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Screening Herbal Compound Candidates for Use as Anti-Inflammatory Drugs for COVID-19 Treatment Using Deep Semisupervised Learning

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ABSTRACT

COVID-19 is a disease caused by the SARS-CoV-2 virus, with various non-specific symptoms, including cough, fever, shortness of breath, and acute inflammation (hyperinflammation). These symptoms tend to worsen when inflammation is not controlled, and its severe cases can lead to death. Therefore, this study aimed to build a stacked autoencoder deep neural network (SAE-DNN) model for identifying herbal compound candidates that can be used as anti-inflammatory drugs for COVID-19 treatment. The model's performance was evaluated based on different data representations. The study process involved data collection and preprocessing, modeling, and testing the model on the herbal data to obtain compound candidates. The results showed that the developed SAE-DNN model with compound representation that combined fingerprint and dipeptide composition produced the best performance. Its values are 0.96722, 0.96419, 0.99596, and 0.96567 for accuracy, recall, the area under the receiver operating characteristic, and F1 score, respectively. Furthermore, a total of 33 herbal compounds were identified as potential anti-inflammatory drugs using the SAE-DNN model.

Keywords: COVID-19, deep learning, drug repurposing, hyperinflammation, semisupervised learning

INTRODUCTION

SARS-CoV-2 is classified as a Coronaviridae virus due to its crown-like shape morphology. According to Shereen *et al*. (2020), its rate of spread is higher than other coronaviruses such as SARS-CoV and MERS-CoV. The symptoms caused by this virus were not specific, mostly asymptomatic, while those that may appear include runny nose, cough, fatigue, and pneumonia (Li *et al*., 2020). Furthermore, COVID-19 patients suffer from hyperinflammation, which is caused by excess cytokines and worsens disease progression (García, 2020). Cytokines are proteins that alert the body about the entry of foreign substances, such as viruses, toxins, and bacteria. They play an important role in providing an immune response, but their excessive production may cause a cytokine storm. In this case, the inflammatory reaction in the body cannot be controlled (Yiu *et al*., 2012). Therefore, the discovery of drugs to prevent hyperinflammation due to COVID-19 is urgently needed.

In addition to the conventional, traditional medicine made from plants continues to play a valuable role. Plant-based treatment has been available for the last 60,000 years. Furthermore, traditional Chinese medicine (TCM) is still used as a complement to western medicine. For example, the TCM Shufengjiedu capsules offer similar efficacy to lopinavir and ritonavir in treating COVID-19 patients (Li *et al*., 2020). Kampo is also used as a complement to western medicine in Japan for cancer treatment, along with radiotherapy and chemotherapy (Yuan *et al*., 2016). Indonesia uses traditional medicine based on herbal plants to cure certain diseases. One of the most popular Javanese scripts that compile a list of medicinal herbs is *Serat Primbon Jampi Jawi Volume I* (SPJJ I). Some of the

plants included in this manuscript are tobacco leaves, lime, and garlic (Mulyani & Widyastuti, 2016). According to Widyatmoko (2018), Indonesia has the largest biodiversity potential in the world after Brazil and Colombia. The country is home to 27,500 species of flowering plants, and 1,300 plants are known to have medicinal properties. Therefore, Indonesia must explore its plant species as drug candidates for COVID-19 prevention and treatment.

Drug repurposing is a discovery strategy that uses compounds that certain institutions have recognized for the treatment of different diseases (Zhou *et al*., 2020). One of its steps is to identify the interactions between compounds and proteins. The two most popular in silico methods were molecular docking and machine learning (Bagherian *et al*., 2020). In silico is highly recommended because these experiments reduce costs and minimize possible risks (Xue *et al*., 2018).

Machine learning method has been extensively employed to predict the interactions between compounds and proteins, such as drug-target interactions (DTIs). In particular, feature-based machine learning method is commonly used in cases involving DTIs. This method uses extracted features from compounds and proteins (Bagherian *et al*., 2020). Bahi and Batouche (2018) predicted DTIs using the stack autoencoder (SAE) and deep neural network (DNN) model. The developed model uses data representation in the form of compound and protein characteristics. It includes semisupervised learning because of the weight initialization process involved before model predictions. Sulistiawan *et al*. (2020) used the SAE-DNN model to determine the herbal compound candidates as drugs against the SARS-CoV-2 virus, which resulted in a model accuracy of 0.94. Therefore, a study using SAE-DNN modeling is proposed to predict candidate compounds as hyperinflammatory drugs for treating COVID-19.

MATERIALS AND METHOD

Data Sources

Initially, 13 proteins that have a significant effect triggering inflammation were gathered because of COVID-19 using computational method. Other proteins were added by looking at existing literature that observed causes of inflammation. A study found that the interleukin-1-beta, interleukin-5, interleukin-8, and interferon-gamma contained effects that triggered inflammation (García, 2020; Yiu *et al*., 2012). For testing purposes, only proteins such as interleukin-6, interleukin-1-beta, interleukin-8, tumor necrosis factor-alpha, and interferon-gamma were included to predict the herbal compound candidates. Most were described in a previous study (Ramadhani, 2022). These proteins were used because of their effects on triggering inflammation. Furthermore, the data were collected from UniProt (https://www.uniprot.org/), which is a database that contains data about proteins, ranging from its sequence in a FASTA format to a summary (The UniProt Consortium, 2021) (Table I).

This study obtained compound data that have interactions with the target proteins and can reduce its effect. The interaction data were collected from a website called SuperTarget by searching each UniProt identifier that was previously gathered. SuperTarget (https://bioinformatics.charite.de/supertarget/) is a secondary database that retrieves all protein and compound interactions from existing databases (Günther *et al*., 2008). The PubChem identifier of the compound was obtained from SuperTarget (Kim *et al*., 2021). These identifiers were used to extract the compound in SDF format from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

The result showed approximately 7,902 interactions and 7,708 observed compounds. An unknown interaction was generated by merging all chemicals and proteins, as the data contained only the existing interactions. Afterward, 123,134 unknown interaction data were collected, resulting in a total of 131,036 compounds and proteins.

A sampling process was implemented with a 1:5 proportion between known and unknown interactions, given the unbalanced data (Sulistiawan *et al*., 2020). Therefore, the total training data obtained for modeling comprised 47,412 known (positive class) and unknown interactions (negative class).

Around 811 data on herbal compounds were obtained for testing from a database called HerbalDB (Syahdi *et al*., 2019). The compounds were paired with five target proteins and about 4,055 combinations of the compound protein interactions were tested.

Research Workflow

The research flow involved data collection and data preprocessing, model development, hyperparameters tuning, and model testing on herbal compound data. Figure 1 shows the research workflow.

Table I. The description of target proteins.

UniProt Identifier	Protein Name	Train Data	Test Data	Citation
VEGFA_HUMAN	*Vascular endothelial growth factor A*	✓	-	(Sahebnasagh, 2021)
MMP12_HUMAN	*Matrix metalloelastase*	✓	-	(Hardy, 2021)
TNFA_HUMAN	*Tumor necrosis factor*	✓	✓	(Guo, 2022)
B2MG_HUMAN	*Beta-2-microglobulin*	✓	-	(Conca *et al,* 2021)
IL8_HUMAN	*Interleukin-8*	✓	✓	(Ramadhani, 2022)
RASH_HUMAN	*GTPase HRas*	✓	-	(Sciacchitano, 2021)
EGFR_HUMAN	*Epidermal growth factor receptor*	✓	-	(Londres *et al*, 2022)
TF65_HUMAN	*Transcription factor p65*	✓	-	(Spinelli, 2021)
SDF1_HUMAN	*Stromal cell-derived factor 1*	✓	-	(Dogan, 2022)
LOX5_HUMAN	*Polyunsaturated fatty acid 5-lipoxygenase*	✓	-	(Ayolla-Serano, 2022)
IL1B_HUMAN	*Interleukin-1 beta*	✓	✓	(Ramadhani, 2022)
IFNG_HUMAN	*Interferon-gamma*	✓	✓	(Ramadhani, 2022)
PGH2_HUMAN	*Prostaglandin G/H synthase 2*	✓	-	(Ricke Hoch, 2021)
IL6_HUMAN	*Interleukin-6*	✓	✓	(Ramadhani, 2022)
HMOX1_HUMAN	*Heme oxygenase 1*	✓	-	(Batra et al., 2022)
PERM_HUMAN	*Myeloperoxidase*	✓	-	
HDAC3_HUMAN	*Histone deacetylase 3*	✓	-	(Sixto Lopez, 2022)

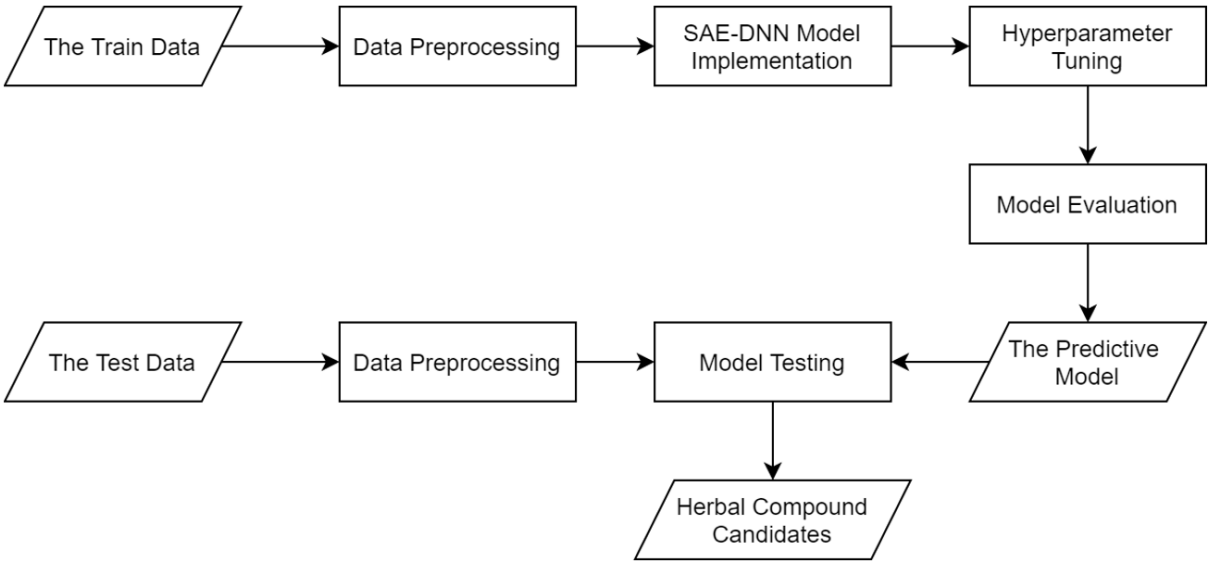

Figure 1. Research workflow

Data Preprocessing

The compounds and proteins were represented in string format. Specifically, the SDF and FASTA representations were used for the compounds and proteins, respectively. The representation is then converted into numerical form, such that modeling can be performed and PubChem fingerprint was used to represent the compounds. For the proteins, three descriptors, namely amino acid composition (AAC), dipeptide composition (DC), and quasi-sequence order (QSO) were considered, compared, and the best was selected to screen the compounds from the herbal dataset.

Table II. Data representation format for model training

s1	s2	…sn−1…	sn−1	sn	p1	p2	…pn−1…	pn−1	pn	label
1	0		1	1	0.25	0		0.01	0.3	1
1	0		1	0	0	0.25		0.3	0.01	0
0	1	…	1	1	0.3	0.01	…	0.25	0.3	1
0	1		0	1	0.01	0		0	0.25	0

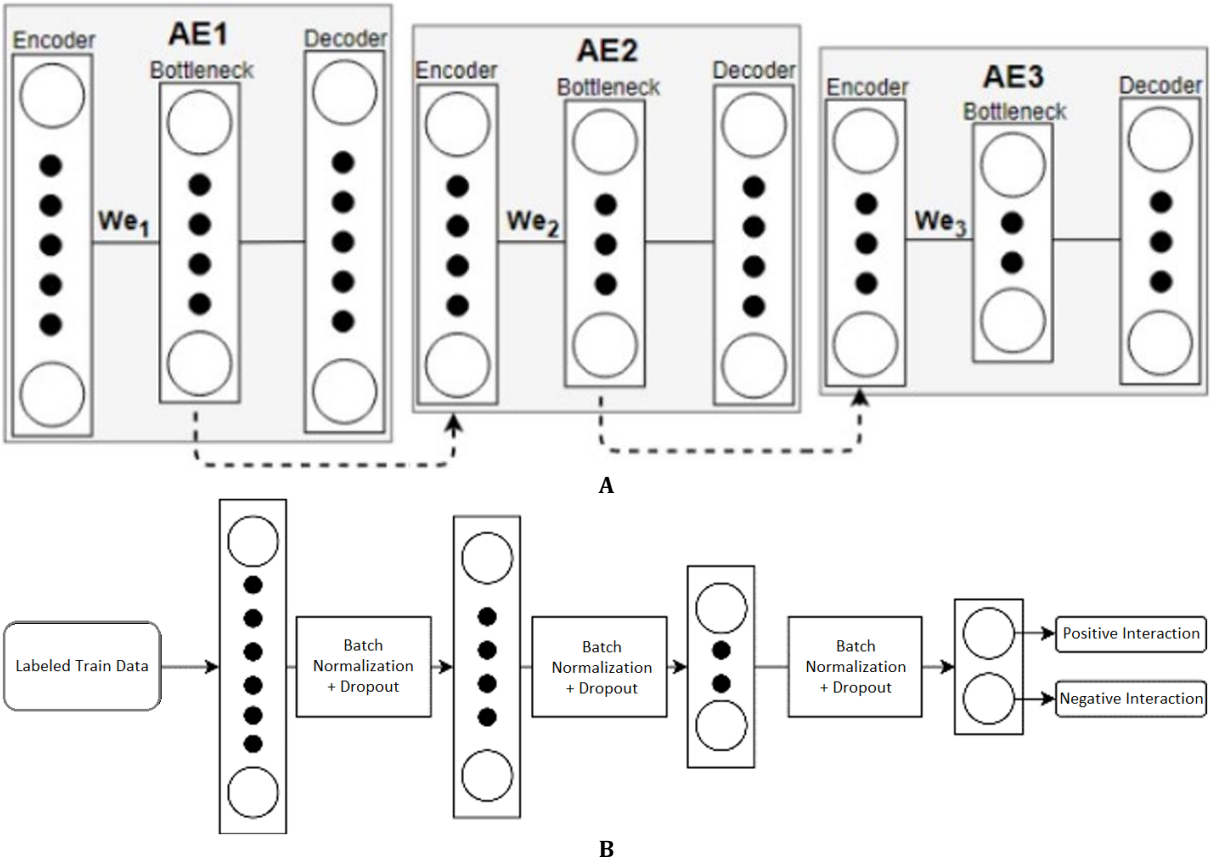

Figure 2. A. Illustration of the stacked autoencoder model (Sulistiawan et al. 2020); B. Illustration of the deep neural network model

The PubChem fingerprint is a representation that stores related compound information into a vector with 881 dimensions. Each element in the vector is assigned a value of 0 and 1 to indicate the absence and availability of information, respectively (Fernández-de Gortari *et al*., 2017). The representation was extracted using the R programming language with a library called ChemmineR. AAC is a protein representation that describes the frequency of amino acid occurrence as a fraction of the protein's length. It has 20 dimensions, with each value representing one amino acid. Furthermore, DC is a protein representation that describes the occurrence frequency of a dipeptide, a combination of two amino acids, within a protein with up to 400 dimensions. QSO stores sequence-related information between one amino acid and another. This representation has 40 + (2 * nlag) dimensions, where nlag is the maximum lag value. In this study, a maximum lag of 30 was used, which is the default value of the protr library. The representations were extracted using the protr library from the R programming language (Xiao *et al*., 2015). Subsequently, each feature was combined with its corresponding identifier.

After obtaining the features, the compounds and protein features were combined as a unified vector. To combine these features, data consisting of protein and compound identifiers were retrieved, along with labels indicating the presence or absence of interactions. Afterward, the features of the proteins and compounds were combined based on their corresponding identifiers. The identifiers were then removed from the data and a dataset was obtained to train the model (Table II).

Model Implementation

A semi-supervised-based deep learning model with a supervised and unsupervised learning process was implemented. Furthermore, two different deep learning models that consisted of SAE were combined for the unsupervised and DNN for the supervised learning process. The SAE model reconstructed the input as the output value using a middle layer called the bottleneck layer (Figure 2A). The bottleneck layer was used rather than random weights for the DNN model.

The weights for the DNN model were trained before predicting the herbal compound candidates. The DNN model consisted of several layers, each containing batch normalization and dropout layers. Batch normalization was a step to normalize the value range from the layer's output (Ioffe & Szegedy, 2015). It was applied to accelerate the training process. The dropout layer was used to randomly remove several nodes and it was applied to avoid the model overfitting the data. Overfitting is a condition where the model follows the data closely, resulting in a lower accuracy result (Srivastava *et al*., 2014). The model generated the predictions that contained an error for each iteration of the training process. The error is calculated by subtracting the model prediction result and the ground truth answer. To reduce this error, backpropagation was applied to adjust the model weights. Therefore, the model performance improved over time (Figure 2B).

Hyperparameters Tuning

Hyperparameters tuning is a process for finding the combination of hyperparameters, which are used to obtain the optimal model. Their combination is expected to improve model performance (James *et al*., 2013) (Table III). Bayesian optimization was adopted to conduct hyperparameters tuning. It is a method for identifying the combination of of values, which in this case is hyperparameters, that can reach the global optimum at a function. In contrast to grid search, Bayesian optimization uses a Bayesian-based method for selecting hyperparameters values. This method reduces the searchspace for a hyperparameters when the results obtained are close to the global optimum. Therefore, the processing time for searches using Bayesian optimization is relatively short (Frazier, 2018).

Table III. Hyperparameters choices for the model.

Hyperparameters	Choice
Hidden Layer Unit (HL0)	[300, 500, 750, 1000, 1250]
Hidden Layer Unit (HLi)	[0.5, 0.66, 0.75]
Activation Function	[ReLU, Tanh, Sigmoid]
Dropout	[0.1, 0.3, 0.5]
Number of Hidden Layers	[2, 3, 4]
Learning Rate	[0.01, 0.001, 0.0001, 0.00001]

Model Evaluation

The model was evaluated using k-fold cross-validation with a value of 10 to determine its performance before being used to screen herbal compounds. This method was used to perform 10 sets of using different training and validation data with a proportion of 90% and 10%, respectively (James *et al*., 2013). Metrics such as accuracy, precision, recall, and area under the receiver operating characteristic (AUROC) were used to quantify the model performance. The F1 score was used to determine the best model to retrieve the herbal compound candidates. Accuracy is a metric that calculates performance in all class labels while precision evaluates how the model can predict the classes precisely. Furthermore, recall determines the model's ability to retrieve all correct answers. AUROC calculates the area of the receiver operating characteristic chart, where the graph has a false and true positive rate on the x and y-axis, respectively. The F1 score takes precision and recall values to determine performance.

Model Testing

The optimal model was used to test the herbal compound dataset. This data comprises compound data from HerbalDB and inflammation-associated proteins, particularly those that have been shown to play a role in hyperinflammation due to COVID-19. The proteins used as targets include interleukin-6 (IL6), interleukin-8 (IL8), tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL1-β), and interferon-gamma (IFNγ).

Table IV. Best combinations of hyperparameters

Hyperparameters	Feature Combination		
	FP-AAC	**FP-DC**	**FP-QSO**
Hidden Layer Unit (HL_0)	500	1250	300
Hidden Layer Unit (HL_i)	0.5 * HL_{i-1}	0.5 * HL_{i-1}	0.75 * HL_{i-1}
Activation Function	ReLU	Sigmoid	ReLU
Dropout	0.1	0.1	0.1
Number of hidden layers	3	2	4
Learning rate	0.01	0.00001	0.01

Table V. Model evaluation result.

Metric	Feature Combination		
	FP-AAC	**FP-DC**	**FP-QSO**
Accuracy	0.98768 ± 0.003	0.98857 ± 0.001	0.98739 ± 0.002
Precision	0.97184 ± 0.013	0.96722 ± 0.008	0.95722 ± 0.013
Recall	0.95394 ± 0.009	0.96419 ± 0.004	0.96709 ± 0.015
AUROC	0.98648 ± 0.007	0.99596 ± 0.002	0.99205 ± 0.002
F1 Score	0.96273 ± 0.008	0.96567 ± 0.003	0.96199 ± 0.007

They were obtained from García (2020) and Yiu *et al*. (2012) who discussed immune reactions and inflammation caused by COVID-19 and the role of proteins in triggering inflammation.

RESULTS AND DISCUSSION

Data Preprocessing

The interaction data were subjected to preprocessing, where the compounds and proteins representation was changed from string to vector format. The data were preprocessed into three combinations of features, namely PubChem fingerprint and AAC feature (FP-AAC), PubChem fingerprint and DC feature (FP-DC), as well as PubChem fingerprint and QSO feature (FP-QSO). The total feature dimensions were 901, 1,281, and 981 for FP-AAC, FP-DC, and FP-QSO, respectively.

Hyperparameters Tuning

This stage used the Bayesian optimization method to determine the best combination of hyperparameters for the model based on data representation. Each combination of hyperparameters was modeled 20 times (Table IV). The table above showed that each model had different hyperparameters, except the dropout value. Furthermore, there is a correlation between the number of hidden neurons and layers. The FP-AAC and FP-QSO models used the ReLU activation function, while the FP-DC uses sigmoid.

Model Evaluation

The three models were evaluated with the best combinations of hyperparameters using a 10-fold cross-validation approach (Table V). Afterward, the model's performance in terms of accuracy, precision, recall, AUROC, and F1 score on each fold was calculated.

These results indicated that all models achieved over 95% performance across the metrics. Furthermore, the FP-AAC model had the best precision performance with a value of 0.98857, while FP-QSO had the best recall with 0.97184. The model with the FP-DC representation had the best accuracy, AUROC, and F1 score performance. The accuracy, precision, recall, AUROC, and F1 scores of the FP-DC model were 0.98857, 0.96722, 0.96419, 0.999596, and 0.96567, respectively. Therefore, the model with an FP-DC representation was used to test the herbal compound data.

Model Testing

The model was tested with FP-DC representation on the herbal compounds extracted from HerbalDB. A total of 1,283 from the 4,055 interactions tested were negative. From the 1,283 negative interactions, those with a probability value above 0.95 were taken. Furthermore, 33 out of 811 herbal compounds were predicted to have positive interactions with the target proteins that play a role in inflammation (Table VI).

Table VI. List of herbal compound candidates from prediction results.

Compound		
Perseitol	Agmatine	Pseudoakuammigine
Quinidine	Glucose	Allicin
Chamazulene	Cinchonidine	Glucobrassicin
Spermidine	Choline	Picrinine
Dulcitol	Citric acid	Glyoxylic acid
Nonacosane	Pimelic acid	Quinine
Hentriacontane	(+)-Quercitol	Cinchonine
Tritriacontane	(−)-Viburnitol	(−)-Pelletierine
Isopropylcyclohexane	(−)-Apparicine	D-Arabitol
Diallyl disulfide	Fructose	Hentriacontan-16-one
L-(+)-Tartaric acid	L-Histidine	Oxalic acid

Evaluation

The model results were evaluated by studying the plants containing thecompounds. The result showed that perseitol; L-(+)-tartaric acid; citric acid; (−)-pelletierine; quinidine and quinine; as well as allicin and diallyl disulfide compounds can be found in avocados; grapes; lemons; pomegranate tree root bark; quinine; and white onions, respectively. Quinine has the potential as an immunosuppressant and inhibits TNF-α as well as increases the production of IFN-α cytokines to suppress viral infections (Latarissa *et al*., 2021). Table 6 shows several derivates of quinine such as quinidine and cinchonidine, which has similar potential in COVID-19 therapy and safer profile compared to chloroquine and hydroxychloroquine were found (Latarissa *et al*., 2021). According to Bakun *et al*. (2021), chamazulene also known as azulene derivates is another compound with several potential as antiviral, anti-inflammation, anti-diabetes, and antineoplastic. Spermidine, also known as a derivate of polyamines, can inhibit infections of the coronavirus and increase the rates of autophagy (Firpo *et al*., 2021). Furthermore, agmatine has the potential to suppress inflammation including pain-related and neuropathy (Yezierski, 2000). Although the model was able to capture anti-inflammatory compounds, the predictive results also identified the compounds that induce inflammation, such as glucose and fructose, which comprise sugar. According to Gao *et al*. (2017), sugar is an inflammatory compound when consumed in large amounts.

CONCLUSION

This study successfully identified herbal compound candidates as anti-inflammatory drugs for COVID-19 treatment using SAE-DNN modeling. Furthermore, data representation with the FP-DC combination achieved satisfactory performance. The metric scores were 0.98857, 0.96722, 0.96419, 0.99596, and 0.96567 for accuracy, precision, recall, AUROC, and F1 score, respectively. This modeling found 33 herbal compound candidates that interact with inflammation-inducing proteins. A total of 31 compounds known to reduce inflammation were found from this candidate list and 2 trigger inflammation.

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REFERENCES

Ayola-Serrano, N. C., Roy, N., Fathah, Z., Anwar, M. M., Singh, B., Ammar, N., Sah, R., Elba, A., Utt, R. S., Pecho-Silva, S., Rodriguez-Morales, A. J., Dhama, K., & Quraishi, S. (2021). The role of 5-lipoxygenase in the pathophysiology of COVID-19 and its therapeutic implications. Inflammation research: official journal of the European Histamine Research Society ... [*et al*.], 70(8), 877–889. https://doi.org/10.1007/s00011-021-01473-y

Bagherian, M., Sabeti, E., Wang, K., Sartor, M. A.,

Nikolovska-Coleska, Z., & Najarian, K. (2020). Machine learning approaches and databases for prediction of drug-target interaction: A survey paper. *Briefings in Bioinformatics*, bbz157. https://doi.org/10.1093/bib/bbz157

Bahi, M., & Batouche, M. (2018). *Deep semi-supervised learning for DTI prediction using large datasets and H2O-spark platform* (p. 7). https://doi.org/10.1109/ISACV.2018.8354081

Bakun, P., Czarczynska-Goslinska, B., Goslinski, T., & Lijewski, S. (2021). In vitro and in vivo biological activities of azulene derivatives with potential applications in medicine. Medicinal chemistry research: an international journal for rapid communications on design and mechanisms of action of biologically active agents, 30(4), 834–846. https://doi.org/10.1007/s00044-021-02701-0

Batra, N., De Souza, C., Batra, J., Raetz, A. G., & Yu, A. M. (2020). The HMOX1 Pathway as a Promising Target for the Treatment and Prevention of SARS-CoV-2 of 2019 (COVID-19). International journal of molecular sciences, 21(17), 6412. https://doi.org/10.3390/ijms21176412

Conca, W., Alabdely, M., Albaiz, F., Foster, M. W., Alamri, M., Alkaff, M., Al-Mohanna, F., Nagelkerke, N., & Almaghrabi, R. S. (2021). Serum β2-microglobulin levels in Coronavirus disease 2019 (Covid-19): Another prognosticator of disease severity? PloS one, 16(3), e0247758. https://doi.org/10.1371/journal.pone.0247758

Dogan, S., Mart Komurcu, S. Z., Korkmaz, M. D., Kaya, E., Yavas, S., Dogan, S., Senturk Ciftci, H., & Dasdemir, S. (2022). Effect of Chemokine Gene Variants on Covid-19 Disease Severity. Immunological investigations, 1–10. Advance online

Fernández-de Gortari, E., García-Jacas, C. R., Martinez-Mayorga, K., & Medina- Franco, J. L. (2017). Database fingerprint (DFP): An approach to representmolecular databases. *Journal of Cheminformatics*, *9*(1), 9. https://doi.org/10.1186/s13321-017-0195-1

Frazier, P. I. (2018). A Tutorial on Bayesian Optimization. *ArXiv:1807.02811 [Cs, Math, Stat]*. http://arxiv.org/abs/1807.02811

Gao, Y., Bielohuby, M., Fleming, T., Grabner, G. F., Foppen, E., Bernhard, W., Guzmán-Ruiz, M., Layritz, C., Legutko, B., Zinser, E., García-Cáceres, C., Buijs, R. M., Woods, S. C., Kalsbeek, A., Seeley, R. J., Nawroth, P. P., Bidlingmaier, M., Tschöp, M. H., & Yi, C.-X. (2017). Dietary sugars, not lipids, drive hypothalamic inflammation. *Molecular Metabolism*, *6*(8), 897–908. https://doi.org/10.1016/j.molmet.2017.06.008

García, L. F. (2020). Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Frontiers in Immunology*, *11*, 1441. https://doi.org/10.3389/fimmu.2020.01441

Günther, S., Kuhn, M., Dunkel, M., Campillos, M., Senger, C., Petsalaki, E., Ahmed, J.,Urdiales, E., Gewiess, A., Jensen, L., Schneider, R., Skoblo, R., Russell, R., Bourne, P., Bork, P., & Preissner, R. (2008). SuperTarget and Matador: Resources for exploring drug-target relationships. *Nucleic Acids Research*, *36*, D919-22. https://doi.org/10.1093/nar/gkm862

Guo, Y., Hu, K., Li, Y., Lu, C., Ling, K., Cai, C., Wang, W., & Ye, D. (2022). Targeting TNF-α for COVID-19: Recent Advanced and Controversies. Frontiers in public health, 10, 833967. https://doi.org/10.3389/fpubh.2022.833967

Firpo, M. R., Mastrodomenico, V., Hawkins, G. M., Prot, M., Levillayer, L., Gallagher, T., Simon-Loriere, E., & Mounce, B. C. (2021). Targeting Polyamines Inhibits Coronavirus Infection by Reducing Cellular Attachment and Entry. ACS infectious diseases, 7(6), 1423–1432. https://doi.org/10.1021/acsinfecdis.0c00491

Hardy, E., & Fernandez-Patron, C. (2021). Targeting MMP-Regulation of Inflammation to Increase Metabolic Tolerance to COVID-19 Pathologies: A Hypothesis. Biomolecules, 11(3), 390. https://doi.org/10.3390/biom11030390

Ioffe, S., & Szegedy, C. (2015). Batch Normalization: Accelerating Deep Network Training by Reducing Internal Covariate Shift. International Conference on Machine Learning, 448–456. http://proceedings.mlr.press/v37/ioffe15.html

James, G., Witten, D., Hastie, T., & Tibshirani, R. (2013). *An introduction to statistical*

learning: With applications in R. New York : Springer, [2013] ©2013. https://search.library.wisc.edu/catalog/9910207152902121

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B. A.,

Thiessen, P. A., Yu, B., Zaslavsky, L., Zhang, J., & Bolton, E. E. (2021). PubChem in 2021: New data content and improved web interfaces. *Nucleic Acids Research*, *49*(D1), D1388–D1395. https://doi.org/10.1093/nar/gkaa971

Li, S., Li, S., Disoma, C., Zheng, R., Zhou, M., Razzaq, A., Liu, P., Zhou, Y., Dong, Z.,

Du, A., Peng, J., Hu, L., Huang, J., Feng, P., Jiang, T., & Xia, Z. (2020). SARS-CoV-2: Mechanism of infection and emerging technologies for prospects. Reviews in Medical Virology, n/a(n/a), e2168. https://doi.org/10.1002/rmv.2168

Latarissa, I. R., Barliana, M. I., Meiliana, A., & Lestari, K. (2021). Potential of Quinine Sulfate for COVID-19 Treatment and Its Safety Profile: Review. Clinical pharmacology: advances and applications, 13, 225–234. https://doi.org/10.2147/CPAA.S331660

Londres, H. D., Armada, J. J., Martínez, A. H., Abdo Cuza, A. A., Sánchez, Y. H., Rodríguez, A. G., Figueroa, S. S., Llanez Gregorich, E. M., Torres Lahera, M. L., Peire, F. G., González, T. M., González, Y. Z., Añé Kouri, A. L., Palomo, A. G., Concepción, M. T., Pérez, L. M., Luaces-Alvarez, L., Iglesias, D. E., Hernández, D. S., Suzarte, M. R., … Ramos, T. C. (2022). Blocking EGFR with nimotuzumab: a novel strategy for COVID-19 treatment. Immunotherapy, 14(7), 521–530. https://doi.org/10.2217/imt-2022-0027

Mulyani, H., & Widyastuti, S. H. (2016). Tumbuhan Herbal Sebagai Jamu Pengobatan Tradisional Terhadap Penyakit Dalam Serat Primbon Jampi Jawi Jilid I. Jurnal Penelitian Humaniora, 21(2), 19.

Ramadhani, H. F., Annisa, A., Tedjo, A., Noor, D. R., & Kusuma, W. A. (2022). Combination of Enrichment Using Gene Ontology and Transcriptomic Analysis Revealed Contribution of Interferon Signaling to Severity of COVID-19. Interdisciplinary perspectives on infectious diseases, 2022, 3515001. https://doi.org/10.1155/2022/3515001

Ricke-Hoch, M., Stelling, E., Lasswitz, L., Gunesch, A. P., Kasten, M., Zapatero-Belinchón, J., Brogden, G., Gerold, G., Pietschmann, T., Montiel, V., Balligand, J. L., Facciotti, F., Hirsch, E., Gausepohl, T., Elbahesh, H., Rimmelzwaan, G. F., Höfer, A., Kühnel, M. P., Jonigk, D., Eigendorf, J., Hilfiker-Kleiner, D. (2021). Impaired immune response mediated by prostaglandin E2 promotes severe COVID-19 disease. PloS one, 16(8), e0255335. https://doi.org/10.1371/journal.pone.0255335

Sahebnasagh, A., Nabavi, S. M., Kashani, H., Abdollahian, S., Habtemariam, S., & Rezabakhsh, A. (2021). Anti-VEGF agents: As appealing targets in the setting of COVID-19 treatment in critically ill patients. International immunopharmacology, 101(Pt B), 108257.

Sciacchitano, S., Sacconi, A., De Vitis, C., Blandino, G., Piaggio, G., Salvati, V., Napoli, C., Marchetti, P., Taurelli, B. S., Coluzzi, F., Rocco, M., Vecchione, A., Anibaldi, P., Marcolongo, A., Ciliberto, G., Mancini, R., & Capalbo, C. (2021). H-Ras gene takes part to the host immune response to COVID-19. Cell death discovery 7(1), 158. https://doi.org/10.1038/s41420-021-00541-w

Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., & Siddique, R. (2020). COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*, *24*, 91–98. https://doi.org/10.1016/j.jare.2020.03.005

Sixto-López, Y., & Correa-Basurto, J. (2022). HDAC Inhibition as Neuroprotection in COVID-19 Infection. Current topics in medicinal chemistry, 22(16), 1369–1378. https://doi.org/10.2174/1568026622666220303113445

Spinelli, G., Biddeci, G., Artale, A., Valentino, F., Tarantino, G., Gallo, G., Gianguzza, F., Conaldi, P. G., Corrao, S., Gervasi, F., Aronica, T. S., Di Leonardo, A., Duro, G., & Di Blasi, F. (2021). A new p65 isoform that binds the glucocorticoid hormone and is expressed in inflammation liver diseases and COVID-19. Scientific reports, 11(1), 22913. https://doi.org/10.1038/s41598-021-02119-z

Srivastava, N., Hinton, G., Krizhevsky, A., Sutskever, I., & Salakhutdinov, R. (2014). Dropout: A Simple Way to Prevent Neural Networks from Overfitting. Journal of Machine

Learning Research, 15(56), 1929–1958.

Sulistiawan, F., Kusuma, W. A., Ramadhanti, N. S., & Tedjo, A. (2020). Drug-Target Interaction Prediction in Coronavirus Disease 2019 Case Using Deep Semi-Supervised Learning Model. *2020 International Conference on Advanced Computer Science and Information Systems (ICACSIS)*, 83–88. https://doi.org/10.1109/ICACSIS51025.2020.9263241

Syahdi, R. R., Iqbal, J. T., Munim, A., & Yanuar, A. (2019). HerbalDB 2.0: Optimization of Construction of Three-Dimensional Chemical Compound Structures to Update Indonesian Medicinal Plant Database. *Pharmacognosy Journal*, *11*(6).

The UniProt Consortium. (2021). UniProt: The universal protein knowledgebase in 2021. *Nucleic Acids Research*, *49*(D1), D480–D489. https://doi.org/10.1093/nar/gkaa1100

Widyatmoko, D. (2018). Upaya Pemanfaatan Biodiversitas Tumbuhan Dalam Rangka Konservasi yang Dapat Digunakan Sebagai Pembelajaran. *Seminar Nasional Pendidikan Biologi dan Biologi 2018*, 41–55.

Xiao, N., Cao, D.-S., Zhu, M.-F., & Xu, Q.-S. (2015). protr/ProtrWeb: R package and web server for generating various numerical representation schemes of protein sequences. *Bioinformatics*, *31*(11), 1857–1859. https://doi.org/10.1093/bioinformatics/btv042

Xue, H., Li, J., Xie, H., & Wang, Y. (2018). Review of Drug Repositioning Approaches and Resources. *International Journal of Biological Sciences*, *14*(10), 1232–1244. PubMed. https://doi.org/10.7150/ijbs.24612

Fairbanks, C. A., Schreiber, K. L., Brewer, K. L., Yu, C. G., Stone, L. S., Kitto, K. F., Nguyen, H. O., Grocholski, B. M., Shoeman, D. W., Kehl, L. J., Regunathan, S., Reis, D. J., Yezierski, R. P., & Wilcox, G. L. (2000). Agmatine reverses pain induced by inflammation, neuropathy, and spinal cord injury. Proceedings of the National Academy of Sciences of the United States of America, 97(19), 10584–10589. https://doi.org/10.1073/pnas.97.19.10584

Yiu, H. H., Graham, A. L., & Stengel, R. F. (2012). Dynamics of a cytokine storm. *PloS One*, *7*(10), e45027. https://doi.org/10.1371/journal.pone.0045027

Yuan, H., Ma, Q., Ye, L., & Piao, G. (2016). The Traditional Medicine and Modern Medicine from Natural Products. *Molecules (Basel, Switzerland)*, *21*(5), 559. PubMed. https://doi.org/10.3390/molecules21050559

Zhou, Y., Wang, F., Tang, J., Nussinov, R., & Cheng, F. (2020). Artificial intelligence in COVID-19 drug repurposing. *The Lancet Digital Health*, *2*(12), e667–e676. https://doi.org/10.1016/S2589-7500(20)30192-8