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Machine Learning model to predict potential Monoamine Oxidase B inhibitors from Cannabis Compound Database

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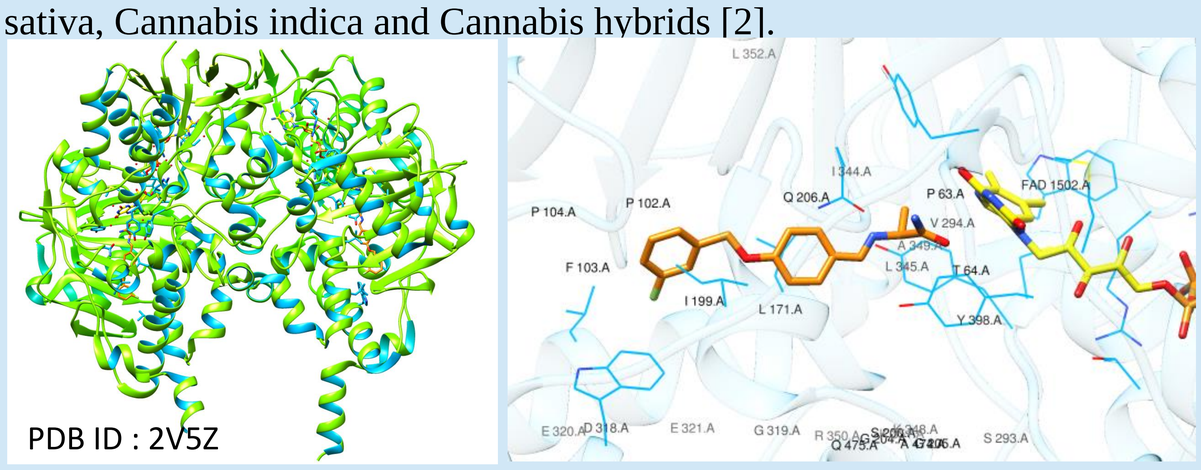
Abstract

Parkinson's disease is characterized by the loss of dopaminergic neurons in the mid brain. Monoamine Oxidase B (MAO-B) has been recognized as a successful target for developing antiparkinsonian and neuroprotective drugs. The selective inhibition of MAO-B is frequently used to treat Parkinson's disease by attenuating oxidative stress, regulating dopamine levels and limiting neuronal damage. In this study, a ChEMBL dataset containing 4815 molecules with reported half-maximal inhibitory concentration (IC_{50}) values for MAO-B was used to build machine learning regression model for selecting potential MAO-B inhibitors from the Cannabis Compound Database. A total of 235 compounds (9.9%) were predicted as active in this stage. Subsequently, virtual screening was performed, and top 20 molecules were selected and rescored using molecular docking. Finally, 2 compounds: CDB000040 and CDB005882 which displayed a docking score of -10.8 and -10.1 kcal/mol respectively were both predicted to be able to cross the blood–brain barrier suggesting these two structures as promising cannabis compounds for MAO-B inhibition among the 6172 molecules tested.

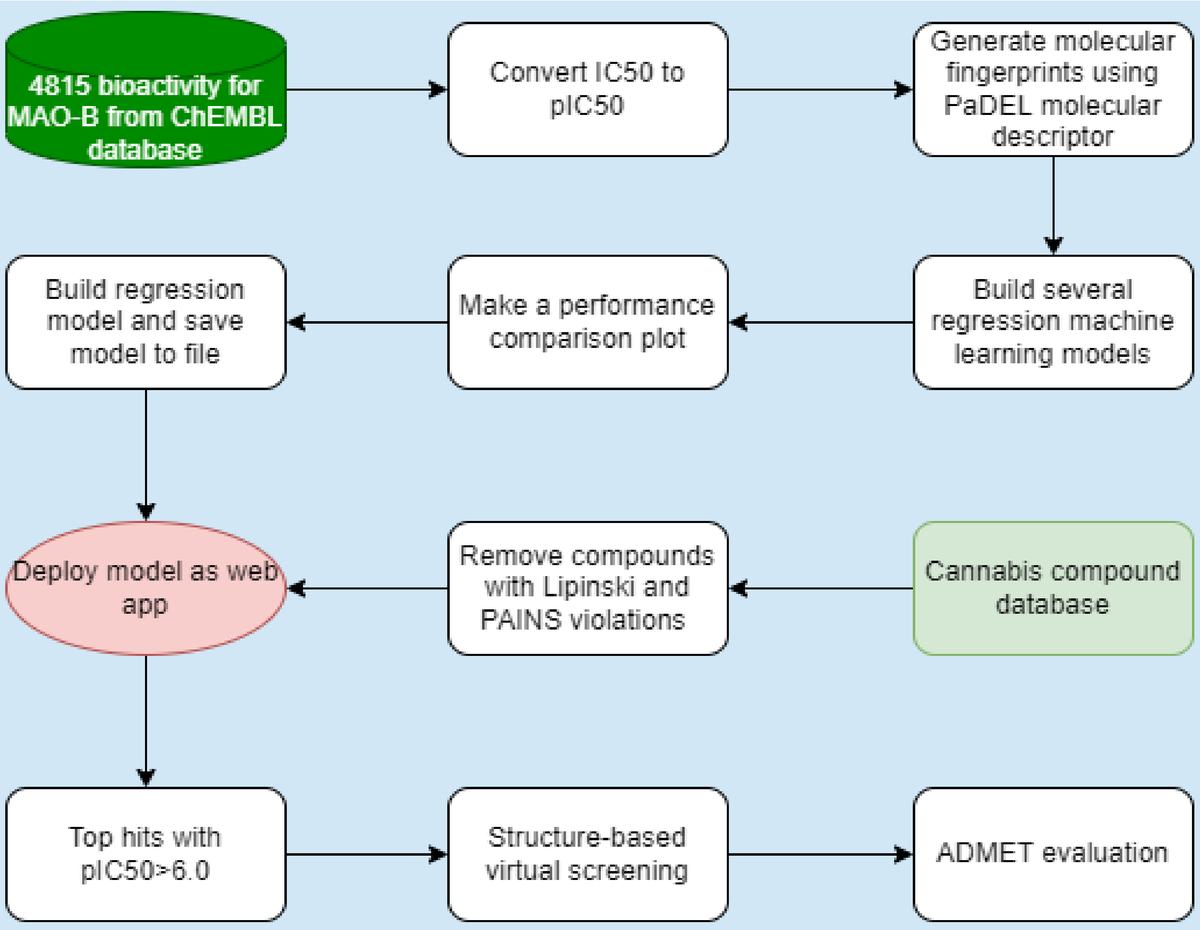
Introduction

Monoamine Oxidase B (MAO-B) (EC 1.4.3.4) is a mitochondrial flavoprotein attached to neurons outer-membrane that catalyzes the oxidative deamination of neurotransmitters and biogenic amines such as adrenaline, noradrenaline and dopamine [1]. Cannabis compound database (https://cannabisdatabase.ca/) is a freely available electronic database containing detailed information about small molecules found in Cannabis sativa, Cannabis indica and Cannabis hybrids [2].



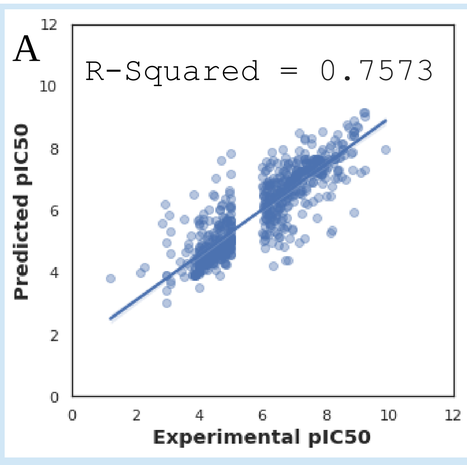
A) Crystallographic structure of MAO-B consisting of two chains. B) Binding cavity of MAO-B active site with bound safinamide (orange color) and FAD cofactor (yellow color).

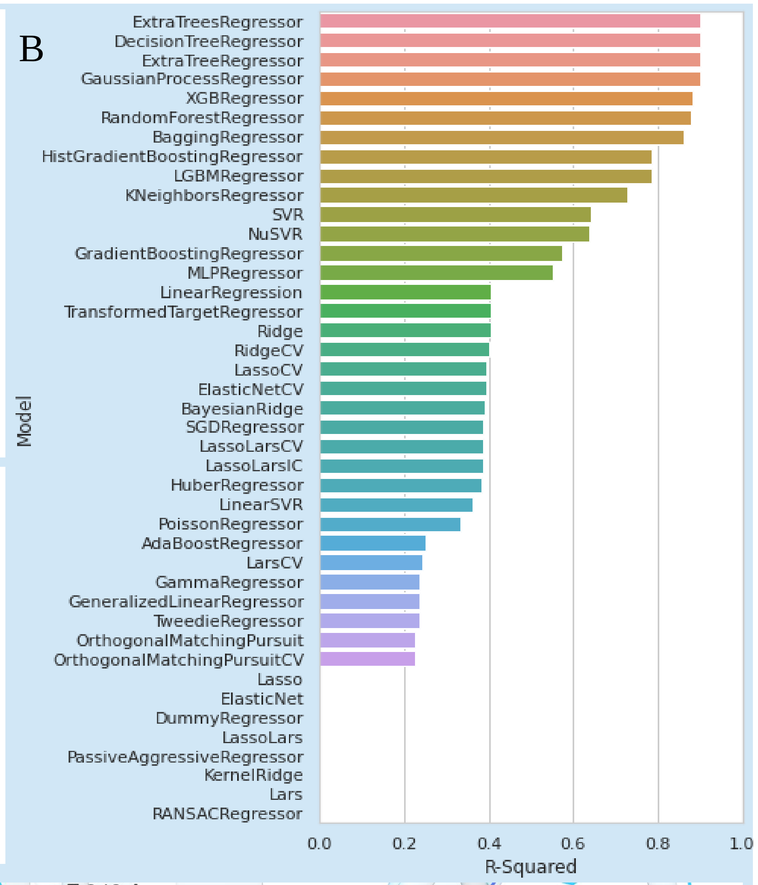
Methodology

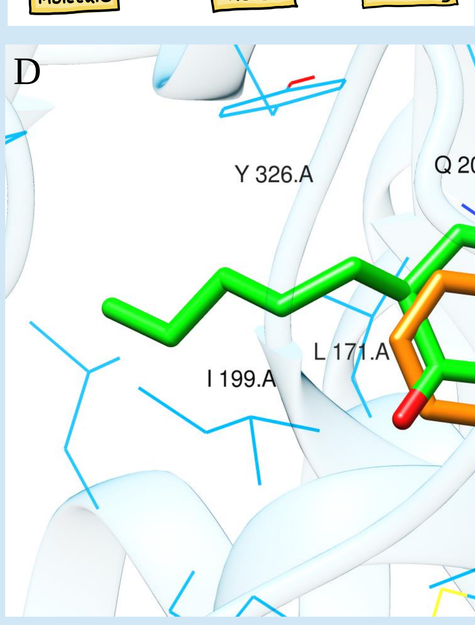


Overview of the combined machine learning and virtual screening workflow used in this study. Structure-based virtual screening was performed using Glide software, ADMET evaluation was performed using Qikprop.

Results







A) Scatter Plot of Experimental vs Predicted pIC50 Values. B) Comparison of different regression models performance. C) Web interface of the deployed MAO-B bioactivity prediction application. D) Docking poses of the selected compounds. CDB000040 is shown in green color, CDB005882 is shown in orange color.

Conclusion

This study combined a machine learning regression model with molecular docking calculations to assess 6172 compounds from the Cannabis compound database as potential MAO-B inhibitors. In conclusion, these emerging methodologies that integrate multiple virtual screening approaches represent interesting alternatives for use as the starting point during drug development, allowing for the identification of potentially actives molecules against diverse diseases, while reducing costs and saving time and money.

References

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[2] Wishart DS, Inchehborouni G, Cao X, Guo AC, Hiebert Giesbrecht M, LeVatte M, Liigand J, Wang F, Bhumireddy S, Wang Y, Zhang J, Mandal R, Dyck J. Chemical composition of Cannabis. (Manuscript in Preparation).