I. INTRODUCTION

The Blood-Brain Barrier (BBB) is a physiological defensive mechanism that separates the circulation from brain tissue and thereby protects the brain. It keeps toxins, viruses, and certain drugs from entering the brain and inflicting damage or altering its activities [1]. Penetration of the BBB is critical for the efficient treatment of neurological disorders such as Alzheimer's, Parkinson's, and brain cancers.

The unique characteristics of the Blood-Brain Barrier (BBB) frequently prevent therapeutic substances from reaching the deeper regions of the brain. Many drug candidates designed for central nervous system activity are rejected due to inadequate brain penetration, even if they have significant efficacy in vitro [2]. The primary challenge in predicting BBB penetration lies in the intricate structure and function of the BBB itself. Factors like the size, polarity, and biological activity of the drug candidate have substansial impact on whether a compound will pass through the BBB. In addition, more than 98% of drugs that have small molecules fail to penetrate the BBB. Accurately predicting a drug's capacity to get through the blood-brain barrier can help reduce side effects, improve treatment efficacy and stimulate innovation in drug development.

BBB penetration is commonly tested through conventional in vitro experiments, which include various methods and artificial membrane penetration tests. These tests are generally suitable for evaluating BBB penetration [2]. However, all the mentioned methods are expensive, time-consuming, and often impractical for large-scale drug screening experiments. Alternatively, BBB penetration can be assessed using computational machine learning approaches. This can enhance the success rate in the drug selection process while also reducing the required time and costs.

In several studies, researchers have frequently used in silico methods to predict BBB penetration. In 2020, Singh and colleagues designed multiple classification models to analyze a dataset containing 605 compounds and implemented a Consensus QSAR approach [3]. This approach produced better results compared to individual models, achieving an accuracy rate of 87%, a sensitivity of 0.88 and a specificity of 0.88.

Also in 2020, Alsenan and colleagues used a Recurrent Neural Network (RNN) to process a dataset containing 2342 compounds [4]. The RNN achieved an accuracy of 96%, with a sensitivity of 0.94 and a specificity of 0.98. In 2021, Shaker and colleagues utilized a Light Gradient Boosting Machine (LightGBM) to predict BBB penetration for a dataset of 7162 compounds [5]. The LightGBM algorithm, a faster and more efficient type of Gradient Boosting Decision Tree (GBDT), demonstrated an accuracy of 89%, with a sensitivity of 0.99 and a specificity of 0.77. Additionally, in 2021, Kumar and colleagues developed a new model called DeePred-BBB based on Deep Neural Networks [6]. Using a dataset of 3605 compounds, they achieved an accuracy of 98%. In the same year, Liu and colleagues created a BBB prediction model using an ensemble of three advanced machine learning methods: Random Forest (RF), Support Vector Machine (SVM), and XGBoost algorithms [7]. This approach achieved an accuracy of 93% with a sensitivity of 0.96.

According to literature surveys, performance can still be improved through the selection of appropriate models. The choice of model, ranging from conventional classification methods to deep learning algorithms, is crucial for achieving accurate predictions. This can be enhanced by combining the cuckoo-search method with ensemble approaches, which is expected to create new potential for improving the accuracy of BBB penetration predictions.

This study aims to develop a predictive model for BBB penetration using an algorithm called Cuckoo-Search. To enhance the performance and optimization of Cuckoo-Search, an ensemble method is required. This method works by combining multiple search algorithms into an ensemble to improve the performance and stability of the optimization. The ensemble approach can help address weaknesses and provide better stability and convergence within the solution search space. By integrating various strategies, the Cuckoo-Search Ensemble aims to create a more robust and adaptive system for solving optimization problems.