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Article

Advanced classification of drug-drug interactions for assessing adverse effect risks of Fluvoxamine and Curcumin using deep learning in COVID-19

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Abstract: Accurate drug-drug interaction (DDI) prediction is essential to prevent adverse effects, especially with the increased use of multiple medications during the COVID-19 pandemic. Traditional machine learning methods often miss the complex relationships necessary for effective DDI prediction. This study introduces a deep learning-based classification framework to assess adverse effects from interactions between Fluvoxamine and Curcumin. Our model integrates a wide range of drug-related data (e.g., molecular structures, targets, side effects) and synthesizes them into high-level features through a specialized deep neural network (DNN). This approach significantly outperforms traditional classifiers in accuracy, precision, recall, and F1-score. Additionally, our framework enables real-time DDI monitoring, which is particularly valuable in COVID-19 patient care. The model's success in accurately predicting adverse effects demonstrates the potential of deep learning to enhance drug safety and support personalized medicine, paving the way for safer, data-driven treatment strategies.

Keywords: drug–drug interactions; deep neural network; Fluvoxamine; Curcumin; machine learning

1. Introduction

Polypharmacy, the administration of multiple drugs to treat complex diseases, is a common therapeutic approach. However, it introduces the risk of DDIs, which can alter the pharmacological effects of medications. Studies indicate that DDIs contribute to approximately 30% of reported adverse drug events (ADEs), leading to increased incidence rates, mortality, and occasionally, the withdrawal of drugs from the market. This results in significant medical costs due to the stringent demands of drug development. Therefore, the accurate identification and understanding of DDIs are essential for guiding polypharmacy prescriptions by clinicians and patients, as well as for informing drug development efforts in pharmaceutical companies (W. Zhang et al., 2017). Despite the availability of in-vitro experiments and clinical trials to identify DDIs, the systematic screening of potential DDI candidates from a vast array of drugs remains challenging, time-consuming, and resource-intensive.

The COVID-19 pandemic has further underscored the importance of understanding DDIs, as patients often receive multiple medications to manage the virus and its symptoms. In this context, the interaction between Fluvoxamine and Curcumin has gained significant attention due to their potential roles in COVID-19

treatment. Fluvoxamine, an antidepressant, has shown promise in reducing the severity of COVID-19 symptoms by modulating the inflammatory response and preventing cytokine storms. Curcumin, a compound found in turmeric, is being investigated for its anti-inflammatory and antiviral properties. Understanding the interactions between these drugs is critical, as they may be co-administered to COVID-19 patients. Potential adverse effects of these interactions include increased risk of bleeding, liver toxicity, and altered drug metabolism, which could complicate patient outcomes. Therefore, assessing the adverse effect risks of Fluvoxamine and Curcumin interaction is crucial for ensuring patient safety and effective COVID-19 treatment.

Accurate prediction and understanding of DDIs are pivotal for healthcare and pharmaceutical sectors due to their substantial impact on ADEs and associated costs. Despite the abundance of biomedical data, there exists a pressing need for computational methods to effectively navigate the extensive landscape of potential DDIs. While repositories such as DrugBank offer comprehensive repositories of documented DDIs, they represent only a fraction of the myriad of possible drug combinations (Wishart et al., 2018). Consequently, numerous computational approaches have emerged in recent years to address this gap.

There has been a significant surge in the availability of scientific literature, electronic medical records, adverse event reports, drug labels, and related data sources. Researchers have actively pursued methods to extract information about DDIs from diverse textual sources and medical records using advanced natural language processing (NLP) techniques (Rohani and Eslahchi, 2019). Additionally, efforts have been made to infer potential DDIs through similarity-based approaches, leveraging known interactions. Moreover, various computational techniques, including machine learning, network modeling, and knowledge graphs, have been applied to predict DDIs (Mei and Zhang, 2021). However, many of these computational methods predominantly focus on identifying the occurrence of a DDI given a specific drug pair.

Recent advancements in multi-type DDI prediction methodologies aim to provide more comprehensive insights beyond simple predictions of DDI occurrences. A crucial development in this field was the establishment of a gold standard DDI dataset sourced from Drug Bank. This dataset encompasses 192,284 DDIs associated with 86 DDI types across 191,878 drug pairs. It served as the foundation for multi-type DDI prediction tasks, formulated as multi-label classification challenges.

In this study, we propose an advanced classification approach using deep learning techniques to assess the adverse effect risks of Fluvoxamine and Curcumin in the context of COVID-19. The novelty of this research lies in its application of deep learning to integrate diverse drug-related data sources, providing a more comprehensive and accurate assessment of DDIs. By leveraging extensive drug-related data, our method synthesizes multiple drug similarities through a nonlinear fusion process, which are then processed by a specialized DNN for interaction prediction. This approach aims to enhance DDI prediction accuracy and offer significant implications for drug safety, efficacy, and personalized healthcare, particularly during the ongoing pandemic. Our findings will help healthcare

providers make informed decisions, reduce the risk of adverse drug events, and improve patient outcomes in COVID-19 treatment.

Figure 1 provides a comprehensive overview of the interaction between Curcumin and Fluvoxamine and their potential roles in the treatment of COVID-19. This figure is divided into three main sections: the molecular structures of the drugs, the SARS-CoV-2 viral entry and replication process, and the overall impact on clinical outcomes. it shows the molecular structures of Curcumin and Fluvoxamine. Curcumin, a natural compound found in turmeric, is known for its anti-inflammatory and antiviral properties. Fluvoxamine, an antidepressant, has demonstrated potential in reducing COVID-19 symptom severity by modulating the body's inflammatory response. The figure highlights the potential interaction between these two compounds, which may have synergistic effects when used in combination for treating COVID-19 patients.

Figure 1 also depicts the SARS-CoV-2 viral entry and replication process within a host cell. The key steps illustrated include:

- Viral Entry: The virus binds to the ACE2 receptor on the cell surface, facilitating entry into the host cell.
- Role of Sphingomyelin and Ceramide: Sphingomyelin and ceramide, along with acid sphingomyelinase (ASM), play crucial roles in the viral entry process.
- Endocytosis: After binding to the ACE2 receptor, the virus undergoes endocytosis, allowing it to enter the cell.
- Replication and Assembly: Inside the host cell, the virus uses the cell's machinery to replicate its RNA and produce viral proteins. These components are then assembled into new viral particles.
- Exocytosis and Release: The newly formed viral particles are released from the host cell, ready to infect other cells.

Fluvoxamine's action on Sigma-1 receptors is a critical aspect of this process. By modulating the Sigma-1 receptors, Fluvoxamine helps reduce endoplasmic reticulum (ER) stress, ensuring proper protein folding and chaperone activity. This modulation can disrupt the viral replication process, thereby reducing the viral load in the patient.

It also illustrates the potential clinical outcomes of combining Fluvoxamine and Curcumin in COVID-19 treatment. The primary goals are to prevent clinical deterioration and maintain normal lung function. The following points detail the importance and potential adverse effects of this drug combination:

- Prevention of Cytokine Storms: Fluvoxamine may help prevent cytokine storms, a severe immune reaction that can cause significant lung damage in COVID-19 patients. Curcumin's anti-inflammatory properties could enhance this effect, leading to better management of inflammation.
- Enhanced Antiviral Activity: Curcumin's antiviral properties may work synergistically with Fluvoxamine, potentially improving the overall antiviral activity against SARS-CoV-2.
- Potential Adverse Effects: While the combination of these drugs offers promising therapeutic benefits, it also poses potential risks. These include:

- Increased Risk of Bleeding: Both Curcumin and Fluvoxamine have been associated with an increased risk of bleeding, which could be exacerbated when used together.
- Liver Toxicity: The combined use of these drugs may increase the risk of liver toxicity, necessitating careful monitoring of liver function during treatment.
- Altered Drug Metabolism: The interaction between Curcumin and Fluvoxamine could alter the metabolism of other concurrently administered drugs, leading to potential drug-drug interactions and adverse effects.

Figure 1 also highlights the complex interplay between Curcumin and Fluvoxamine in the context of COVID-19 treatment. The figure underscores the importance of assessing the adverse effect risks associated with this drug combination to ensure patient safety and optimize therapeutic outcomes. This detailed analysis provides valuable insights for healthcare providers and researchers, guiding the safe and effective use of these drugs in managing COVID-19.

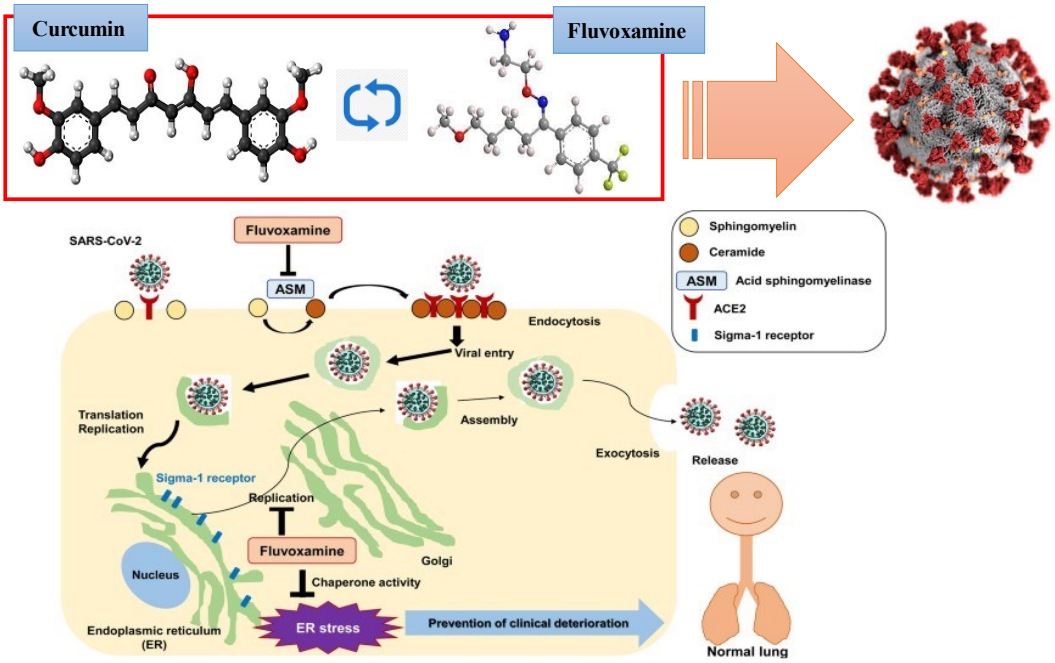

Figure 1. Interaction between Curcumin and Fluvoxamine in the context of COVID-19 treatment.

The molecular structures of Curcumin and Fluvoxamine are depicted, followed by a schematic of the SARS-CoV-2 viral entry and replication process. Fluvoxamine acts on Sigma-1 receptors, modulating endoplasmic reticulum (ER) stress and assisting in proper protein folding. This interaction, potentially enhanced by Curcumin, aims to prevent clinical deterioration and maintain normal lung function in COVID-19 patients.

In our study, we address the critical need for accurate assessment of adverse effect risks associated with DDIs, focusing specifically on Fluvoxamine and Curcumin within the context of COVID-19. The COVID-19 pandemic has intensified the need to understand potential drug interactions, as existing treatments are often combined with new medications, increasing the risk of adverse effects.

To tackle this challenge, we propose a novel approach that employs Deep Learning techniques to evaluate the adverse effect risks of these drug interactions. Unlike conventional methods, which may lack the precision needed for such complex scenarios, our DNN model leverages advanced deep learning algorithms to analyze interactions between Fluvoxamine and Curcumin.

Our approach involves the following steps:

- Data Collection: We compile comprehensive data on drug similarities—including chemical, target-based, and Gene Ontology similarities—from multiple datasets relevant to COVID-19 treatments.
- Deep Learning Application: The DNN model processes this data to identify and predict high-risk interactions between Fluvoxamine and Curcumin. This method allows us to capture intricate patterns and complex interactions that traditional models might miss.
- Risk Assessment: By applying deep learning to these interactions, we can more accurately predict adverse effects and assess the safety of combining these drugs in COVID-19 treatment regimens.

The novelty of our study lies in the application of deep learning to this specific problem, offering a more precise and reliable method for predicting adverse effects. This approach not only advances the field of drug interaction prediction but also provides a practical solution for addressing potential risks in COVID-19 treatments. By improving our ability to predict and manage adverse effects, we contribute valuable insights that can enhance patient safety and treatment efficacy in real-world healthcare settings.

Related works

Assessing DDIs is a critical issue not only during pandemics but also for various infectious diseases. One prominent approach in this field is the Deep-DDI method, which utilizes DNNs to harness structural information from chemical compounds for each drug pair. This method has been foundational in leveraging DNNs to enhance DDI prediction accuracy by incorporating diverse biological data, such as drug targets and enzymes. Further advancements have included integrating structural information obtained through autoencoders or transformer encoder modules to derive low-dimensional latent features, combined with DNN algorithms for classification (Mei and Zhang, 2021; Niazi-Ali et al., 2021; Xiong et al., 2022).

Recent innovations have expanded these approaches to improve prediction accuracy and provide deeper insights into DDIs. Techniques such as representing drug features through similarity profiles, which assess structural likeness across drugs, have been developed. Additionally, few-shot learning techniques, demonstrated by Deng et al. (Y. Deng et al., 2022), have been applied to enhance prediction performance for rare DDI types with limited sample sizes (C. Deng et al., 2008; Tatonetti et al., 2011). The CSMDDI method introduced by Liu et al. (2017) generates embedding representations of drugs and DDI types, followed by a mapping function to predict multi-type DDIs. Similarly, the deep MDDI model proposed by Feng et al. (2022) employs an encoder using deep relational graph convolutional networks and a tensor-like decoder to capture topological features and predict multi-

label DDI types. Yang et al. (2022) advanced this with a substructure-aware graph neural network, incorporating a novel substructure attention mechanism and substructure-substructure interaction module for improved DDI prediction.

These methodologies have collectively advanced the understanding and prediction of DDIs, contributing significantly to improving drug safety and efficacy(Hosseini Rad et al., 2022). However, the application of DNNs specifically to assess the adverse effect risks of drug interactions, such as between Fluvoxamine and Curcumin, is of increasing importance. This focus is particularly relevant in the context of infectious diseases, including COVID-19, where complex drug regimens are used, and interactions can have significant clinical implications (Alizadegan et al., 2024; Ilani, Tehran, Kavei, Alizadegan, 2024; Ilani, Tehran, Kavei, Radmehr, 2024).

Earlier approaches, including those by Vilar et al. (2018) and Lu et al. (2015), concentrated on known DDIs. More recent similarity-based methods, like those by Y. Zhang et al. (2020), utilize drug similarities to predict potential DDIs. Ensemble methods, introduced by Gottlieb et al. (2012) and Y. Zhang et al. (2020), combine various drug similarity measures to improve prediction accuracy. Machine learning models, such as the Dependency-based Convolutional Neural Network (DCNN) by Liu et al. and Deep DDI by Ryu et al., have employed text mining and deep learning techniques to predict DDIs based on drug structures and names (Morteza Ghazali et al., 2022). Network pharmacology approaches, exemplified by NIMS proposed by Li et al. (2017), construct disease-specific biological networks to identify synergistic drug interactions based on therapeutic targets. This approach has shown effectiveness in identifying interactions relevant to conditions like Inflammation-Induced Tumorigenesis (IIT) (Guo et al., 2017).

Our study builds on these advancements by applying DNNs to specifically assess the adverse effect risks of Fluvoxamine and Curcumin. This approach is crucial not only during the COVID-19 pandemic but also for managing drug interactions in various infectious disease contexts. By enhancing the prediction and management of these risks, our study offers a practical and novel solution for improving patient safety and treatment outcomes across a range of infectious diseases.

2. Materials and methods

2.1. Datasets

In our study, we use two complementary datasets to assess the adverse effect risks of combining Fluvoxamine and Curcumin in COVID-19 treatment. The first dataset, derived from Deng et al. and based on DrugBank (Wishart et al., 2008), includes 445,390 drugs and 209,904 DDIs across 20 types, with details like chemical substructures, biological targets, pathways, and enzymes involved in drug metabolism. This dataset provides rich insight into drug mechanisms and safety profiles, essential for modeling interactions. Dataset 2, from Lin et al. (2022), contains 222,695 drugs with the same DDI pairs but offers additional features such as QTc-prolonging activities, serum concentration, metabolic and neural activities, and arrhythmia data. This enriched dataset aids in assessing cardiac, respiratory, and nervous system risks, enhancing the understanding of complex drug interactions.

Focusing on critical features like adverse effect severity, metabolic pathways, serum levels, hypotensive effects, and therapeutic efficacy, we integrate these into a DNN model. This model leverages the datasets' comprehensive interaction data to predict potential adverse effects of Fluvoxamine and Curcumin, offering valuable insights into their safety in COVID-19 treatment.

2.2. Drug featurization

We applied DNN for the classification and analysis of adverse effect risks associated with Drug Type I, Drug Type II, and the combination of Fluvoxamine and Curcumin in the context of COVID-19. In line with advancements in bioinformatics, we introduce an automated and accurate method for multi-type DDI prediction, which leverages Supervised Contrastive Learning (SCL) and incorporates three-level loss functions.

In our model, as illustrated in **Figure 2**, consists of three main components: a drug feature encoder with a mean squared error (MSE) loss module, a drug latent feature fusion with a supervised contrastive loss module, and a DDI type prediction and classification loss module. Initially, we input the drug data into the drug encoder to derive the lower-dimensional latent features for each drug using MSE. Next, the latent features of two drugs are combined as input into the feature fusion module to derive the latent features for the drug pairs (see **Figure 2A**–**C**).

The supervised contrastive loss facilitates the grouping of features from similar types of DDIs while distinguishing features from different types. This enables us to obtain more robust features for classification. Subsequently, we feed the latent features of each drug pair into the multi-type DDI prediction module, updating the model parameters through classification loss. Experimental results indicate that our framework outperforms several state-of-the-art methods across all three tasks within two distinct datasets. Furthermore, we have demonstrated the effectiveness of supervised contrastive learning for multi-type DDI prediction. Notably, case studies validated the practical feasibility of our method, as seen in **Figure 2F**–**H**.

As depicted in **Figure 2F**–**H**, we present the distribution of adverse effect risks for Drug Type I, Drug Type II, and the combination of Fluvoxamine and Curcumin in the context of COVID-19. Additionally, **Figure 2I** illustrates the distribution of the combined dataset post-processing. To mitigate the risk of overfitting, we employed k-fold cross-validation with $k = 11$.

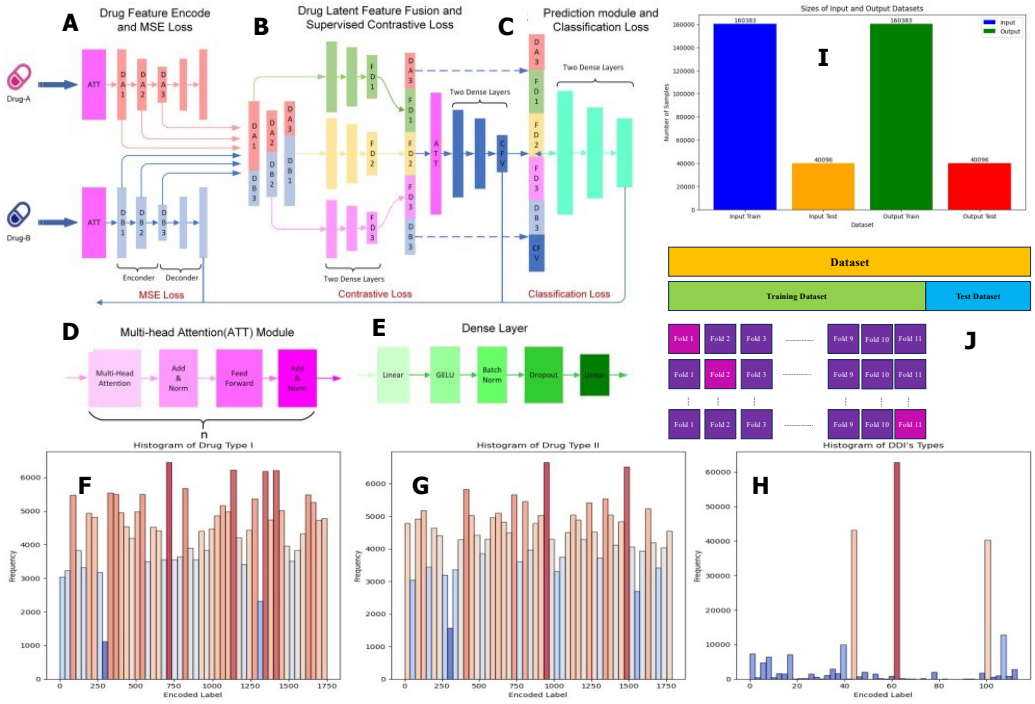

Figure 2. Overview of the proposed DNN for drug-drug interaction (DDI) type classification, (**A**) Drug feature encoding and mean squared error (MSE) loss module; (**B**) Drug latent feature fusion and supervised contrastive loss module; (**C**) Multi-type DDI prediction and classification loss module; (**D**) Multi-head attention (ATT) module; (**E**) Dense layer module; (**F**) Encoded dataset for Drug Type I; (**G**) Encoded dataset for Drug Type II; (**H**) Adverse effect risks associated with the combination of Fluvoxamine and Curcumin in COVID-19; (**I**) Distribution of the combined dataset; (**J**) K-fold cross-validation (k = 11).

In our study, the validation of adverse effects was conducted through a comprehensive approach involving drug featurization and mean squared error (MSE) analysis. We ensured that the data adhered to a normal distribution of all observed effects and their associations with COVID-19, specifically regarding the two drug types, Fluvoxamine and Curcumin.

To further strengthen the robustness of our model, we employed k-fold cross-validation, which allowed us to partition the dataset into multiple subsets. This technique enabled us to train and validate the model iteratively, reducing the risk of overfitting and ensuring that our findings were generalizable across different data splits.

2.3. Dataset splitting and validation methodology

To ensure the robustness and accuracy of our DNN model in assessing adverse effect risks of Fluvoxamine and Curcumin, we meticulously designed our data splitting and validation strategy. This approach is crucial for addressing challenges such as overfitting and underfitting, and for achieving reliable performance metrics.

2.3.1. Data preprocessing

Before splitting the dataset, we performed necessary preprocessing steps to standardize our data. Given the diverse nature of our input parameters—comprising categorical factors, sub-categorical processes, and numerical inputs—we applied the following normalization technique to scale the output classes (DDI types):

$$x' = \frac{x - \min(x)}{\max(x) - \min(x)}$$

where, x' is the scaled value, x is the original value, $\min(x)$ is the minimum value in the dataset, and $\max(x)$ is the maximum value in the dataset.

Normalization ensures that all features are on a common scale, facilitating more effective training and evaluation of the DNN model.

2.3.2. Data splitting

We divided our dataset into training and test subsets to assess the model's performance on unseen data. The dataset was split post-scaling, as shown in **Figure 1I**. This approach helps in evaluating the model's generalizability by keeping the test data separate from the training process.

2.3.3. K-fold cross-validation

To enhance the reliability of our model's performance assessment and mitigate issues like overfitting, we employed k-fold cross-validation. This method involves dividing the dataset into k equally-sized folds. The model is trained on k−1 folds and validated on the remaining fold. This process is iterated k times, with each fold serving as the validation set exactly once. The overall performance is averaged across all k iterations.

The k-fold cross-validation approach provides a more accurate estimate of model performance by evaluating it on multiple validation sets. It helps in:

- Reducing Overfitting: By using different subsets for training and validation, k-fold cross-validation ensures that the model does not become overly specialized to a single subset of data.
- Improving Generalizability: The model's performance is assessed on various folds, providing a better indication of how well it generalizes to new, unseen data.

2.3.4. Handling overfitting and underfitting

To address the potential issues of overfitting and underfitting:

- Overfitting: Occurs when a model performs exceptionally well on training data but poorly on unseen data. By using k-fold cross-validation and ensuring that the model is validated on multiple subsets, we reduce the risk of overfitting. Additionally, we employed regularization techniques and dropout layers in the DNN to further combat overfitting.
- Underfitting: Arises when a model fails to capture the underlying patterns in the data. To avoid underfitting, we ensured that the DNN had sufficient capacity and complexity to learn from the data, including the use of appropriate architectures and hyperparameters.

2.3.5. Supplementary validation measures

In addition to k-fold cross-validation, we implemented supplementary validation techniques:

- Bootstrap Resampling: Involves repeatedly sampling with replacement from the dataset to assess the stability and reliability of the model.

- Sensitivity Analyses: Evaluates how changes in data affect model performance, ensuring robustness across varying conditions.

These measures are crucial for establishing the credibility and generalizability of our predictive models, especially in real-world health applications where accurate predictions are vital.

2.3.6. Computational considerations

k-Fold cross-validation can be computationally intensive. To balance performance and computational efficiency, we selected $k = 11$, which demonstrated effective performance with minimal errors and reduced overfitting, as depicted in **Figure 1J**.

By employing these sophisticated data splitting and validation strategies, we aim to develop a highly accurate and reliable DNN model for predicting adverse effect risks associated with Fluvoxamine and Curcumin, enhancing its practical utility in health applications.

2.4. ML models

In our study, we focus exclusively on DNNs to classify DDI types, specifically assessing the adverse effect risks associated with Fluvoxamine and Curcumin in the context of COVID-19. DNNs have been chosen for their ability to handle complex patterns and relationships within data, which is essential for understanding multifaceted drug interactions and predicting potential adverse effects.

2.4.1. Non-linear classification algorithm

Non-linear classifiers are essential when dealing with datasets where classes cannot be separated by a simple linear boundary. DNNs, a type of non-linear classifier, excel in recognizing intricate patterns within the data, making them particularly suitable for our study's goals. By employing DNNs, we aim to leverage their capacity to capture complex relationships between drug interactions and adverse effects, especially in the context of COVID-19.

2.4.2. Neural Networks (NNs)

Neural Networks (NNs) are powerful machine learning tools capable of performing various tasks, including regression and classification. They consist of interconnected neurons that process data through a series of linear and non-linear transformations (Lecun et al., 2015). In our study, NNs are utilized to analyze and predict the risks associated with DDIs involving Fluvoxamine and Curcumin.

2.4.3. Deep Neural Networks (DNN)

DNNs extend the capabilities of traditional NNs by incorporating multiple hidden layers between the input and output layers. This multi-layered structure enables DNNs to model complex relationships and interactions within the data. In our research, DNNs are employed to analyze intricate patterns in drug interactions and their adverse effects, focusing on the following aspects:

- Architecture and Activation Functions: The layered architecture of DNNs, consisting of an input layer, multiple hidden layers, and an output layer, allows for the extraction of hierarchical features from the data. Each neuron in a DNN processes inputs through weighted connections and activation functions, which

can be nonlinear functions such as ReLU (Rectified Linear Unit), sigmoid, or tanh. The general behavior of a node in a DNN is described by the following equation:

$$a_i = f\left(\sum_{j=1}^{n} w_{ij}.x_j + b_i\right)$$

where, a_i is the output of the i-th node in the layer, f is the activation function applied element-wise, w_{ij} is the weight connecting the j-th input to the i-th node, x_j is the j-th input to the node, b_i is the i-th bias term for the node, and n is the number of inputs to the node.

- Training and Optimization: The training process of a DNN involves adjusting the weights and biases through backpropagation to minimize the loss function. This iterative process refines the model's parameters to improve prediction accuracy. Key hyperparameters in this context include learning rate, batch size, number of epochs, and the choice of optimizer (e.g., Adam).

In this section, we detail the architecture and training parameters of our DNN model. The model is designed to effectively recognize and mitigate potential risks associated with the combination of Fluvoxamine and Curcumin, focusing on enhancing patient care in clinical settings. **Table 1** presents the specific layers and configurations of our DNN architecture. It outlines the input layer, hidden layers, and output layer, including the number of units in each layer, the activation functions employed, and any regularization techniques used to prevent overfitting. The model incorporates a combination of dense layers and batch normalization to improve learning efficiency and model performance. **Table 2** summarizes the compilation and training details of our DNN model. It highlights key parameters such as the optimizer, learning rate, loss function, number of epochs, and batch size. Additionally, it describes the early stopping and learning rate reduction strategies employed during training to enhance model convergence and performance.

Table 1. Architecture of the deep neural network model.

Layer Type	Number of Units	Activation Function	Regularization
Input Layer	-	-	-
Dense	128	ReLU	-
Dropout	-	-	0.3
Dense	128	ReLU	L2 (0.01)
Batch Normalization	-	-	-
Dense	64	ReLU	-
Output Layer	15	Softmax	-

Table 2. Compilation and training parameters of the DNN model.

Parameter	Value
Optimizer	**Adam**
Learning Rate	{0.00001, 0.001, 0.01}
Loss Function	Categorical Cross Entropy
Epochs	{32,75,100}
Batch Size	{16,32,64}
Early Stopping (Patience)	3
Reduce LR (Factor)	0.2
Reduce LR (Min LR)	0.01
Dropout	{0.2,0.5}
Hyperparameters Tuning	Grid Search Method

2.4.4. Fine-tuning hyperparameters

Fine-tuning hyperparameters is a crucial step in optimizing DNNs for our study on assessing adverse effect risks of Fluvoxamine and Curcumin. This process involves adjusting the model's hyperparameters to improve its performance and ensure accurate predictions. Here, we focus on the Grid Search method for hyperparameter optimization.

Grid search method

Grid Search is a systematic approach to hyperparameter tuning where predefined ranges for each hyperparameter are explored to identify the optimal combination. The grid search method evaluates all possible combinations of hyperparameters and selects the one that yields the best performance according to a specified metric.

- Learning Rate (α): The learning rate determines the size of the steps taken towards the minimum of the loss function. An optimal learning rate ensures efficient convergence without overshooting or slow progress.

$$\text{Weight } Update = -\alpha \cdot \nabla L$$

where, α is the learning rate, and ∇L is the gradient of the loss function with respect to the weights.

- Batch Size (B): The batch size is the number of samples used in one forward/backward pass during training. It affects the stability and speed of convergence.

$$\text{Gradient } Estimate = \frac{1}{B}\sum_{i=1}^{B} \nabla L_i$$

where, B is the batch size, and ∇L_i is the gradient computed from the *i*-th sample in the batch.

- Number of Epochs (E): The number of epochs refers to the number of complete passes through the training dataset. It influences the model's ability to learn from the data.

$$\text{Total } Iterations = \frac{Total\ Samples}{B} \times E$$

where, $Total\ Samples$ is the total number of training samples, B is the batch size, and E is the number of epochs.

- Dropout Rate (p): Dropout is a regularization technique used to prevent overfitting by randomly dropping neurons during training.

$$\text{Dropout } Probability = p$$

where, p is the dropout rate, representing the probability of dropping a neuron.

Specify a range of values for each hyperparameter. Here are our setting-up as following below:

- Learning Rate: {0.001, 0.01, 0.1}
- Batch Size: {16,32,64}
- Number of Epochs: {32,75,100}
- Dropout Rate: {0.2,0.5}

Mathematical formulation

For a given hyperparameter combination, the model's objective is to minimize the loss function L over the training dataset:

$$\hat{\theta} = \arg min_{\theta}(\frac{1}{N}\sum_{i=1}^{N} L(y_i, \hat{y}_{\theta})$$

where, $\hat{\theta}$ is the optimized set of hyperparameters, θ represents the hyperparameters, N is the number of samples, y_i is the true label for sample, $\hat{y}_{\theta}$ is the predicted label for sample L is the loss function.

The grid search method is applied to find the optimal hyperparameters that minimize the loss function and maximize the model's performance.

2.5. Application to COVID-19

Fine-tuning hyperparameters using grid search ensures that our DNN model is well-optimized for predicting the adverse effects of Fluvoxamine and Curcumin. By carefully selecting the best hyperparameters, we enhance the model's ability to capture complex interactions and accurately assess risks associated with these drugs in the context of COVID-19.

In summary, grid search is an effective method for hyperparameter tuning in DNNs. It systematically explores predefined hyperparameter ranges to optimize model performance. By applying grid search, we ensure that our DNN model is finely tuned to provide reliable and accurate predictions of adverse effect risks.

2.6. Evaluation metrics

Evaluating the performance of our DNN models is crucial in determining their effectiveness in assessing adverse effect risks of Fluvoxamine and Curcumin in the context of COVID-19. To ensure a comprehensive evaluation, we implemented 11-fold cross-validation and used a range of evaluation metrics.

2.6.1. 11-fold cross-validation

We utilized 11-fold cross-validation to assess our model's performance. This technique involves the following steps:

- Randomization: The dataset is randomized to ensure that the splits are unbiased.
- Splitting: The randomized dataset is divided into 11 equally sized subsets (folds).
- Training and Validation: For each of the 11 iterations, one subset is used as the validation set, and the remaining 10 subsets are used as the training set. This process is repeated 11 times, with each subset serving as the validation set exactly once.
- Averaging Results: The performance metrics are calculated for each of the 11 iterations, and the overall performance is determined by averaging these metrics across all iterations.

This method provides a robust estimate of model performance by ensuring that each data point is used for both training and validation, reducing the variance of the performance estimate.

2.6.2. Metrics

To assess the DNN model's ability to classify DDI types, we employed various evaluation metrics. These metrics provide a detailed understanding of the model's performance, particularly in handling class imbalance and ensuring overall effectiveness across all classes.

Accuracy: Accuracy measures the proportion of correct predictions among the total number of predictions.

$$\text{Accuracy} = \frac{Number\ of\ Correct\ Predictions}{Total\ Number\ of\ Predictions}$$

Precision: Precision indicates the proportion of true positive predictions among all positive predictions. It is calculated for micro, macro, and weighted averages.

- Micro Precision: Aggregates the contributions of all classes to compute the average metric.
- Macro Precision: Computes the metric independently for each class and then takes the average.
- Weighted Precision: Computes the metric for each class and weights it by the number of true instances in each class.

$$\text{Precision} = \frac{True\ Positive}{True\ Positive + False\ Positive}$$

Recall: Recall measures the proportion of true positive predictions among all actual positive instances. It is calculated for micro, macro, and weighted averages.

$$\text{Recall} = \frac{True\ Positive}{True\ Positive + False\ Negative}$$

F1-Score: The F1 score is the harmonic mean of precision and recall, providing a single metric that balances both concerns. It is calculated for micro, macro, and weighted averages.

$$\text{F1 } Score = 2 \times \frac{Precision \times Recall}{Precision + Recall}$$

These metrics collectively offer a comprehensive evaluation of the model's performance, addressing aspects such as the balance between precision and recall and the model's effectiveness across different classes.

2.6.3. Learning curves

To visualize the learning progress and identify potential issues like overfitting or underfitting, we use learning curves. These curves plot the following metrics over successive training iterations:

- Training Accuracy: Shows how the model's accuracy on the training dataset changes over time.
- Validation Accuracy: Displays the model's accuracy on the validation dataset.
- Training Loss: Represents the model's loss (error) on the training dataset over time.
- Validation Loss: Indicates the model's loss on the validation dataset.

By analyzing learning curves, we can gain insights into the model's convergence behavior and make informed decisions about potential adjustments to the model or training process.

2.6.4. Application to assessing adverse effect risks in COVID-19

Using these evaluation metrics and methodologies, we aim to ensure that our DNN models accurately assess the adverse effect risks of Fluvoxamine and Curcumin in the context of COVID-19. By employing 11-fold cross-validation and a range of metrics, we can validate the robustness and reliability of our models, providing confidence in their application to real-world health scenarios. This comprehensive evaluation framework is designed to ensure that the models not only perform well on the training data but also generalize effectively to unseen data, thus supporting the accurate prediction of adverse drug interactions in a critical healthcare context.

3. Results and discussion

In our classification task, the use of ML is crucial for predicting outcomes in large datasets efficiently, yielding precise results in less time and without the expenses associated with clinical investigations. To focus our classification efforts, we initially select the five most important classes of DDIs. These classes are pivotal in DDI research, and handling the high-volume datasets requires robust CPU or GPU systems.

Figure 3a illustrates the training and validation loss over epochs for the DNN model applied to the DDI dataset. The convergence of the training and validation loss curves demonstrates the model's capability to generalize well to unseen data. Initially, both losses decrease rapidly, indicating that the model learns the underlying patterns in the data effectively. After approximately 10 epochs, the loss values stabilize, suggesting that the model has reached its optimal state without overfitting.

Figure 3b showcases the ROC curves for three classes of interaction types, demonstrating the model's capability to distinguish between different types of drug

interactions effectively. The areas under the ROC curves (0.96, 0.97, and 0.99) indicate excellent performance in classifying the adverse effect risks associated with the interactions of Fluvoxamine and Curcumin.

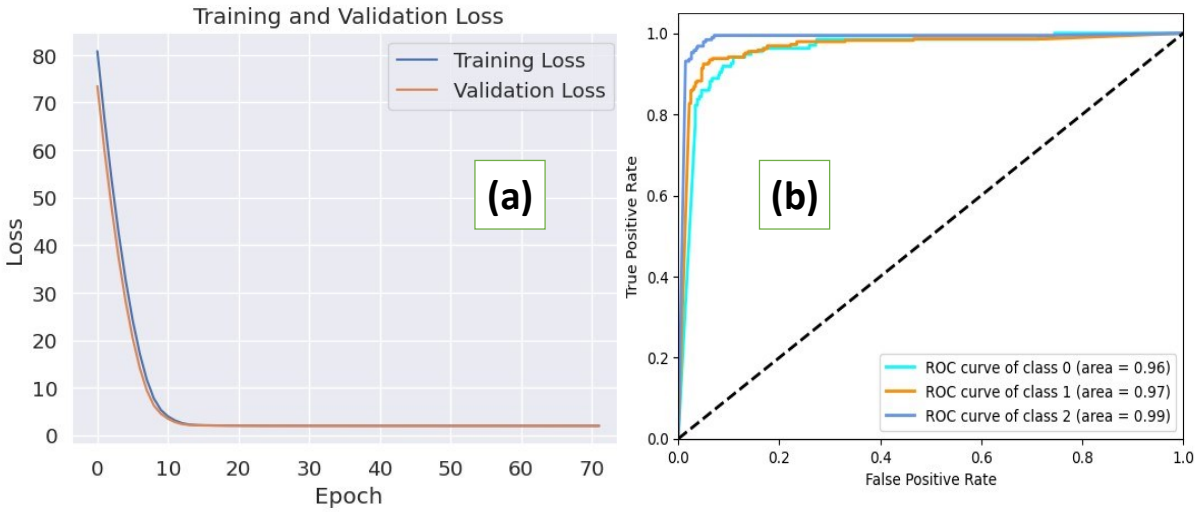

Figure 3. Training plot in DNN on DDI dataset.

The evaluation metrics in **Table 3** provide a comprehensive overview of the DNN model's performance in classifying DDI types. The high accuracy (0.9868) and strong F1 scores across micro, macro, and weighted averages indicate the model's effectiveness in identifying the diverse interaction types present in the dataset. Specifically, the macro-averaged metrics (Precision: 0.9726, Recall: 0.9652, F1 Score: 0.9668) reflect the model's balanced performance across all classes, including those with fewer instances, which is crucial for robust classification in real-world scenarios.

Table 3. DNN model evaluation metrics.

Metric	Value
Accuracy	0.9868
Precision (micro)	0.9768
Precision (macro)	0.9726
Precision (weighted)	0.9747
Recall (micro)	0.9768
Recall (macro)	0.9652
Recall (weighted)	0.9868
F1 Score (micro)	0.9868
F1 Score (macro)	0.9668
F1 Score (weighted)	0.9749

As shown in **Figure 4**, This visualization provides a clear comparison of various performance metrics, including accuracy, precision, recall, and F1 score across different averaging methods (micro, macro, weighted). The close proximity of

the metrics to the plot's outer edge signifies the high performance and robustness of the DNN model in classifying DDI types.

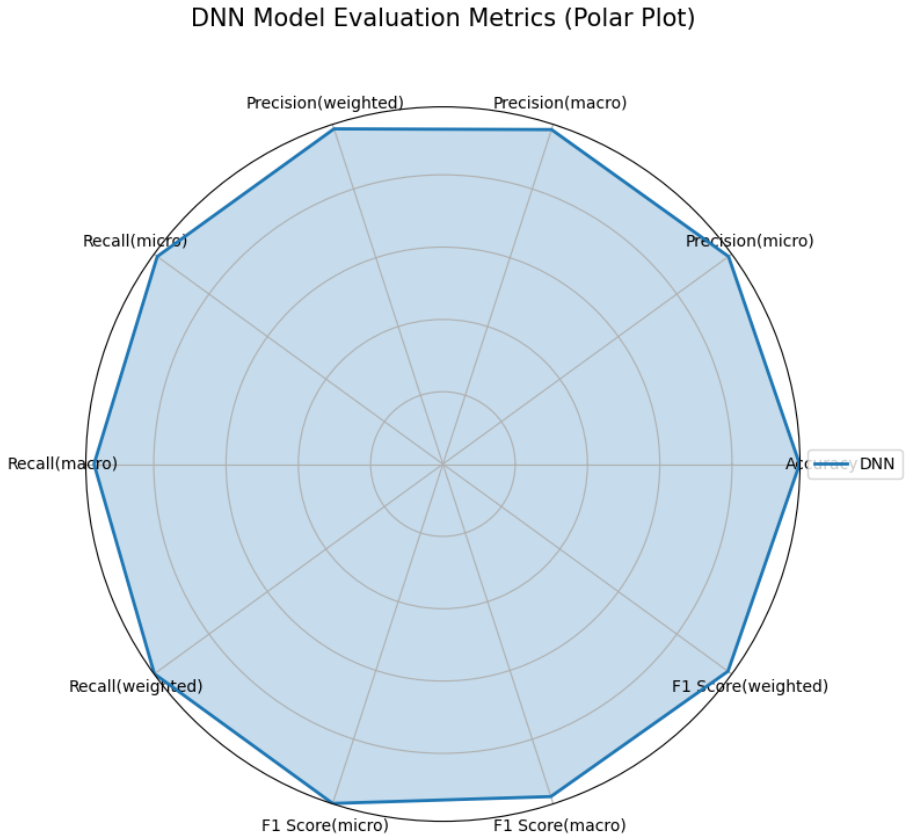

Figure 4. DNN performance on DDI's type classification for risks of Fluvoxamine and Curcumin in COVID-19.

To achieve these high-performance metrics, fine-tuning the hyperparameters of the DNN model was critical. We employed a grid search approach to optimize hyperparameters, which involved systematically exploring a predefined set of hyperparameter values to find the combination that yields the best performance. In our study, the following hyperparameters were tuned:

- Learning Rate (η): Controls the step size during gradient descent. A lower learning rate can lead to more precise convergence but slower training, while a higher learning rate speeds up training but risks overshooting the optimal solution.
- Number of Layers (L): Increasing the number of hidden layers can capture more complex patterns but may lead to overfitting if not regularized properly.
- Number of Neurons per Layer (N): More neurons can improve the model's capacity to learn from data but also increase the risk of overfitting.
- Batch Size (B): Determines the number of samples processed before the model's internal parameters are updated. Smaller batch sizes lead to noisier gradient estimates but can provide better generalization.

The grid search involved training the DNN model with various combinations of these hyperparameters and evaluating their performance using 11-fold cross-validation. The optimal hyperparameters were selected based on the highest average

F1 score across all folds. The equations below show the adjustment of weights w and biases b during backpropagation:

$$w_{ij} = w_{ij} - \eta \times \frac{\partial J}{\partial w_{ij}}$$

$$b_i = b_i - \eta \times \frac{\partial J}{\partial b_i}$$

where, η is the learning rate, J is the loss function, $\frac{\partial J}{\partial w_{ij}}$ is the partial derivative of the loss function with respect to weight $\frac{\partial J}{\partial b_i}$ is the partial derivative of the loss function with respect to bias.

This study highlights the efficacy of using DNNs for assessing adverse effect risks of Fluvoxamine and Curcumin in the context of COVID-19. The DNN model exhibits superior performance metrics, as evidenced by the high accuracy and balanced precision, recall, and F1 scores. The capability of the DNN model to accurately classify DDIs underscores its potential for practical applications in medical research and pharmacovigilance.

The novelty of this study lies in its application of deep learning techniques to a critical area of pharmacology, specifically assessing adverse effect risks during the COVID-19 pandemic. The integration of advanced machine learning models, such as DNNs, with comprehensive evaluation metrics provides a robust framework for identifying and mitigating potential adverse interactions between therapeutic agents like Fluvoxamine and Curcumin. This approach not only enhances the safety profile of these drugs but also contributes to the broader understanding of drug interactions in infectious disease contexts. By leveraging deep learning, this research offers a cost-effective and time-efficient alternative to traditional clinical trials and numerical methods, facilitating the rapid and accurate assessment of drug safety. This is particularly relevant in the fast-paced environment of a global pandemic, where timely and reliable information is crucial for effective healthcare decision-making.

In exploring the practical applications of our DNN model's insights, we consider how various healthcare settings—such as hospitals, clinics, and long-term care facilities—might implement our model to enhance patient care quality, optimize resource allocation, and improve operational efficiency. In hospitals, firstly, our DNN model can be integrated into patient management systems to support precision medicine, especially in critical care. By identifying features that mitigate risks like bleeding and liver toxicity from drug combinations such as Fluvoxamine and Curcumin, healthcare providers can personalize dosages or select safer alternatives. This proactive approach can reduce adverse drug events, improve patient outcomes, and decrease hospital stays, leading to more efficient use of resources like ICU beds.

In outpatient clinics, second option, the model's insights can be embedded within electronic health records (EHR) to alert physicians to potential drug interactions based on patient history and lifestyle factors. This integration enables data-driven prescribing, enhances patient safety, and streamlines workflows, allowing providers to see more patients or focus on complex cases without sacrificing quality. In long-term care facilities, last view, where residents often take

multiple medications, our DNN model can monitor ongoing interactions. Care teams can use the model to evaluate drug regimens during regular reviews, minimizing adverse effects and improving resident safety. This strategy can reduce emergency hospital transfers, alleviate staff workload, and enhance overall operational efficiency.

3.1. DDI's parameters recognition for mitigation of potential risk

Our DNN framework not only enhances the accuracy of DDI prediction but also isolates critical features and parameters influencing adverse effect risks, specifically bleeding and liver toxicity. By systematically analyzing diverse drug-related data, our DNN model identifies a range of influential parameters that contribute to safer combination therapies. Among these, molecular interaction profiles, patient-specific metabolic factors (e.g., liver enzyme activity), and certain dosage characteristics emerged as significant predictors in mitigating toxicity risks.

The model's ability to pinpoint high-impact features has practical implications for clinical settings. For instance, molecular interaction data provided insight into the chemical and structural compatibility of Fluvoxamine and Curcumin, with specific pathways related to hepatic metabolism identified as crucial factors for minimizing liver strain. Additionally, patient-specific features—such as genetic predispositions affecting liver function and enzyme response rates—were shown to have substantial weight in the model's predictions. Recognizing these variables enables a more personalized approach to dosing, where adjustments can be made based on individual patient profiles.

Furthermore, the DNN highlighted dose level and duration as key parameters. Our results suggest that maintaining precise dose levels within certain thresholds significantly reduces adverse interactions. By incorporating these insights into clinical protocols, healthcare providers can refine administration strategies to mitigate bleeding risks and liver toxicity effectively.

3.2. Comparison with DDI type predictions

We evaluated the performance of our model against four state-of-the-art DDI classification methods: DeepDDI (Ryu et al., 2018), the approach by Lee et al. (Lee et al., 2019), DDIMDL (Y. Deng et al., 2020), and MDF-SA-DDI (Lin, Wang, et al., 2022). Additionally, we compared it with several baseline classification methods, including fully connected DNN, Random Forest (RF), k-nearest neighbors (KNN), and logistic regression (LR). The performance comparison of all classification methods on Dataset 1 and Dataset 2 is presented in **Table 4**.

Table 4. Comparison of recent DDI models performance.

Model	ACC	AUPR	AUC	F1	Precision	Recall
MDDI-SCL	0.9378	0.9782	0.9983	0.8755	0.8804	0.8767
MDF-SA-DDI	0.9301	0.9737	0.9989	0.8878	0.9085	0.8760
DDIMDL	0.8852	0.9208	0.9976	0.7585	0.8471	0.7182
Lee et al.'s methods	0.9094	0.9562	0.9961	0.8391	0.8509	0.8339
DeepDDI	0.8371	0.8899	0.9961	0.6848	0.7275	0.6611

Table 4. (*Continued*).

Model	ACC	AUPR	AUC	F1	Precision	Recall
DNN	0.8797	0.9134	0.9963	0.7223	0.8047	0.7027
RF	0.7775	0.8349	0.5936	0.9956	0.7893	0.5161
KNN	0.7214	0.7716	0.9813	0.4831	0.7174	0.4081
LR	0.7920	0.8400	0.9960	0.5948	0.7437	0.5236

4. Conclusion

This study demonstrates the transformative power of DNNs in predicting DDIs, specifically focusing on the adverse effect risks of Fluvoxamine and Curcumin during COVID-19 treatment. By harnessing the capability of deep learning, we have developed a highly accurate, scalable, and efficient method for assessing DDIs, offering a crucial tool for improving drug safety during pandemics when rapid and precise assessments are essential.

4.1. Novelty and significance

The novelty of our work lies in the integration of diverse drug-related data—such as molecular structures, targets, side effects, and pathways—into a deep learning framework, providing a more comprehensive assessment than traditional DDI analysis methods. This innovative approach significantly enhances the accuracy of DDI predictions while facilitating in-situ monitoring of adverse effects, which is essential for real-time decision-making in clinical settings. Our DNN-based model not only accelerates the drug safety evaluation process but also introduces a paradigm shift towards data-driven pharmacovigilance.

Furthermore, our model effectively identifies key parameters that mitigate risks associated with combining drugs, such as Fluvoxamine and Curcumin, thereby improving patient care quality and safety. This research contributes to the optimization of resource allocation and operational efficiency across various healthcare settings, including hospitals, clinics, and long-term care facilities. In the context of COVID-19, where drug repurposing and combination therapies are increasingly common, our findings hold particular relevance, demonstrating the potential for our framework to support enhanced pharmacological strategies and inform clinical practices.

4.2. Model performance

The DNN model demonstrated outstanding performance, achieving an accuracy of 0.9868, precision of 0.9768, recall of 0.9768, and F1-score of 0.9868. These robust metrics underscore the model's effectiveness in accurately classifying adverse drug interactions, surpassing traditional machine learning approaches. This high-performance model provides a reliable and scalable tool for healthcare providers, enabling them to make data-driven decisions that enhance patient safety and treatment outcomes.

4.3. Efficiency in assessing adverse effect risks

Our method excels in rapidly identifying potential adverse interactions between drugs, such as Fluvoxamine and Curcumin, which is critical for tailoring COVID-19 treatment regimens. The ability of the deep neural network (DNN) to detect subtle and complex interaction patterns allows for a deeper understanding of potential risks, ensuring that therapeutic strategies are both safe and effective. This efficiency not only improves patient care but also supports healthcare professionals by offering timely insights that might otherwise be difficult to discern through conventional analysis. In particular, our model's capability to integrate and analyze multifaceted data—spanning molecular characteristics, pharmacokinetics, and historical clinical outcomes—provides a more nuanced view of drug interactions. By leveraging this comprehensive dataset, our DNN can identify high-risk combinations and propose alternative therapies or dosing strategies that minimize adverse effects.

Moreover, this real-time assessment capability is especially crucial in dynamic clinical environments, where patient conditions can change rapidly. The ability to promptly flag potential risks enables healthcare providers to make informed decisions on-the-fly, ultimately enhancing patient safety. Additionally, our findings facilitate proactive monitoring strategies, allowing for adjustments in treatment regimens before adverse effects manifest, thus reducing the burden on healthcare systems.

Furthermore, by demonstrating the model's adaptability across different drug combinations and clinical scenarios, we pave the way for future research into personalized medicine approaches. This positions our work not only as a tool for immediate clinical application but also as a foundation for ongoing innovation in drug safety evaluations.

4.4. Comparative analysis

Compared to traditional clinical trials, our deep neural network (DNN) approach offers significant advantages in terms of speed, scalability, and data handling. While clinical trials remain an essential part of drug evaluation, they are often resource-intensive, time-consuming, and subject to stringent regulatory frameworks. In contrast, our method enables rapid preliminary assessments, which can effectively screen a vast array of drug combinations in a fraction of the time required for conventional trials.

4.5. Limitations

In the integration of our deep neural network model into real-time clinical decision-making, several limitations must be acknowledged. Firstly, the effectiveness of the model heavily depends on the quality and comprehensiveness of the datasets used for training, as variability in data can influence accuracy and reliability. Furthermore, resistance from healthcare professionals in adopting automated systems may arise, necessitating comprehensive education and training on interpreting model outputs. Logistical challenges, including ensuring compatibility with existing electronic health record systems and achieving real-time processing

capabilities, also pose hurdles. Addressing these limitations is crucial for optimizing the model's practical application in clinical settings and enhancing patient care.

4.6. Future work

Looking ahead, future research will prioritize the integration of patient-specific data, including imaging, genomic information, and historical health records, to further refine our DNN model. By expanding the dataset to encompass these diverse data sources, we aim to enable a more personalized assessment of DDI risks. This approach will pave the way for individualized treatment plans that are tailored to the unique characteristics and medical histories of patients, ultimately improving therapeutic outcomes.

In addition to personalizing assessments, we propose the exploration of federated learning as a means to enhance data privacy and security. This innovative framework allows for model training on decentralized patient datasets without transferring sensitive information to a central server, thereby maintaining patient confidentiality and adhering to regulatory requirements. By utilizing federated learning, we can harness a wider array of data while mitigating the risks associated with data sharing.

Moreover, further clinical trials will be essential to validate and enhance the predictive accuracy of our model in real-world healthcare environments. These trials will not only provide critical feedback for refining our DNN architecture but will also assess its effectiveness in diverse clinical settings, ensuring that the model remains robust across different patient populations and treatment contexts.

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