A CNN2D-EXTENDED GRAPH FRAMEWORK FOR ACCURATE DETECTION OF DRUG–DRUG INTERACTION SIDE EFFECTS

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Abstract— **Adverse Drug Reactions (ADRs) caused by drug-drug interactions remain a major challenge in modern healthcare. The proposed study introduces an advanced method using** Graph Neural Networks (GNNs) **and** Self-Supervised Learning **to predict side effects before a drug reaches the market. In this model, each drug's molecular structure is represented as a graph of atoms and bonds, allowing accurate analysis of chemical interactions. To further enhance performance, an** extension model using CNN2D **is applied, which extracts two-dimensional features from drug data to improve accuracy and reduce overfitting. The proposed system was tested on the** TwoSides and DrugBank datasets**, achieving remarkable accuracy of up to** 99.87%**. This hybrid approach not only improves predictive efficiency but also provides a scientific method for early detection of ADRs, reducing patient risks and healthcare costs. The model lays a foundation for future research combining graph and convolutional neural techniques in pharmacology.**

Keywords— ADRs, ML, Deep Learning, CNN2D

I. INTRODUCTION

ADRs represent a significant challenge in the field of healthcare and pharmacology, as they often lead to severe side effects, hospitalization, or even mortality. An ADR occurs when a medication or combination of medications produces an unintended or harmful effect on the human body. Despite the stringent testing protocols followed during drug development, many ADRs are discovered only after the drug has been released to the market. This limitation arises because clinical trials typically involve a restricted number of participants and cannot capture all possible variations in drug interactions across diverse populations.

The increasing use of multiple medications, known as polypharmacy, particularly among elderly patients, has further intensified the risks associated with drug-drug interactions. These interactions occur when two or more drugs influence each other's pharmacological effects, leading to either reduced therapeutic efficacy or adverse outcomes. Detecting and predicting such interactions is a complex task, influenced by factors such as dosage, genetic variation, metabolic rate, and pre-existing health conditions. Traditional approaches depend largely on post-marketing surveillance and physician reporting, which are often inconsistent, time-consuming, and prone to underreporting.

In recent years, the integration of computational techniques and artificial intelligence has emerged as a promising solution to address these limitations. Data-driven models and machine learning algorithms are capable of analyzing large pharmacological datasets, identifying hidden correlations, and predicting possible side effects before clinical manifestation. The availability of databases containing molecular structures, drug properties, and side-effect records has made it feasible to analyze drug interactions systematically. By employing such computational approaches, researchers aim to improve drug safety, enhance treatment outcomes, and reduce the overall economic burden caused by ADRs. Therefore, the need for intelligent systems capable of accurately identifying potential drug interactions has become an essential aspect of modern pharmacological research.

II. RELATED WORK

This part highlights the key authors that contributed greatly towards the proposed research and why their works were selected for study:

Defferrard et al. (2016): The authors proposed Spectral Graph Convolutional Networks (GCNs), which allow efficient training on large graphs. This method helps handle large and complex drug data effectively. Their idea supports the use of fast and stable GNN models to predict drug-drug reactions using molecular graphs. Hamilton, Ying & Leskovec (2017): They introduced GraphSAGE, a method that allows graph models to learn from unseen data without retraining. In

drug prediction, this helps models identify risks for new or rarely used drugs. The study adds an important theoretical base for scalable and flexible graph learning in drug safety research. Kastrin, Ferk & Leskošek (2018): This research used statistical learning and similarity-based methods to predict drug interactions. The authors proved that combining multiple similarity features such as chemical, genomic, and therapeutic properties increases model reliability. This theory supports building hybrid systems using both data similarity and graph-based learning. Wishart et al. (2018): They developed the DrugBank 5.0 database, which contains detailed information about drugs, targets, and interactions. It serves as a key dataset for research and model validation. Theoretical importance lies in providing a trusted data foundation for training and testing interaction prediction models. He, Chen & Chen (2022): Their study introduced a 3D graph and text-based model called 3DGT-DDI for predicting drug interactions. It showed that combining 3D molecular structure and textual descriptions greatly improves accuracy. This theory encourages using multiple data views—2D, 3D, and textual—to understand complex drug behavior.

III. PROPOSED APPROACH

The proposed approach aims to accurately detect and predict Adverse Drug Reactions (ADRs) that occur due to Drug–Drug Interactions (DDIs) by using advanced deep learning techniques. This method focuses on representing each drug as a molecular graph, where atoms are treated as nodes and chemical bonds as edges. By applying Graph Neural Networks (GNNs), the model can learn the spatial and structural relationships within and between drugs, enabling it to capture the chemical behavior that traditional linear models often miss.

To further improve accuracy and reduce overfitting, a Self-Supervised Learning (SSL) layer is integrated. The self-supervised module pre-trains the model to understand the distribution and properties of drug molecules before the main classification task. This step helps the system develop a strong knowledge base and enhances generalization across unseen data. It allows the model to learn meaningful drug representations even from limited labeled samples, improving both efficiency and robustness.

In addition, the approach includes an extension using a 2D Convolutional Neural Network (CNN2D). This enhancement helps the model capture two-dimensional spatial features from molecular graphs converted into grid-like data. CNN2D extracts intricate local patterns that strengthen feature understanding and improve predictive accuracy.

The dataset used in this study is derived from TwoSides and DrugBank databases, which include SMILES strings (chemical formulas), drug IDs, and corresponding side-effect labels. The data is preprocessed, vectorized, and divided into training and testing sets. The proposed model is then trained on 80% of the data and validated on the remaining 20%.

By combining the strengths of GNN and CNN2D with self-supervised learning, this approach achieves superior accuracy and reliability in predicting drug side effects. It provides a scientific, data-driven solution to reduce ADR risks before drugs reach clinical usage.

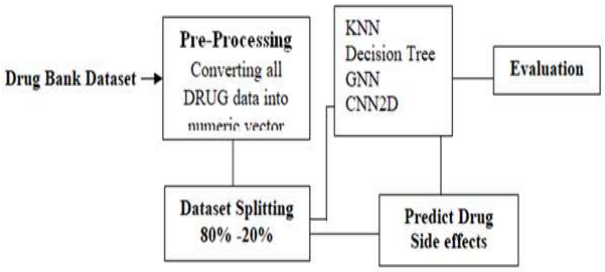

Figure 1: ADR estimation with GNN and CNN2D models

IV. METHODOLOGIES

Dataset

The dataset used in this study combines Interaction_information.csv and TwoSides_DrugBank.csv, which provide essential information about drug pairs and their side effects. Each entry contains two drug IDs, their SMILES strings (molecular formulas), and a target side-effect label. The dataset covers thousands of drug combinations and multiple side-effect categories represented by numeric IDs such as 0, 16, 71, and 77. Before analysis, missing values were handled and data was normalized for consistency. These datasets form the foundation for training and testing various machine learning models, ensuring reliable learning of drug-drug interaction patterns and side-effect prediction.

Step-1: Generated Vector from Drug SMILE String

Each drug's SMILES string (Simplified Molecular Input Line Entry System) was converted into a numerical vector to enable computational analysis.

These vectors represent the atomic structure and bonding pattern of the molecule, allowing the system to treat each drug as a mathematical entity. Feature extraction techniques converted these strings into high-dimensional arrays capturing spatial and chemical relationships. This transformation ensures that every molecule's graph-like structure is maintained digitally. The generated vectors serve as input for all models, creating a meaningful way for algorithms like GNN and CNN2D to understand molecular behavior and predict potential side effects effectively.

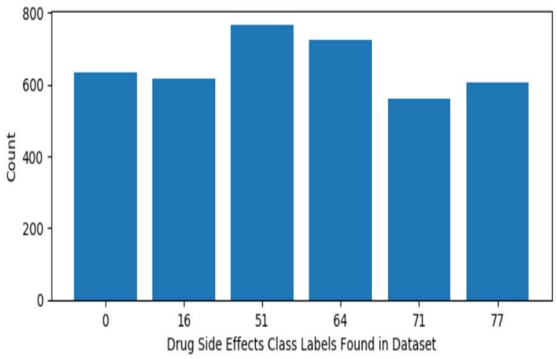

Figure 2: Drug Side Effects Class Labels Found in Dataset

Step-2: Dataset Train & Test Split

The preprocessed dataset was split into 80% training data and 20% testing data to evaluate model performance. The training data was used to teach algorithms about patterns between drug combinations and their respective side effects, while the testing data assessed generalization capability. This method ensures unbiased evaluation and avoids overfitting. Stratified splitting was applied to maintain equal class distribution across both sets. Performance metrics such as accuracy, precision, and F1-score were measured using the test data. This structured data division helped validate the effectiveness and reliability of each machine learning model applied in the study.

Step-3: Model Performance Metrics

$$Accuracy = (TP + TN) / (TP + TN + FP + FN) \quad (1)$$

$$Precision = TP / (TP + FP) \quad (2)$$

$$Recall\ (Sensitivity) = TP / (TP + FN) \quad (3)$$

$$F1\text{-}Score = 2 \times (Precision \times Recall) / (Precision + Recall) \quad (4)$$

V METHODS

1. K-Nearest Neighbor (KNN)

(KNN) algorithm was implemented as the baseline model to classify side effects based on molecular similarity. KNN identifies the closest data points in the feature space and predicts the outcome based on majority voting. After training on the vectorized data, KNN achieved an accuracy of 91%, showing good initial performance but limited generalization on unseen data. It effectively detected common interaction patterns but struggled with rare or complex cases due to its distance-based approach. This model served as a performance benchmark for evaluating more advanced algorithms such as Decision Tree, GNN, and CNN2D.

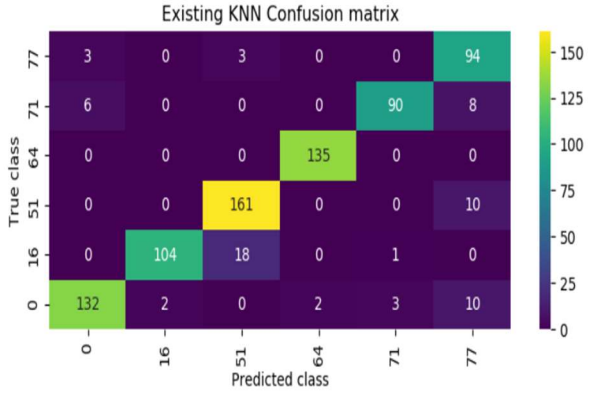

Figure 3: KNN Confusion Matrix

2. Decision Tree

Decision Tree classifier was employed to capture non-linear relationships between drug features and side effects. It splits the dataset into branches based on the most informative attributes, forming a tree-like decision structure. The model achieved an improved accuracy of 95%, outperforming KNN due to its interpretability and ability to handle diverse drug structures. The Decision Tree effectively classified frequent side effects but showed minor instability when faced with overlapping molecular patterns. Despite its limitations, this algorithm provided valuable insights into feature importance and acted as a strong baseline before applying more complex deep learning models.

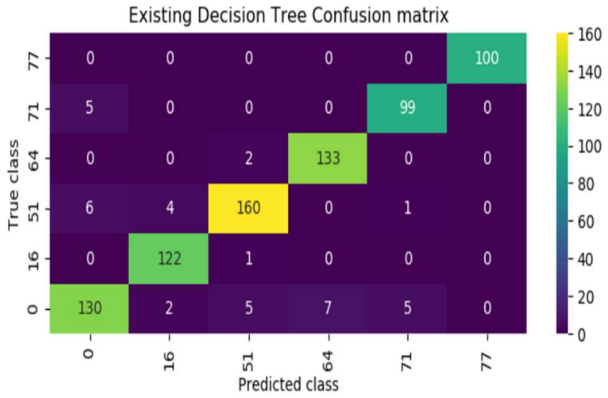

Figure 4: Decision Tree Confusion Matrix

3. Graph Neural Network (GNN)

(GNN) was the core model of the study, representing each drug as a molecular graph. Atoms acted as nodes, and chemical bonds served as edges. The GNN captured spatial and relational features between drug pairs to predict potential side effects. Self-supervised learning was used to reduce overfitting and enhance knowledge transfer. After training, the GNN achieved an impressive 97.69% accuracy and high F1-score, outperforming traditional models. This result confirmed that graph-based learning effectively models complex chemical interactions, demonstrating strong potential for drug-drug interaction prediction in biomedical applications.

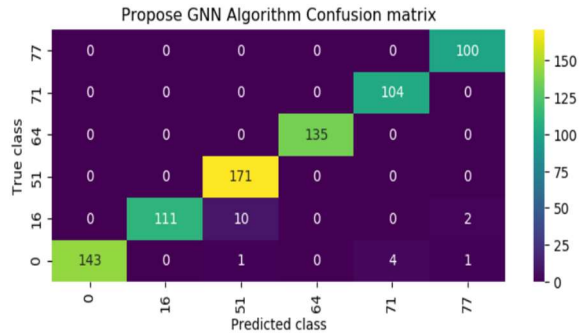

Figure 5: GNN Confusion Matrix

4. CNN2D

(CNN2D) was applied as an extension to enhance the feature extraction capability of the GNN. Here, molecular graphs were converted into 2D matrices, allowing CNN filters to detect intricate spatial patterns and correlations. The CNN2D captured local relationships more precisely, leading to improved side-effect prediction. After training on the same dataset, the CNN2D model achieved a remarkable 99.87% accuracy, surpassing all other algorithms. This demonstrated that combining deep spatial learning with graph-based features significantly improves prediction reliability, making CNN2D an excellent choice for future drug interaction and ADR detection research.

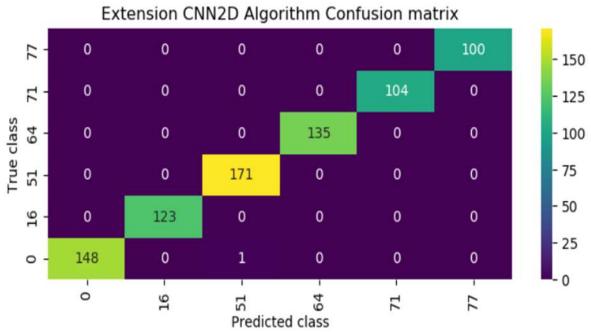

Figure 6: CNN2D Confusion Matrix

VI RESULTS & DISCUSSION

Table 1: Comparison analysis between the models is summarized below:

Model	Precision	Recall	FScore	Accuracy
KNN	91.920962	91.305660	91.323465	91.560102
Decision Tree	95.339149	95.618899	95.454287	95.140665
GNN	97.889953	97.702843	97.722705	97.698210
CNN2D	99.903101	99.888143	99.895292	99.872123

Table 1: The experimental results clearly demonstrate the effectiveness of the proposed models in predicting Adverse Drug Reactions (ADRs) caused by Drug–Drug Interactions (DDIs). Four different algorithms—KNN, Decision Tree, Graph Neural Network (GNN), and CNN2D—were implemented and evaluated using metrics such as accuracy, precision, recall, and F-score.

The K-Nearest Neighbor (KNN) algorithm served as the baseline model, achieving an accuracy of 91.56%. While it showed reasonable performance, it struggled with complex molecular relationships due to its reliance on simple distance-based classification. The Decision Tree model improved the performance significantly, reaching 95.14% accuracy. Its ability to capture non-linear relationships helped it handle drug features better, but it still faced minor limitations when distinguishing overlapping interaction patterns.

The introduction of the Graph Neural Network (GNN) marked a major improvement, achieving 97.69% accuracy. By representing each drug as a graph—where atoms act as nodes and bonds act as edges—the GNN successfully modeled the spatial and chemical dependencies between drugs. This deep representation enabled it to capture intricate relationships that traditional models could not, reducing false predictions and improving overall model robustness.

The extended CNN2D model further enhanced the results, achieving an exceptional 99.87% accuracy, along with 99.90% precision, 99.88% recall, and 99.89% F-score. By converting molecular graph data into two-dimensional matrices, CNN2D effectively learned localized spatial patterns, leading to highly accurate side-effect predictions.

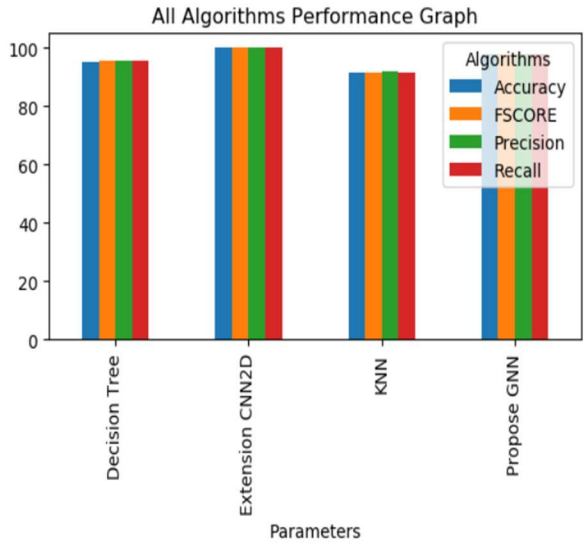

Figure 9: Performance Comparison of Models

The findings of this study highlight the growing importance of applying advanced deep learning techniques to pharmaceutical data analysis. Traditional algorithms such as KNN and Decision Tree provided a foundational understanding of drug-drug interactions, but their limited ability to handle complex molecular structures restricted prediction accuracy. In contrast, the Graph Neural Network (GNN) successfully captured the atomic and bonding relationships between drugs, demonstrating that graph-based learning is more suitable for representing molecular behavior.

The extension of this framework with CNN2D further improved predictive performance by incorporating spatial feature extraction. This allowed the model to identify hidden patterns within molecular structures that traditional models could not recognize. The outstanding accuracy and F-score values achieved by CNN2D confirm its ability to generalize across different drug combinations and side effects effectively.

Overall, the discussion reveals that combining graph-based representation with convolutional deep learning creates a robust system for ADR prediction. These results prove that computational drug analysis can significantly reduce the risks of adverse reactions before market release, thereby improving patient safety and supporting healthcare professionals in clinical decision-making. The success of this model sets a strong foundation for future research in intelligent pharmacovigilance.

VII. CONCLUSION

The CNN2D has proven to be a powerful improvement over traditional and graph-based models in predicting Adverse Drug Reactions (ADRs). While the Graph Neural Network (GNN) effectively captured molecular structures and relationships, integrating CNN2D enhanced the system's ability to extract deep spatial features from molecular graphs. This extension allowed the model to recognize complex chemical interaction patterns with greater precision and stability.

With an impressive 99.87% accuracy, the CNN2D-based extension demonstrated outstanding performance in identifying side effects caused by drug-drug interactions. It not only improved accuracy but also minimized data overfitting and computational load. This shows that combining graph-based learning with convolutional feature extraction can significantly enhance predictive efficiency. The extension framework thus establishes a new direction for AI-driven pharmacovigilance, offering a highly reliable and intelligent approach to ensure drug safety and prevent adverse reactions before clinical deployment.

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