 µM (8.3%± 5.4) (Fig.2B) and ACM 1mM (11.4% ± 4.1) (Fig.2C). Concentrations of 1mM of the drugs DLS and GFX were also measured, without verifying an increase in the inhibitory profile. We observed a wide range of IC_{50} values for the drugs tested: GFX (IC_{50}=352 µM ± 11.0), ACM (IC_{50}=680 µM ± 6.1), and DLS (IC_{50} ≥1mM). These findings corroborate predictions of the ML model that show the greater potential of GFX for TXAS inhibition and the consequent antiplatelet action. Even though this drug cannot be repositioned as an antiplatelet, these results help to understand possible adverse effects or drug interactions.

Figure 2. The effects of drugs on platelet aggregation induced bu AA. Dexlansoprasol (100 and 500 µM (A), gatiflaxacin (100 and 500 µM) (B), and acemethacin (100 µM, 500 µM, and 1 µM) (C). DMSO (dimethyl sulfoxide). *p <0,05 (Tukey).



Conclusion

We use machine learning classification models based on molecular docking and physicochemical properties of ligands for virtual screening to identify potential TXAS inhibitors from FDA-approved drugs. Three drugs with a good prediction for TXAS inhibition in an ML model were tested *in vitro* for antiplatelet activity. They showed similar results compared to the *in silico*, in which Gatifloxacin presented a higher potential for inhibition of TXAS and a higher antiplatelet activity. These results can help understand possible adverse effects or drug interactions that affect the coagulation system.

Acknowledgments

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