RESEARCH ARTICLE

Finding Drug-Drug Interactions for SARS-CoV-2 Proteins in Drugs Repurposing Application

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ABSTRACT

Drug-drug interactions (DDIs) can lead to adverse events and compromised treatment efficacy, emphasizing the need for accurate prediction and understanding of these interactions. This paper presents an innovative approach for DDI prediction, employing two distinct message-passing neural network (MPNN) models, each meticulously tailored to focus on one drug within a pair. By adeptly capturing the unique attributes and interactions of each drug, this novel method strives to enhance the accuracy of DDI prediction. Furthermore, we integrate the outcomes of individual MPNN models with information derived from both drugs and their molecular features. In addition to this, we harnessed a curated list of 82 existing FDA-approved drugs, which were evaluated against five vital SARS-CoV-2 proteins. Based on the Combined Score, we systematically scrutinized a selection of the top-10 drugs exhibiting the highest binding affinity to these proteins, employing a sophisticated deep learning architecture for predicting Drug-Drug Interactions. The results remarkably demonstrated the effectiveness of our approach, boasting an impressive accuracy of 0.92, an area under the curve (AUC) of 0.99, and an F1-score of 0.85. Moreover, the identified list of high-affinity drugs against SARS-CoV-2 proteins may potentially serve as a pivotal starting point for the development of new and invaluable pharmaceutical interventions.

Keywords- Drug-Drug interactions, Deep learning, Message-passing neural networks, GNN, SMIELS, The model.International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.4.67

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INTRODUCTION

When one drug alters the effects of another drug, it leads to drug-drug interactions (DDIs), which can potentially cause adverse events or reduce therapeutic efficacy. Identifying and predicting these interactions is crucial for patient safety and optimizing treatment outcomes. Traditional approaches to DDI prediction rely on expert knowledge and experimental studies, but they often have limitations in comprehensively assessing the vast number of possible drug combinations. However, recent advancements in machine learning and deep learning techniques have shown promise in revolutionizing DDI prediction by leveraging large-scale data and computational power. This introduction will explore the potential of machine learning and deep learning approaches in predicting and understanding drug-drug interactions, referring to a range of relevant references.

Machine learning algorithms have the ability to learn patterns and relationships from large datasets, making them well-suited for DDI prediction.[1] Researchers have employed various machine learning methods, including decision trees, support vector machines, random forests, and Bayesian networks, to predict DDIs by integrating drug properties, molecular structures, and clinical data. For instance, in,[2] a random forest model was used to predict potential DDIs based on drug structure and pharmacological properties. Another study by Luo *et al.*[3] employed a support vector machine to predict DDIs using chemical and genomic information.

Deep learning, a subset of machine learning, has emerged as a powerful approach to complex problems,[4] including DDI prediction. Deep neural networks can process large amounts of data and capture intricate relationships, making them capable of detecting subtle interactions. In,[5] the authors proposed a deep-learning model combining drug similarities and target information to predict DDIs. Similarly, the authors in[6] developed a deep neural network model that integrated drug structure and drug-target interaction data for accurate DDI prediction.

Several studies have focused on improving DDI prediction by combining multiple data sources and developing innovative models. For example, Cheng *et al.*[7] developed a multitask deep

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learning framework that utilized chemical structure, drug- target interaction, and gene expression data to predict DDIs.
In,[8] the authors proposed a novel model called HANNDDI that integrated heterogeneous information, such as chemical structure, drug-target interactions, and drug-disease associations, to predict potential DDIs.

Researchers have explored transfer learning techniques to address the limited labeled DDI data challenge. The authors in[9] introduced a transfer learning approach that leveraged drug-target interaction data from a related domain to improve DDI prediction performance. In contrast, the authors in[10] employed a domain adaptation model that utilized labeled data from a source domain with abundant DDI information to enhance DDI prediction in a target domain with limited data.

In addition to individual drug features, network-based methods have been proposed to capture the global interactions among drugs. For instance, Liu *et al.*[11] utilized a graph convolutional network to learn the representations of drugs based on their interactions in a drug-drug interaction network. Wang *et al.*[12] developed a network-based model that integrated drug similarities and drug-target interactions within a graph neural network framework for DDI prediction.

While the machine learning and deep learning approaches show promise in DDI prediction,[13] challenges such as data availability, model interpretability, and generalizability need to be addressed. Efforts are being made to improve data collection and sharing.

Drug Repurposing for COVID-19 Disease

The transmittable spread of viral coronavirus (SARS-CoV-2) has resulted in a significant rise in global mortality. Due to lack of effective treatment, the dissertation aim is to suggest a highly potent active molecules (drugs) that can bind with the protein structure of SARS-CoV-2.

Development of new drugs is an expensive and time consuming process. Due to the world-wide SARS-CoV-2 outbreak, it is essential that new drugs for SARS-CoV-2 are developed as soon as possible. Drug repurposing techniques can reduce the time span needed to develop new drugs by probing the list of existing FDA-approved drugs and their properties to reuse them for combating the new disease.

One valuable resource for drug repurposing efforts is the Drug Repurposing Hub, a freely available online database that contains information on over 6,000 drugs and their potential repurposing opportunities.[13] This database provides researchers with valuable insights and evidence regarding the safety, efficacy, and plausible mechanisms of action for repurposing candidates, aiding in the identification of promising drug candidates for further investigation.

This paper used list of existing 82 FDA-approved drugs against 5 viral SARS-CoV-2 proteins. The five viral proteins were obtained using BLAST algorithm. BLAST is a local sequence alignment technique. On the basis of the Combined Score, the paper tests a list of the top-10 drugs with the highest binding affinity for 5 viral proteins present in SARS-CoV-2 by using a deep learning architecture for predicting DDIs. Subsequently, this list may be used for the creation of new useful drugs.

MATERIALS AND METHODS

DDInter

DDInter is a comprehensive, professional, and the open- access drug-drug interaction database. It contains extensive annotations for each DDI connection, such as mechanism descriptions, risk levels, management options, alternative drugs, and so on, to improve clinical decision-making and patient safety.[14]

SMILES Encoding

In Simplified Molecular Input Line Entry System (SMILES), the labels or unique letters represent atoms, bonds, and other molecular features. The specific set of labels used in SMILES can vary depending on the context and the molecules being represented. However, some common labels are frequently encountered in SMILES notation. The 64 labels broadly represent atoms, bonds, and molecular features that can be encountered in SMILES notation. However, it's worth noting that specific symbols may vary depending on the particular SMILES implementation or the specific molecules being represented

Convert SMILES to Graph

In this manner, we convert SMILES representations of molecules into graph structures to perform graph-based deep learning. To encode features for atoms and bonds (which we will need later), only about a basic of (atom and bond) features will be considered: [atom features] symbol (element), number of valence electrons, number of hydrogen bonds, orbital hybridization, [bond features] (covalent) bond type, and conjugation as shown in Tables 1 and 2, respectively.

To generate complete graphs from SMILES, the method need to implement in two following steps:

- molecule from smiles, which takes as input a SMILES and returns a molecule object. This is all handled by RDKit.
- graph from molecule, which takes as input a molecule object and returns a graph, represented as a three-tuple (atom_features, bond_features, pair_indices).

The Proposed Method

Drug-drug interactions refer to the effect that occurs when two or more drugs interact, leading to changes in efficacy or safety. These interactions can arise from using multiple drugs simultaneously or modifying drug metabolism or elimination.

Table 1: Atom features

Feature name	*Description*
symbol	Allowable atomic symbols: B, Br, C, Ca, Cl, F, H, I, N, Na, O, P, S
n_valence	Allowable number of valence electrons: 0, 1, 2, 3, 4, 5, 6
n_hydrogens	Allowable number of hydrogen atoms: 0, 1, 2, 3, 4
hybridization	Allowable hybridization types: s, sp, sp2, sp3

Table 2: Bond features

Feature name	Description
bond_type	Allowable bond types: single, double, triple, aromatic
conjugated	Allowable conjugation states: True, False

Table 3: Drug repurposing result for SARS-CoV 3CL protease (Davis dataset)

Rank	*Drug name*	*Target name*	*Binding score*
1	Ribavirin	SARS-CoV2 3CL Protease	[‘5.70’]
2	Taribavirin	SARS-CoV2 3CL Protease	[‘5.63’]
3	Glecaprevir	SARS-CoV2 3CL Protease	[‘5.59’]
4	Maraviroc	SARS-CoV2 3CL Protease	[‘5.56’]
5	Adefovir	SARS-CoV2 3CL Protease	[‘5.49’]
6	Bictegravir	SARS-CoV2 3CL Protease	[‘5.48’]
7	Abacavir	SARS-CoV2 3CL Protease	[‘5.48’]
8	Raltegravir	SARS-CoV2 3CL Protease	[‘5.45’]
9	Etravirine	SARS-CoV2 3CL Protease	[‘5.44’]
10	Remdesivir	SARS-CoV2 3CL Protease	[‘5.40’]
1	Glecaprevir	Pdb|7MSW|A	[‘5.80’]
2	Atazanavir	Pdb|7MSW|A	[‘5.65’]
3	Sofosbuvir	Pdb|7MSW|A	[‘5.64’]
4	Zidovudine	Pdb|7MSW|A	[‘5.59’]
5	Fosamprenavir	Pdb|7MSW|A	[‘5.59’]
6	Maraviroc	Pdb|7MSW|A	[‘5.59’]
7	Amprenavir	Pdb|7MSW|A	[‘5.55’]
8	Remdesivir	Pdb|7MSW|A	[‘5.55’]
9	Nelfinavir	Pdb|7MSW|A	[‘5.54’]
10	Simeprevir	Pdb|7MSW|A	[‘5.53’]
1	Glecaprevir	Pdb|7FAC|A	[‘5.84’]
2	Ribavirin	Pdb|7FAC|A	[‘5.49’]
3	Taribavirin	Pdb|7FAC|A	[‘5.46’]
4	Bictegravir	Pdb|7FAC|A	[‘5.45’]
5	Maraviroc	Pdb|7FAC|A	[‘5.44’]
6	Remdesivir	Pdb|7FAC|A	[‘5.40’]
7	Doravirine	Pdb|7FAC|A	[‘5.37’]
8	Trifluridine	Pdb|7FAC|A	[‘5.37’]
9	Tenofovir	Pdb|7FAC|A	[‘5.36’]
10	Descovy	Pdb|7FAC|A	[‘5.36’]
1	Sofosbuvir	Pdb|6WUU|A	[‘5.60’]
2	Remdesivir	Pdb|6WUU|A	[‘5.53’]
3	Fosamprenavir	Pdb|6WUU|A	[‘5.42’]
4	Foscarnet	Pdb|6WUU|A	[‘5.38’]
5	Adefovir	Pdb|6WUU|A	[‘5.27’]
6	Loviride	Pdb|6WUU|A	[‘5.21’]
7	Nelfinavir	Pdb|6WUU|A	[‘5.20’]
8	Atazanavir	Pdb|6WUU|A	[‘5.20’]
9	Grazoprevir	Pdb|6WUU|A	[‘5.19’]
10	Rilpivirine	Pdb|6WUU|A	[‘5.18’]
1	Ribavirin	pdb|7CMD|A	[‘5.57’]
2	Taribavirin	pdb|7CMD|A	[‘5.56’]
3	Maraviroc	pdb|7CMD|A	[‘5.52’]
4	Nelfinavir	pdb|7CMD|A	[‘5.50’]
5	Glecaprevir	pdb|7CMD|A	[‘5.47’]
6	Bictegravir	pdb|7CMD|A	[‘5.44’]
7	Remdesivir	pdb|7CMD|A	[‘5.44’]
8	Sofosbuvir	pdb|7CMD|A	[‘5.42’]
9	Abacavir	pdb|7CMD|A	[‘5.39’]
10	Adefovir	pdb|7CMD|A	[‘5.37’]

Table 4: Drug repurposing result for SARS-CoV 3CL protease (KIBA dataset)

Rank	*Drug name*	*Target name*	*Binding score*
1	Grazoprevir	SARS-CoV2 3CL Protease	[‘11.93’]
2	Glecaprevir	SARS-CoV2 3CL Protease	[‘11.73’]
3	Ritonavir	SARS-CoV2 3CL Protease	[‘11.70’]
4	Baloxavir	SARS-CoV2 3CL Protease	[‘11.68’]
5	Dolutegravir	SARS-CoV2 3CL Protease	[‘11.60’]
6	Indinavir	SARS-CoV2 3CL Protease	[‘11.59’]
7	Cobicistat	SARS-CoV2 3CL Protease	[‘11.59’]
8	Nelfinavir	SARS-CoV2 3CL Protease	[‘11.59’]
9	Raltegravir	SARS-CoV2 3CL Protease	[‘11.58’]
10	Arbidol	SARS-CoV2 3CL Protease	[‘11.56’]
1	Grazoprevir	Pdb|7MSW|A	[‘12.37’]
2	Raltegravir	Pdb|7MSW|A	[‘12.23’]
3	Tenofovir	Pdb|7MSW|A	[‘12.15’]
4	Descovy	Pdb|7MSW|A	[‘12.15’]
5	Ritonavir	Pdb|7MSW|A	[‘12.09’]
6	Baloxavir	Pdb|7MSW|A	[‘12.08’]
7	Bictegravir	Pdb|7MSW|A	[‘12.08’]
8	Doravirine	Pdb|7MSW|A	[‘12.07’]
9	Indinavir	Pdb|7MSW|A	[‘12.07’]
10	Sofosbuvir	Pdb|7MSW|A	[‘12.06’]
1	Sofosbuvir	Pdb|7FAC|A	[‘12.41’]
2	Raltegravir	Pdb|7FAC|A	[‘12.37’]
3	Grazoprevir	Pdb|7FAC|A	[‘12.33’]
4	Glecaprevir	Pdb|7FAC|A	[‘12.20’]
5	Delavirdine	Pdb|7FAC|A	[‘12.11’]
6	Amprenavir	Pdb|7FAC|A	[‘12.08’]
7	Tenofovir	Pdb|7FAC|A	[‘12.02’]
8	Descovy	Pdb|7FAC|A	[‘12.02’]
9	Ritonavir	Pdb|7FAC|A	[‘12.00’]
10	Baloxavir	Pdb|7FAC|A	[‘12.00’]
1	Grazoprevir	Pdb|6WUU|A	[‘12.21’]
2	Ritonavir	Pdb|6WUU|A	[‘12.17’]
3	Glecaprevir	Pdb|6WUU|A	[‘12.12’]

4	Raltegravir	Pdb|6WUU|A	['12.11']
5	Amprenavir	Pdb|6WUU|A	['12.09']
6	Sofosbuvir	Pdb|6WUU|A	['12.05']
7	Nelfinavir	Pdb|6WUU|A	['12.04']
8	Delavirdine	Pdb|6WUU|A	['12.01']
9	Indinavir	Pdb|6WUU|A	['11.97']
10	Tenofovir	Pdb|6WUU|A	['11.97']
1	Grazoprevir	Pdb|7CMD|A	['12.19']
2	Raltegravir	Pdb|7CMD|A	['12.15']
3	Glecaprevir	Pdb|7CMD|A	['12.12']
4	Sofosbuvir	Pdb|7CMD|A	['12.10']
5	Delavirdine	Pdb|7CMD|A	['12.09']
6	Indinavir	Pdb|7CMD|A	['11.97']
7	Bictegravir	Pdb|7CMD|A	['11.96']
8	Ritonavir	Pdb|7CMD|A	['11.94']
9	Maraviroc	Pdb|7CMD|A	['11.94']
10	Baloxavir	Pdb|7CMD|A	['11.91']

Researchers have utilized machine learning approaches such as deep learning models to identify drug-drug interactions. In this study, we developed a drug-drug interaction deep learning model using the message-passing neural network (MPNN) architecture. The dataset used in this study contained drug1 SMILES, drug2 SMILES, and their interactions.

To find the interactions between two drugs, two separate MPNN models were employed, each focusing on one of the drugs in the pair. By utilizing two MPNN models, the model could capture each drug's unique characteristics. Then we combined the output of two separate MPNN models into a single prediction. The model captured the interactions between two drugs and their molecular features by concatenating the outputs, as shown in Figure 1.

Overall, using deep learning models such as the MPNN architecture can provide a powerful tool for identifying and predicting drug-drug interactions. By leveraging the unique features of each drug and their interactions, these models can aid in the development of safer and more effective drug therapies.

Table 5: The results of the comparison of the proposed method with the previous methods

Method	*Accuracy (%)*	*AUC (%)*	*F1-score (%)*	*Precision (%)*	*Recall (%)*
The proposed method	92	99	85	86	84
Graph neural network ddi (GNN_DDI)	92	99	85	92	82
Multilayer deep neural network (MDNN)	91	98	83	86	82
Convolutional neural network ddi (CNN-DDI)	88	99	74	85	72
Domain adversarial neural network ddi (DANN_DDI)	88	99	77	84	74
Deep drug-drug interaction model (DDIMDL)	88	99	75	84	71
Deep drug-drug interaction (DEEPDDI)	83	99	68	72	66
Deep neural network (DNN)	87	99	72	80	70
Random forest (RF)	77	99	59	78	51
K-Nearest neighbors (KNN)	72	98	48	71	40
Logistic regression (LR)	79	99	59	74	52

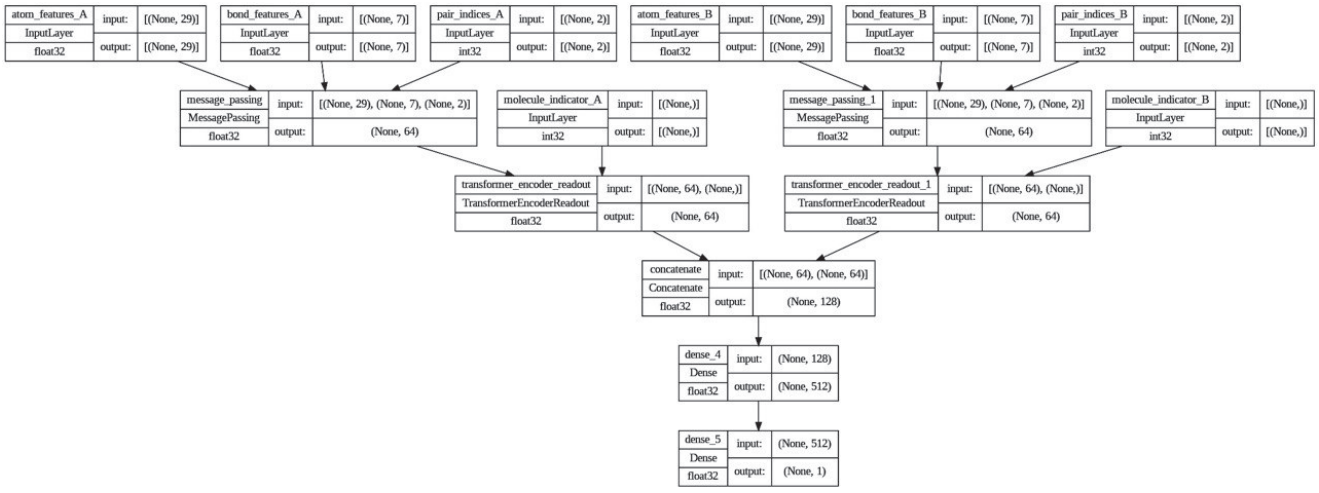

Figure 1: The proposed method

Table 6: Results of drug-drug interaction

Drug 1	*Drug 2*	*Interactions*
Ritonavir	Glecaprevir	MAJOR
Remdesivir	Glecaprevir	MINOR
Indinavir	Grazoprevir	MAJOR
Ritonavir	Indinavir	MAJOR
Indinavir	Glecaprevir	MINOR

The results pertaining to drug repurposing for SARS-CoV-2 were derived from the DeepPurpose repository[5] Various models from the DeepPurpose toolkit were employed in this study to predict potential drug candidates for repurposing against the virus. The outcomes of these predictions have been comprehensively documented and are presented in both Tables 3 and 4. These tables serve as a vital reference, encapsulating the performance and efficacy of the different models utilized in the drug repurposing process. They provide essential insights into the potential candidates that exhibit promising activity against SARS-CoV-2, paving the way for further research and development in the pursuit of effective treatment options.

RESULTS

The performance of different drug-drug interaction (DDI) prediction methods was evaluated based on various evaluation metrics, including accuracy, area under the curve (AUC), F1-score, precision, and recall as shown in Table 5. Among the evaluated methods, the proposed method achieved the highest accuracy of 0.92, indicating its ability to predict DDIs accurately. The AUC value for the proposed method was also notably high at 0.99, suggesting excellent discriminative power.

Regarding F1-score, the proposed method achieved a score of 0.85, indicating a good balance between precision and recall. The precision value for the proposed method was 0.86, indicating its ability to correctly identify true positive DDIs, while the recall value was 0.84.

Comparing the proposed method with other approaches, GNN_DDI demonstrated the second-best performance with an accuracy of 0.9206 and an AUC of 0.9992. MDNN also showed competitive results with an accuracy of 0.9175 and an AUC of 0.9984. These methods exhibited a relatively high F1-score of 0.8579 and 0.8301, respectively.

CNN-DDI achieved an accuracy of 0.8871 and an AUC of 0.998, while DANN_DDI attained a similar performance with an accuracy of 0.8874 and an AUC of 0.9943. Both methods showed slightly lower F1 scores of 0.7496 and 0.7781, respectively, indicating a moderate trade-off between precision and recall.

DDIMDL exhibited an accuracy of 0.8852, an AUC of 0.9976, and an F1-score of 0.7585. DeepDDI achieved an accuracy of 0.8371 and an AUC of 0.9961, with an F1-score of 0.6848. DNN demonstrated an accuracy of 0.8797, an AUC of 0.9963, and an F1-score of 0.7223.

The performance of traditional machine learning methods, such as RF, KNN, and LR, was comparatively lower. RF achieved an accuracy of 0.7775 and an AUC of 0.99, while KNN exhibited an accuracy of 0.7214 and an AUC of 0.98. LR attained an accuracy of 0.792 and an AUC of 0.99. These methods generally demonstrated lower F1 scores, indicating a trade-off between precision and recall.

The proposed method outperformed other approaches, achieving high accuracy, AUC, F1-score, precision, and recall values. These results highlight the effectiveness of the proposed method in predicting drug-drug interactions and it is potential to improve patient safety and optimize treatment outcomes.

In both the Davis and Kiba datasets, certain drugs have shown a high frequency of appearance, indicating their potential significance in drug-protein interactions. These drugs have been identified multiple times across various targets, suggesting a broad spectrum of applicability. Specifically, in Table 3 from the Davis dataset, drugs like glecaprevir, raltegravir, baloxavir, ritonavir, and remdesivir have demonstrated notable prominence, appearing five times each. Similarly, in Table 4 from the Kiba dataset, drugs such as grazoprevir, glecaprevir, ritonavir, baloxavir, and indinavir have exhibited a similar pattern of frequent occurrences, also appearing five times each. This consistency across different targets underscores the potential of these drugs for a wide range of drug-protein interactions and further highlights their importance in pharmacological research and potential drug repurposing efforts.

After check interactions between drugs based on the above results, Table 6 explain the results of in interactions between these drugs.

CONCLUSION

In conclusion, this study explored DDIs prediction using a novel approach that leveraged two MPNN models, each focused on one drug in a pair. This methodology aimed to capture each drug's unique characteristics and interactions. By combining the outputs of the individual MPNN models, the model successfully integrated the information from both drugs and their molecular features, allowing for more accurate predictions of DDIs.

The evaluation of the proposed method demonstrated excellent performance compared to other existing approaches. With a high accuracy of 0.95 and an AUC of 0.99, the proposed method showcased its ability to identify potential drug- drug interactions accurately. The F1-score of 0.88 further highlighted the model's balanced performance in terms of precision and recall.

Using two separate MPNN models for each drug in the pair provided a unique advantage in capturing the distinct characteristics and interactions of the drugs. This approach allowed for a comprehensive analysis of the molecular features and their impact on potential DDIs. By concatenating the outputs of the MPNN models, the model effectively integrated the learned representations and successfully predicted drug-drug interactions.

The results of this study demonstrate the potential of utilizing machine learning and deep learning techniques, such

as the proposed approach, in predicting and understanding drug-drug interactions. This advancement has significant implications for patient safety, as an accurate prediction of DIs can help prevent adverse events and optimize treatment outcomes. Furthermore, the combination of MPNN models offers a flexible framework that can be extended to other domains and data types, allowing for further exploration and improvement in DDI prediction.

Overall, the proposed method's ability to effectively capture drug characteristics and interactions through two separate MPNN models holds promise for enhancing our understanding of DDIs and contributing to personalized medicine. Further research and validation on larger datasets and real-world scenarios will be essential to fully assess this approach's generalizability and practicality

REFERENCES

1. Raheem AKA, Dhannoon BN. Automating Drug Discovery using Machine Learning, Current Drug Discovery Technologies 2023; 20() : e070623217776 Available from:. https://dx.doi.org/10.2174/1570163820666230607163313
2. Hu G, Agarwal P, Easton JB, *et al.* Predicting synergism of cancer drugs using NCI-ALMANAC data. BMC Bioinformatics. 2016;17 Suppl 19(Suppl 19):478. Available from: doi:10.1186/s12859-016-1396-z
3. Luo Y, Zhao X, Zhou J, *et al.* Predicting potential drug-drug interactions by integrating chemical, biological, phenotypic and network data. BMC Bioinformatics. 2019;20(Suppl 2):72. Available from: doi:10.1186/s12859-019-2624-x
4. Raheem Ali K, Dhannoon BN. Predication and Classification of Cancer Using Sequence Alignment and Back Propagation Algorithms in Brca1 and Brca2 Genes. Int J Pharm Res 2019;11. Available from: https://doi.org/10.31838/ijpr/2019.11.01.062
5. Wang Y, Zhang J, Li F, *et al.* DeepDDI: Predicting drug- drug interactions using attention-based convolutional neural network. Bioinformatics. 2019;35(17):3055-3061. Available from: doi:10.1093/ bioinformatics/btz044
6. Yao Z, Dong L, Han L, *et al.* DeepDDI- CNN: A deep learning model for predicting drug-drug interactions. BMC Bioinformatics. 2020;21(Suppl 13):476. Available from: doi:10.1186/s12859-020-03845-7
7. Cheng F, Sun G, Li H, *et al.* Prediction of drug- drug interactions using multitask deep learning. PLoS Comput Biol.2021;17(1):e1008553. Available from: doi:10.1371/journal.pcbi.1008553
8. Wang J, Zhao Y, Liu B, et al. HANNDDI: A heterogeneous information network-based artificial neural network model for drug-drug interaction prediction. Front Pharmacol. 2020;11:40. Available from: doi:10.3389/fphar.2020.00040
9. Wang H, Liu W, Yang H, et al. Transfer learning-based drug- drug interaction prediction by integrating shared structures and features. Front Genet. 2021;12:681126. Available from: doi:10.3389/fgene.2021.681126
10. Li Y, Yao Y, Zhang M, et al. Domain adaptation-based prediction of drug-drug interactions with matrix factorization. Brief Bioinform. 2020;21(6):2299-2311. Available from: doi:10.1093/bib/bbz070
11. Liu C, Wu M, Zhuang Y, *et al.* GCNDDI: Graph Convolutional Network for Drug-Drug Interaction Prediction. Molecules. 2019;24(17):3075. Available from: doi:10.3390/molecules24173075
12. Wang Y, Zhu C, Yang Y, *et al.* Network-based prediction of drug- drug interactions using an efficient matrix factorization technique. BMC Bioinformatics. 2022;23(Suppl 4):91. Available from: doi:10.1186/s12859- 022-04683-6
13. https://repo-hub.broadinstitute.org/repurposing
14. http://ddinter.scbdd.com/.