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Letter of Acceptance for Abstract

Dear Authors: Riska Aprilia(1), Mohammad Hamim Zajuli Al Faroby(2,*), Muhammad Adib Kamali(1), Muhammad Dzulfikar Fauzi(3)

We are pleased to inform you that your abstract (ABS-35, Oral Presentation), entitled:

"Herb Compounds Screening as Meningitis Inhibitor Candidates using Neural Network and Random Forest Methods"

has been reviewed and accepted to be presented at ICIMICE 2023 conference to be held on 25-26 October 2023 in Semarang, Indonesia.

Please submit your full paper and make the payment for registration fee before the deadlines, visit our website for more information.

Thank You.

Best regards,

Arief Hidayat, M.Kom.
ICIMICE 2023 Chairperson

Herb Compounds Screening as Meningitis Inhibitor Candidates using Neural Network and Random Forest Methods

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Abstract. Meningitis is an inflammation of the meninges that occurs in the protective lining of the brain and spinal cord caused by bacterial, viral, or fungal infections. This disease is difficult to recognize because it has initial symptoms like the flu where the patient has a fever and headache. Current efforts to prevent the disease by strengthening antibodies. Meanwhile, drug candidates for the treatment of this disease still have not found optimal results in reducing mortality due to meningitis. This study aims to find and analyses herbal compound candidates that might be inhibitors of meningitis. Compound data was acquired from a validated open database. The data acquired are smiles of the chemical bond structure of the compounds. In the data processing process, compound feature extraction is required by applying the concept of molecular fingerprint. The results of feature extraction are used as datasets to build classification models by applying the Multilayer Perceptron (MLP) and Random Forest algorithms. The two models are compared, and a more robust model is selected to be used as a prediction model for herbal compound search. The MLP model has a better accuracy of 0.97 compared to the Random Forest model. The results of screening using the MLP learning model obtained Symphytine, cis-Linalool oxide and 3-O-Methylcalopocarpin compounds have the highest probability compared to thousands of other herbal compounds. This candidate compound can be used as a recommendation for drug discovery to treat patients who contract Meningitis.

INTRODUCTION

Meningitis, which involves inflammation or infection of the membranes covering the brain and spinal cord, is a serious condition caused by a bacterial, viral, fungal, or parasitic infection. Common symptoms include a stiff neck, high fever, sensitivity to light, confusion, headache, drowsiness, seizures, nausea, and vomiting. Meningitis can lead to death, and the main preventive measures involve vaccination and living a healthy lifestyle (1). The death rate due to meningitis in Indonesia reached 4,313 out of 78,018 cases in 2016, making this country with the highest case and death rates in Southeast Asia (2). However, efforts to treat meningitis are still limited. The cause involves proteins in bacteria that do not yet have inhibitors to stop the spread of this disease, which can result in rapid death (3). Therefore, research on compounds that have the potential to become inhibitors in the treatment of meningitis symptoms is necessary.

Previously, studies have found synthetic compound candidates as meningitis disease inhibitors. Researchers have used the XGBoost algorithm with the extracted dataset as training data to build a classification model to find synthetic compounds that inhibit meningitis (4). Therefore, this Final Project aims to make observations on candidate herbal compounds derived from Indonesian medicinal plants. The analytical method used involves Neural Network and Random Forest algorithms. These two algorithms will be compared to produce a classification model based on the extracted feature data. The ultimate goal is to get better predictive results of compounds in providing treatment for

meningitis. It is hoped that the herbal compounds identified as candidates can assist medical personnel in clinical trials, bringing healing solutions to meningitis sufferers. It is hoped that this will provide a more natural treatment option with a lower risk of the impact of drug consumption compared to chemicals.

Based on this background, the authors wanted to analyze the probability of herbal compounds using random forest and multilayer perceptron methods to be used as meningitis inhibitor candidates which was carried out in silico. The results of the study are useful to guide laboratory personnel and future researchers to test compounds identified as potential in the treatment of meningitis sufferers as recommendations for drug discovery. However, this study has limitations in the form of using limited datasets from open sources, focusing on Indonesian herbal compounds contained in Herbal DB, and limitations of analysis which are more inclined to the in silico level rather than in vivo/in vitro. Thus, this study aims to bridge the gap in the treatment of meningitis through innovative computational approaches and analysis of herbal compounds.

MATERIAL AND METHODS

Material

A 2022 study, produced a compound with the code CHEMBL53984 as a candidate for meningitis inhibitors carried out by acquiring compound data from an online database. Data is extracted from features with molecular fingerprint and smiles code to obtain the dataset as a classification model. The classification model obtained was trained using the XGB method which can be a predictive model for the discovery of in silico compound candidates well and significantly compared to other methods (5). A 2020 study, produced 9 compounds that can bind directly to ibeA with the SPR test to prevent virulence meningitis by Caspr1 protein as an E. coli ibeA invasion protein. The data was processed using an online virtual screening server by applying comparative modeling methods to produce a dominant model of 3D homology targets and also carried out toxicity tests to determine the effectiveness of compounds on targets using in vivo animal models (6).

Protein Meningitis

Protein comes from the Greek proteas, which means the main or the first to come first. The word was introduced by Dutch chemist Gerardus Mulder (1802-1880). He argues that protein is the most important substance in every organism (7).

Understanding meningitis according to neurologists (8), explains that the disease occurs when the lining that protects the brain and spinal cord or commonly called the meninges is inflamed or infected. The disease is caused by viruses, fungi, or bacteria. This meningitis disease was initially quite difficult to recognize because it was considered to have symptoms similar to flu, fever, and headache. In addition, factors that increase the risk of meningitis are environments that have a level of cleanliness, avoid overcrowding in residential environments such as dormitories and campsites and avoid direct contact with meningitis sufferers. The type of treatment given to meningitis sufferers differs in handling depending on the cause of the disease. In meningitis caused by viruses, the drugs given are antiviral drugs and patients will improve with adequate rest and drinking lots of water. Meningitis is caused by bacteria, drugs given are antibiotics or corticosteroids that function to kill the causative bacteria. While in meningitis caused by fungi, the drugs consumed are antifungal drugs with adequate rest and a healthy lifestyle. In addition, the prevention of meningitis that occurs in infants is by immunization which aims to form immunity (9).

Meningitis protein is a target protein that can cause meningitis viruses and bacteria to develop. Further exploration is needed to prevent the development of viruses and bacteria (anti-meningitis) by searching for active compounds that have the potential to bind and inhibit the faster growth of these meningitis target proteins. Based on previous research, 7 vital meningitis proteins were found as target proteins to be analyzed. The target protein is seen in Figure 1.

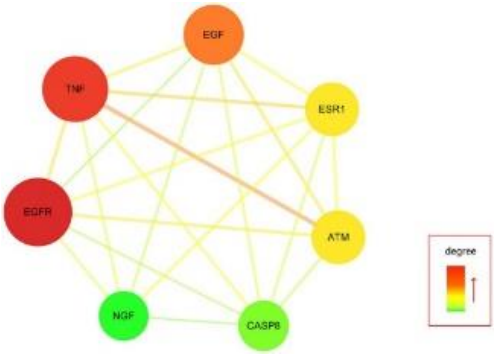

FIGURE 1. Seventh Protein Vital Target of Meningitis

The seven vital pharmacological target proteins for meningitis include ATM, CASP8, NGF, EGFR, TNF, EGF, and ESR1 which will be analyzed using protein interaction analysis (PPI). The target protein has several clusters of active compounds as anti-meningitis. In addition, the screening of active compounds on the seven potential target proteins as vital targets has not been studied for each compound and resulted in a longer time when analyzing all possible compounds that can bind meningitis (5,10). Computing devices play an important role in data analysis by providing efficiency in finding suitable active compounds. The application of machine learning algorithms is useful as a process of analyzing network interactions in proteins (11) and besides being efficient with time, the process of searching for active compounds that can bind and inhibit proteins using computational devices provides other benefits, namely lower costs to obtain a suitable compound compared to carrying out an analysis of biological objects directly on the object or better known as a research manual (12).

Bioinformatics Database

Protein data is available in several world databases. The data was acquired from open-source bioinformatics databases available online namely Protein Data Bank (GDP), National Center for Biotechnology Information (NCBI), PubChem, DUDE: Database, and Drugbank. Protein data will be taken from the protein database which aims to complement each other if, in one of the databases, there are still no proteins registered.

Active Compound Data

Active compounds are chemical compounds that have certain biological properties or activities that can interact with certain biological targets in the body, such as enzymes, receptors, or metabolic pathways. This biological activity can be pharmacological effects, medical therapy, or other biological effects. Active compounds are often a focus in drug research and development because of their potential to be the basis for drugs or therapeutic agents.

Decoy Compound Data

Protein data is available in several world databases. The data was acquired from open-source bioinformatics databases available online namely Protein Data Bank (GDP), National Center for Biotechnology Information (NCBI), PubChem, DUDE: Database, and Drugbank. Protein data will be taken from the protein database which aims to complement each other if, in one of the databases, there are still no proteins registered.

Feature Extraction

Data feature extraction is carried out to convert the acquired compound data into molecular fingerprints. Research into machine learning-based drug testing that uses molecular fingerprinting to extract properties from chemical compounds. There are two standard trace molecules found in RDKit, the first being PubChem with 881 molecular features (5,13,14), and the standard molecule Klekota-Roth the second has 4,860 molecules characteristics (15). The identified molecular structural bonds have certain structural bonds. In the example of a molecular structure in Figure 2 with a ring bond, the substructure is the encoded trait 1. If the compound data has no chemical bonds in the substructure, if this is an important characteristic, the substructure characteristic will be encoded as 0 (5).

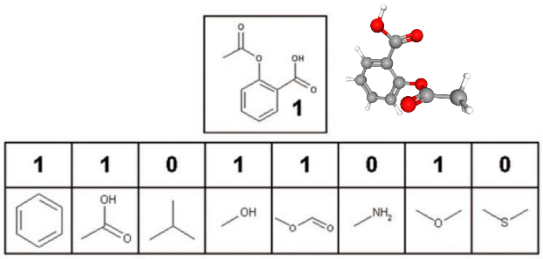

FIGURE 2. Example of feature extraction in aspirin compounds using molecular fingerprint

The process of extracting features in the data in the form of smiles (Simplified Molecular Input Line Entry System). The system can represent a compound writing form in the form of a string. the smiles of these compounds are represented quickly and precisely in binary form 1 and 0 (16). Researchers previously gave an example of Figure 2 compounds regarding the extraction of characteristics in aspirin compounds using molecular fingerprints that have binaries 1 and 0 (5). The aspirin compound above has smiles CC(=O)OC1=CC=CC=C1C(=O)O which has the name IUPAC (chemical compound naming system), namely 2-acetyloxybenzoic acid. It should be noted that the representation of compounds in a series cannot be used as a reference that these compounds are the same because a smiles is just a simple chain form of a compound. Therefore, these smiles must be turned into fingerprints that can be used to determine the similarity of a compound with another compound. Using fingerprints as a proxy for the data of a compound makes comparisons of similarity more accurate because it can be judged from the properties contained in the structure of the compound itself (16).

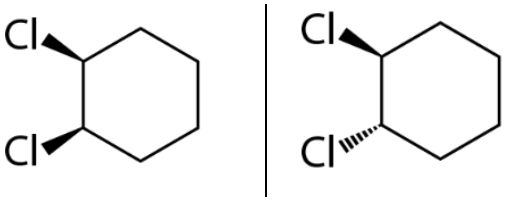

FIGURE 3. Examples of differences between cis (left) and trans (right) in compounds

This research uses a type of smiles fingerprint that is commonly used, namely the PubChem fingerprint which has as many as 881 features can be seen in the example of Figure 4 PubChem's fingerprint will encode the compound into an 881-bit binary feature. Each binary in the PubChem fingerprint is a molecular identifier that chemists commonly use to classify compounds. Some examples of identifiers used are the number of carbons in a compound that has more than 4 and the presence of a cis/trans structure (16). Cis is a unidirectional substituent group while trans has a substituent group that is in the opposite direction. The difference can be seen in the example of Figure 3 above.

	PubchemFP0	PubchemFP1	PubchemFP2	PubchemFP3	PubchemFP4	PubchemFP5
1	1	1	1	0	0	0
2	1	1	1	0	0	0
3	1	1	1	1	0	0
4	1	1	0	0	0	0
5	1	0	0	0	0	0
6	1	1	0	0	0	0
7	1	1	0	0	0	0
8	1	1	0	0	0	0

FIGURE 4. Example of some binary code on PubChem fingerprint extracted feature

Method

This research was conducted with stages of literature study, data collection, data preprocessing, feature extraction, model classification, and prediction of herbal compounds. The literature stage that is used as a research reference is found through reference sources, books, the internet, proceedings, and papers and journals from various national and international publications. The data collection phase carried out includes herbal compound data obtained from Herbaldb, active compound data, and decoy from DUDE: Database and drug bank and has been validated using the PubChem database. The important attributes acquired are the name of the protein compound, ID PubChem, and Smiles. The next stage is data preprocessing where the acquired data is cleaned by deleting duplicate data, data, drop decoy data to balance the amount of active and decoy data, drop data after extraction of zero-value features

vertically from a combination of active compound, decoy, and herbal data that has been extracted using the PubChem 881 feature to obtain codes 1 and 0 from molecular fingerprints. In compounds that have been extracted, features are given additional class columns, namely active compounds (class 1), and decoy compounds (class 2). The next stage is feature extraction which uses the concept of molecular fingerprint. The concept is used to extract chemical compounds in the form of smiles. Smiles has a string type which is then translated into binary codes 1 and 0 using the RDKit tool whose results will be used as a dataset to build a classification model. Datasets that have been in good condition through preprocessing and feature extraction that have been done are then used to build classification models using Multilayer Perceptron (MLP) and Random Forest (RF) algorithms. The next process of model classification results with 70% training data sharing and 30% testing obtained a more robust model using the GridSearchCV hyperparameter tuning method based on grid parameters adopted from previous studies for the best parameter search. The best parameters were analyzed and compared between the two algorithms used using confusion matrix model performance tests, accuracy, precision, recall, f1 score, and ROC AUC, as well as searching Log Loss on data conducted training, testing, and validation. The best model produced based on the analysis carried out is then used as a predictive model for the search for herbal compound candidates.

RESULT AND DISCUSSION

Data Collection

The data used in this study include 7 vital target proteins consisting of ATM, Capse8, EGF, EGFR, ESR1, NGF, and TNF with a total of 1145 active compounds obtained, 35050 herbal compounds that have been dropped into 3505 data to avoid imbalances that cause overfitting and underfitting during model classification, and 5455 herbal compounds from the total cleaned from 6757 total compound data that were not found PubChem and smiles ID attributes.

Preprocessing and Extraction Features

The acquired data is extracted features into binary form and sanitized by removing data that is vertically 0 (zero) for each feature on a combination of all three data types (active, decoy, herbal). The process of obtaining clean herbal compounds as much as 5455 data from the original database, namely by scrapping the compound name search to generate into PubChem ID and smiles.

Model Classification

Data that has been clean and ready to use, is carried out as a dataset for the search for the best model as an herbal prediction model. Based on the hyperparameter tuning method, GridSearchCV is selected to find the best parameter using the following grid parameters in Table 1.

TABLE 1. Result Best Parameter Analysis

Reference	Tuning Hyperparameter Grid Search CV		CV	Random Forest Classifier
	Param Grid	Best Param		Accuracy
Experiment 1 (17)	max_features = [sqrt, log2] n_estimators = [10, 100, 200, 250, 275, 290, 300, 310, 325, 350, 500, 700, 1000, 1500, 2000]	'max_features': 'sqrt', 'n_estimators': 325	5	0.9770609318996416
Experiment 2 (18)	n_estimators = [10, 100, 300, 325, 340, 350, 380, 400, 425, 450, 500, 550, 600, 800, 900, 1000, 1300, 1500] max_features = [sqrt, log2]	'max_features': 'sqrt', 'n_estimators': 600	5	0.9792114695340501

Experiment 3 (19)	'max_features':['sqrt','log2', 'auto'], 'n_estimators' : [10, 100, 300, 325, 340, 350, 380, 400, 425, 450, 500, 550, 600, 800, 900, 1000, 1300, 1500], 'criterion' : ['entropy'], 'max_depth' : [25],	'criterion': 'entropy', 'max_depth': 25, 'max_features': 'auto', 'n_estimators': 1300	5	0.9777777777777777
Experiment 4 (19,20)	'max_features':['sqrt','log2', 'auto'], 'n_estimators' : [10, 100, 300, 325, 340, 350, 380, 400, 425, 450, 500, 550, 600, 800, 900, 1000, 1300, 1500], 'criterion' : ['entropy', 'squared_error'], 'max_depth' : [None, 25, 300],	'criterion': 'entropy', 'max_depth': 25, 'max_features': 'auto', 'n_estimators': 600	5	0.9777777777777777
Experiment 5 (17–21)	'max_features':['sqrt', 'auto'], 'n_estimators' : [300, 325, 340, 350, 380, 400, 425, 450, 500, 550, 600], 'criterion' : ['entropy'], 'max_depth' : [None, 20, 25, 30], 'min_samples_split': [2, 5, 10]	'criterion': 'entropy', 'max_depth': None, 'max_features': 'sqrt', 'min_samples_split': 2, 'n_estimators': 340	5	0.9799283154121864
Reference	**Tuning Hyperparameter Grid Search CV**		**CV**	**MLP Neural Network Classifier**
	Param Grid	**Best Param**		**Accuracy**
Experiment 1 (22)	'activation' : ['tanh',' relu'], 'hidden_layer_sizes' : [(100), (50,50), (50,100, 50)], 'solver' : ['sgd', 'adam'], 'alpha' : [0.1, 0.01, 0.001]	'activation': 'tanh', 'alpha': 0.1, 'hidden_layer_sizes': (50, 100, 50), 'solver': 'adam'	5	0.9770609318996416
Experiment 2 (23)	'activation' : ['relu'], 'solver' : ['adam', 'sgd'],	'activation': 'relu', 'solver': 'adam'	5	0.9756272401433692
Experiment 3 (24)	'hidden_layer_sizes' : [(32), (64), (128), (256), (512), (32,32), (64,32), (128,32), (256, 32)],	'hidden_layer_sizes': (64, 32)	5	0.974910394265233
Experiment 4 (25)	max_iter = 100 hidden_layer_sizes : [(10, 30, 10), (20,)], activation : [‘tanh’, ‘relu’], solver : [‘sgd’, ‘adam’], alpha : [0.0001, 0.05], learning_rate : [‘constant’, ‘adaptive’]	'activation': 'relu', 'alpha': 0.0001, 'hidden_layer_sizes': (20,), 'learning_rate': 'constant', 'max_iter': 100, 'solver': 'adam'	5	0.9713261648745519

Experiment 5 (20,25)	'max_iter' : [100,200], 'hidden_layer_sizes' : [(10, 30, 10), (20,)], 'activation' : ['tanh', 'relu'], 'solver' : ['sgd', 'adam'], 'alpha' : [0.0001, 0.05], 'learning_rate' : ['constant', 'adaptive']	'activation': 'relu', 'alpha': 0.05, 'hidden_layer_sizes': (20,), 'learning_rate': 'constant', 'max_iter': 200, 'solver': 'adam'	5	0.9727598566308244
Experiment 6 (20,22–25)	'activation': ['tanh','relu'], 'alpha': [0.1, 0.0001, 0.05], 'hidden_layer_sizes': [(20,), (50, 100, 50), (64, 32)], 'solver': ['adam', 'sgd'], 'learning_rate': ['constant'], 'max_iter': [100, 200],	'activation': 'relu', 'alpha': 0.05, 'hidden_layer_sizes': (64, 32), 'learning_rate': 'constant', 'max_iter': 200, 'solver': 'adam'	5	0.9591397849462365

The best parameter results were carried out using a confusion matrix that produced True Negative (TN), True Positive (TP), False Positive (FP), and False Negative (FN) values and tested the following Accuracy, Precision, Recall, and f1 score metrics in tables 2 and 3.

TABLE 2. Confusion Matrix result on training, test, and validation data

Performance Metrics	**RF**			**MLP**		
	Train	**Test**	**Validasi**	**Train**	**Test**	**Validasi**
TP	139	302	42	793	328	328
TN	407	1034	181	2462	1033	1033
FP	0	9	2	0	10	10
FN	0	50	9	0	24	24
ROC AUC	1.00	0.98		1.00	0.99	
Log Loss / Best Threshold		0.18 / 0.52				
Log Loss / Epochs					0.02 / 113	

TABLE 3. Result of Accuracy, Precision, Recall, and F1 Score metrics on Random Forest (RF) and Multilayer Perceptron (MLP)

Experiment	**Test Data Performance**	**Training**	**Testing**	**Validation**
RF	Akurasi	1.00	0.96	0.95
	Presisi	1.00	0.97	0.95
	Recall	1.00	0.86	0.82
	F1-score	1.00	0.90	0.88
MLP	Akurasi	1.00	0.97	0.97
	Presisi	1.00	0.97	0.97
	Recall	1.00	0.93	0.93
	F1-score	1.00	0.94	0.94

Test the performance of other models to visualize the results of the model classification, using the ROC AUC graph and to determine the loss value of the model used using Log Loss shown in Figures 5.

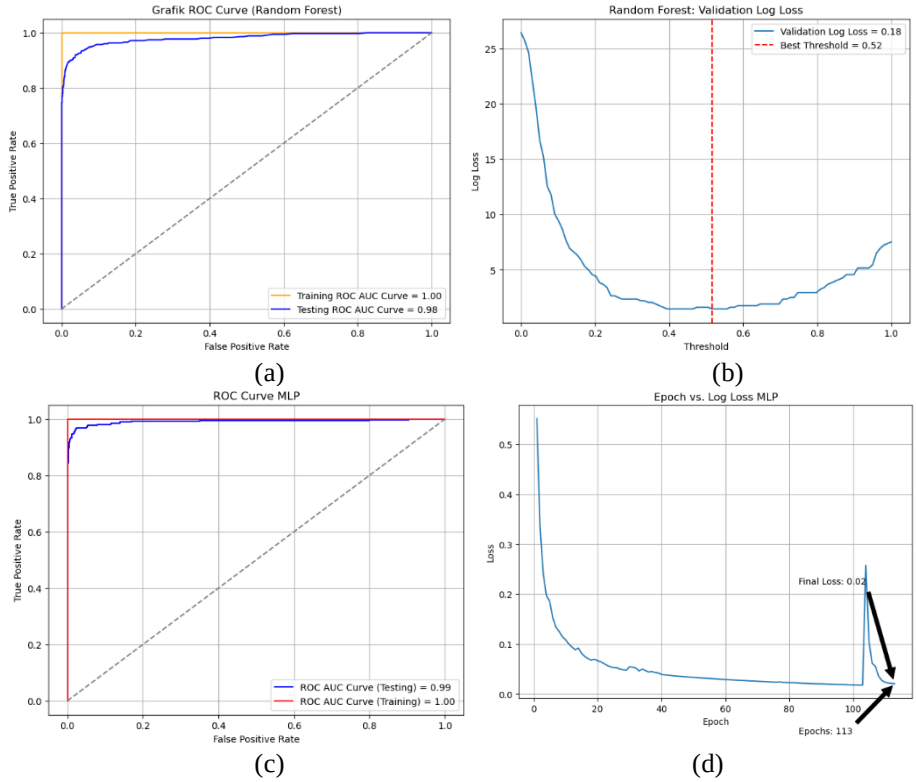

FIGURE 5. ROC AUC and Log Loss Random Forest (a,b) or ROC AUC and Log Loss Multilayer Perceptron (c,d) charts

Based on the analysis of test performance from the parameters obtained from the best parameters, the difference between RF: MLP accuracy in the division of data successively training, testing, and validation, namely 100%, 96%, 95%: 100%, 97%, 97%. Precision RF: MLP, 100%, 97%, 95%: 100%, 97%, 97%. RF Recall: MLP, 100%, 86%, 82%: 100%, 93%, 93%. F1 Score RF : MLP, 100%, 90%, 88% : 100%, 94%, 94%. It can be seen that the MLP model is superior in calculating the percentage of metrics obtained from the confusion matrix so the model is used as a prediction model using parameters taken from the best MLP parameters.

Screening Herbal

The acquired data is extracted features into binary form and sanitized by removing data that is vertically 0 (zero) for each feature on a combination of all three data types (active, decoy, herbal). The process of obtaining clean herbal compounds as much as 5455 data from the original database, namely by scrapping the compound name search to generate into PubChem ID and smiles.

TABLE 4. Predictive results of herbal compounds

Herbal Compound Name	PubChem	Smiles	0
Symphytine	5281754	C/C=C(\C)/C(=O)O[C@@H]1CCN2[C@@H]1C(=CC2)COC(=O)[C@@]([C@H](C)O)(C(C)C)O	0.999968159753745
cis-Linalool oxide	6428573	C[C@]1(CC[C@@H](O1)C(C)(C)O)C=C	0.9999670694355985
Sulfate	1117	[O-]S(=O)(=O)[O-]	0.9999625745004597

3-O-Methylcalopocarpin	467497	CC(=CCC1=CC2=C(C=C1OC)OC[C@@H]3[C@H]2OC4=C3C=CC(=C4)O)C	0.9999623716143573
Capitellataquinone A	101741040	CC(C)(C1CC2=C(O1)C(=CC3=C2C(=O)C4=C(C3=O)C(=CC=C4)O)CO)O	0.9999562865129958
1,2-Dehydro-alpha-cyperone	13192441	CC1=C2CC(CCC2(C=CC1=O)C)C(=C)C	0.9999555753554848
Hydroxyanigorufone	11471752	C1=CC2=C3C(=C1)C=C(C(=O)C3=C(C=C2)C4=CC=C(C=C4)O)O	0.9999546392019536
Anethole	637563	C/C=C/C1=CC=C(C=C1)OC	0.9999502085853899
trans-p-Feruloyl-beta-D-glucopyranoside	13962928	COC1=C(C=CC(=C1)/C=C/C(=O)O[C@H]2[C@@H]([C@H]([C@@H]([C@H](O2)CO)O)O)O)O	0.9999502085853899
Echinocystic Acid	73309	C[C@]12CC[C@@H](C([C@@H]1CC[C@@]3([C@@H]2CC=C4[C@]3(C[C@H]([C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)O)C)(C)C)O	0.9999496825346256

CONCLUSION

This study uses Random Forest (RF) and Multilayer Perceptron (MLP) algorithms which are used as model classifications to find the best model based on model performance tests. Based on the results of the analysis, the robust model to be used as a prediction model is the MLP algorithm with the best parameters 'activation': 'tanh', 'alpha': 0.1, 'hidden_layer_sizes': (50, 100, 50), 'solver': 'adam'. The results of the metric calculation obtained based on the confusion matrix can be concluded based on the acquisition of accuracy and f1 scores, namely with RF validation of 95% and 88% while MLP is 97% and 94%. As well as the calculation of ROC AUC RF: MLP accuracy of 98%: 99% with the calculation of Log Loss 0.18 in RF against Threshold 0.52 and 0.2 in MLP against Epoch 113.

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