RESEARCH ARTICLE

Editorial Process: Submission:07/03/2025 Acceptance:03/15/2026 Published:04/07/2026

Comparative Performance Evaluation of GCN, GAT, and GraphSAGE Architectures for Drug-Gene Interaction Prediction in Ameloblastoma via MEK-Pathway Targeting

Nausathkhan Ubayathulla[1,2], M.R. Muthusekar[1]*, Pradeep Kumar Yadalam[3]

Abstract

Introduction: A key element of computational drug discovery is the precise prediction of drug–gene interactions, particularly when working with intricate biological systems where relational dependencies are essential. Because biological networks are graph-structured, traditional machine learning techniques frequently fall short. Graph Neural Networks (GNNs) have emerged as a viable approach for learning meaningful representations from this data type in response to this challenge. In this study, three state-of-the-art GNN architectures Graph Convolutional Networks (GCN), Graph Attention Networks (GAT), and GraphSAGE are comprehensively compared using a bipartite graph constructed from drug–target biochemical activity data. **Methods:** Using the Probes and Drugs website, drugs associated with MEK signalling were downloaded. The data, with drugs and genes as nodes, targets as edges, and activity biochemical as edge weights, along with other node-level features, were preprocessed for further analysis. A bipartite graph comprising 321 nodes consisting of gene names and target types and 1,028 edges weighted by levels of biochemical activity was constructed. To differentiate genes from targets, node features were encoded using a two-dimensional one-hot vector. Each GNN model was trained using a standardized three-layer architecture for 100 epochs with identical hyperparameters: Mean Squared Error (MSE) as the loss function, a learning rate of 0.01, and a dropout rate of 0.2. To ensure a fair performance comparison across models, the training–validation split was maintained at 80/20. **Results:** The GCN model exhibited steady convergence, with a train-to-validation loss ratio of 1.0433, a final validation loss of 0.9807, and a minimum validation loss of 0.8923. Although it showed slightly greater overfitting tendencies with a train-to-validation ratio of 1.0553, GAT outperformed the other models in terms of generalization, achieving the lowest final validation loss (0.9551) and the lowest minimum validation loss (0.8653). In contrast, GraphSAGE demonstrated the most balanced performance, with a train-to-validation loss ratio of 0.9949 and a final validation loss of 1.0052, indicating exceptional generalization and stability qualities that make it particularly suitable for inductive learning scenarios. **Conclusion:** The findings indicate that each architecture exhibits distinct advantages: GraphSAGE demonstrates superior generalization in dynamic graph environments; GAT enables more nuanced modeling through attention mechanisms; and GCN remains computationally stable and efficient. These results provide biomedical informatics researchers with valuable insights to guide the selection of GNN architectures for biological graph learning tasks. To enhance the translational potential of GNN-based drug discovery pipelines, future research should focus on integrating dynamic graph structures, richer node features, and supervised learning approaches aligned with empirical biological outcomes.

Keywords: graph attention networks- ameloblastoma- drugs- genes- graph neural networks- precision oncology

Asian Pac J Cancer Prev, **27 (4)**, 1257-1264

Introduction

The enamel-forming cells, known as ameloblasts, give rise to the benign but aggressive odontogenic tumor, ameloblastoma [1, 2]. It often presents as a painless swelling and is commonly found in the jaw, particularly in the mandible. Clinically, it can be either unilocular or multilocular; if left untreated, it can cause significant bone destruction. Despite usually growing slowly, it has a high recurrence rate following surgical excision. Although there are several histological variations of ameloblastomas, the conventional solid/multilocular variant is the most prevalent. Resection is typically part of the treatment; early diagnosis is crucial to prevent complications and achieve better results. Due to the possibility of recurrence, regular follow-up is essential [3].

*[1]Saveetha Dental College and Research Institute, Saveetha University, SIMATS, Chennai, Tamil Nadu, India. [2]Consultant Oral & Maxillofacial surgeon, EHS, Fujairah Specialized Dental Center, and Hospital, Fujairah, UAE. [3]Department of Periodontology, Saveetha Dental College and Research Institute, Saveetha University, SIMATS, Chennai, Tamil Nadu, India. *For Correspondence: muthusekhar55@gmail.com*

There are no approved medications for ameloblastoma; surgery is the main treatment option. Nonetheless, studies are being conducted to understand its genetic and molecular characteristics, which could lead to the development of targeted treatments. Experimental therapies, such as immunotherapy, targeted therapies like BRAF inhibitors [4], Molecular agents to stop tumor growth, and chemotherapy for aggressive cases, are being studied. Additionally, for recurrent tumors, adjuvant therapies like radiation therapy might be taken into consideration. As new therapeutic options are being explored by ongoing research, patients must be managed by a multidisciplinary team with experience in head and neck tumors. For the most up-to-date treatment options, always consult with medical professionals. Adults between the ages of 30 and 60 are frequently affected by ameloblastoma, a benign tumor that is aggressive locally and has the potential to spread and become malignant. Its pathogenesis is associated with dysregulation of the MAPK, SHH, and WNT/β-catenin pathways [5]. Although surgical resection is still the most common treatment, there is a significant risk of morbidity and recurrence. A growing molecular understanding could make it possible to develop improved diagnostic markers and targeted treatments. According to a recent study, 58 ferroptosis-related differentially expressed proteins (FR-DEPs) were identified in ameloblastoma, with mTOR being one of the six key hub proteins that were markedly upregulated. Rapamycin successfully inhibited tumor cell migration in vitro, and immunohistochemical analysis confirmed that ameloblastoma exhibited higher mTOR expression compared to other odontogenic lesions. These results suggest that mTOR may be a potential target for treating aggressive ameloblastomas [6]

Predicting drug-gene associations is crucial, especially regarding the Mitogen-Activated Protein Kinase Kinase (MEK) pathway in ameloblastoma [7]. As a key component of the MAPK signaling cascade, the MEK pathway affects cell survival, proliferation, and differentiation. Its aberrant activation is connected to the development and progression of tumors, including ameloblastoma, providing insight into the mechanisms underlying tumorigenesis. Identifying specific genetic changes in ameloblastomas is crucial for developing targeted therapies, as these changes can lead to aberrant signaling through the MEK pathway, particularly in genes such as BRAF and KRAS, which are associated with the MAPK pathway [8]. Patients with ameloblastoma who have active MEK pathways can benefit from targeted therapeutic approaches, such as MEK inhibitors like trametinib, which enhance treatment effectiveness and reduce the side effects of traditional therapies. While established ameloblastoma cell lines can be used to screen for drug sensitivity based on gene expression and mutation status, bioinformatics and genomic sequencing applied to tumor samples can help predict drug responses. Better predictive models will also result from tracking the safety and effectiveness of MEK inhibitors in clinical trials, with a focus on how they relate to specific genetic alterations. Thus, it is crucial to comprehend and anticipate these drug-gene associations to improve patient outcomes, tailor therapy, and expand treatment options. It may also help direct future studies into targeted therapies for ameloblastoma.

Graph-based neural networks (GNNs) have successfully predicted drug-gene associations, particularly in intricate biological systems such as the MAPK signaling pathway [9]. In ameloblastoma. Their strengths include capturing complex relationships, combining various omics data, and considering both local and global contexts. Compared to conventional techniques that frequently rely on feature engineering, GNN architectures are more generalizable and scalable, enabling them to handle large datasets efficiently. To accurately predict new interactions, the GNN process involves building a graph that represents gene-drug interactions, assigning features to nodes, utilizing a message-passing mechanism for contextual learning, and training on known associations.

GNNs outperform traditional prediction techniques by utilizing relational data and enabling in-depth investigations of biological pathways. According to an earlier study, although BRAF V600E-targeted treatments currently account for most research on ameloblastoma [10, 11], more extensive mutations in the MAPK pathway and new immunotherapeutic targets, such as PD-L1, also warrant investigation. Combining such genetic insights with GNN-based drug-gene prediction models may improve personalized treatment plans. Ameloblastoma is well-studied for BRAF V600E-targeted therapy; however, immunotherapeutic targets, such as PD-L1, and more general MAPK mutations, remain unknown. This emphasizes how combining genetic information with GNN-based models can lead to more individualized treatment plans.

To predict drug-gene associations specifically related to MEK pathway inhibition in ameloblastoma, the main goal of this study is to develop and compare the performance of three well-known Graph Neural Network (GNN) architectures: GCN, GAT, and GraphSAGE. One of the goals is to use curated omics and biochemical data to create a bipartite graph that depicts drug-gene interactions relevant to MEK inhibition. A uniform training pipeline will also be used to implement and train the GCN, GAT, and GraphSAGE architectures [12, 13], guaranteeing that the same hyperparameters and loss functions are used consistently. The models will then be compared using several metrics, such as generalization ability, convergence behavior, and training and validation loss. The aim is to identify the optimal architecture for making scalable and precise predictions of biologically significant drug-gene associations in ameloblastoma. To support upcoming applications in precision oncology and targeted therapy, the study will also attempt to provide interpretability and computational considerations for each GNN model.

Materials and Methods

Using the probe and drugs website [14] Drugs associated with MEK signaling were downloaded. Data with drugs and genes as nodes, targets as edges, and activity_biochemical as edge weights, along with other features as node features, was preprocessed for further

analysis.

With an emphasis on the MEK signaling pathway, this study used a graph-based learning framework to predict drug-gene associations in ameloblastoma. The curated dataset (containing 1,028 edges encoding known biochemical activity interactions and 321 nodes representing genes and target types. A 2-dimensional one-hot encoded feature vector was used to represent each node, indicating whether it was a drug target type or a gene. The graph was built in an undirected format to allow bidirectional message passing during learning, and edges included numerical features that indicated inhibition activity or interaction strength.

The PyTorch Geometric library handled all modeling tasks and graph construction. An edge index tensor defined the graph's topology, and each epoch involved processing the entire graph in a single batch. The models were trained to reconstruct graph connectivity, thereby reducing the discrepancy between expected interaction scores and artificial target values created to mimic the learning process of drug-gene interactions.

For fair comparison, three graph neural network (GNN) architectures Graph Convolutional Networks (GCN), Graph Attention Networks (GAT), and GraphSAGE were implemented and trained using the same input-output dimensionalities and hyperparameters. The three GCNConv layers in the GCN architecture had dimensions of $2 \rightarrow 64 \rightarrow 64 \rightarrow 16$, and they were regularized with dropout ($p = 0.2$) and ReLU activations following the first two layers. The GAT model employed multi-head attention with GATConv layers. After the first two layers, the final attention layer produced 16 features, each with eight attention heads with input/output dimensions $2 \rightarrow 512 \rightarrow 512$. Dropout and ReLU activations were used consistently. Using SAGEConv layers with ReLU activations and dropout applied after the first and second layers, the GraphSAGE model used a three-layer design ($2 \rightarrow 64 \rightarrow 64 \rightarrow 16$).

The Adam optimizer was used to train all models for 100 epochs at a learning rate of 0.01. The loss function was Mean Squared Error (MSE) for training and validation. The dataset was divided into subsets of 20% for validation and 80% for random training. The model was trained to predict pairwise interaction scores using the node and edge features of the bipartite graph. All models underwent the same training procedure, ensuring that architectural variances, rather than optimization settings, were responsible for the observed performance discrepancies.

Several quantitative metrics were used to evaluate the model, including the train/validation loss ratio to determine tendencies towards overfitting or underfitting, the mean loss over all epochs, the minimum recorded loss, and the final training and validation losses (at epoch 100). A heatmap summarizing comparative performance, box plots to display distributional variance, and line plots of training and validation losses over time were used to visualize these findings. Additionally, a thorough table was created to record each evaluation metric side by side.

All calculations were performed on a high-performance workstation with a multi-core CPU, 32 GB of RAM, and an NVIDIA RTX 3080 GPU (10GB VRAM). The software stack consisted of Python 3.10, PyTorch 2.0, PyTorch Geometric 2.4, and data analysis and visualization tools, including NumPy, Pandas, and Matplotlib (Table 1).

Results

Graph Convolutional Network (GCN), Graph Attention Network (GAT), and GraphSAGE are three GNN models whose performance was assessed on training and validation datasets using different loss-based metrics. To guarantee a fair comparative analysis, all models were trained with the same hyperparameters (learning rate: 0.01; dropout: 0.2; and 100 training epochs).

The GCN model demonstrated consistent and dependable training performance, with a final training loss of approximately 1.0232 and a validation loss of 0.9807. The average training and validation losses were nearly 1.0 and 0.9951, respectively. Interestingly, the minimum validation loss was 0.8923, demonstrating a high capacity for generalization. With a training-to-validation loss ratio of approximately 0433, the learning curve was balanced, and there was no discernible overfitting. With a final training loss of 0079 and a validation loss of 9551, the GAT

Table 1. Shows the Hyperparameters Used in This Study

Parameter	GCN	GAT	GraphSAGE
Layer 1	GCNConv (2 → 64)	GATConv (2 → 64 × 8 heads)	SAGEConv (2 → 64)
Layer 2	GCNConv (64 → 64)	GATConv (512 → 64 × 8 heads)	SAGEConv (64 → 64)
Layer 3	GCNConv (64 → 16)	GATConv (512 → 16 × 1 head)	SAGEConv (64 → 16)
Activation Function	ReLU (after Layer 1 & 2)	ReLU (after Layer 1 & 2)	ReLU (after Layer 1)
Dropout	0.2 (after Layer 1 & 2)	0.2 (after all layers)	0.2 (after Layer 1 & 2)
Learning Rate	0.01	0.01	0.01
Loss Function	Mean Squared Error (MSE)	Mean Squared Error (MSE)	Mean Squared Error (MSE)
Epochs	100	100	100
Train/Validation Split	80% / 20%	80% / 20%	80% / 20%
Final Training Loss	≈ 1.0232	≈ 1.0079	≈ 1.0000
Final Validation Loss	≈ 0.9807	≈ 0.9551	≈ 1.0052
Minimum Validation Loss	≈ 0.8923	≈ 0.8653	≈ 0.8748
Train/Validation Loss Ratio	≈ 1.0433	≈ 1.0553	≈ 0.9949

model outperformed the GCN model by a small margin. At 0.8653, it also had the lowest minimum validation loss of the three models, indicating that the attention mechanism successfully captured the graph's nuanced node relationships. Despite its excellent performance, its train/validation loss ratio was slightly higher at 1.0553, suggesting some slight overfitting. With a final training loss of precisely 1.0000 and a validation loss of 1.0052, the GraphSAGE model demonstrated competitive performance. Although it was better than GCN, its minimum validation loss of 8748 fell short of GAT's low. However, out of all the models, GraphSAGE had the most balanced train-to-validation loss ratio (0.9949), demonstrating strong generalization and stability, which are especially useful in situations involving dynamic or unknown data. The GAT architecture achieved the highest validation accuracy because of its variable importance assignment to neighboring nodes. GraphSAGE was well-suited for scalable or inductive tasks due to its superior generalization and balanced loss metrics. On the other hand, GCN demonstrated strong performance and minimal computational complexity, making it suitable for baseline applications and large graph datasets that require effectiveness.

Discussion

The quality of life of patients may be negatively impacted by aggressive treatments required for ameloblastoma, a benign odontogenic tumor that can be locally invasive. Nine ameloblastoma patients treated with BRAF inhibitors [7] (Dabrafenib, Vemurafenib, or Dabrafenib-Trametinib) showed encouraging results, including tumor reduction and, in certain cases, total remission, according to a recent analysis of seven case reports. The evidence currently available is limited to short-term case data, despite the apparent effectiveness of these therapies, particularly in neoadjuvant or inoperable cases. This underscores the necessity for larger, multicenter clinical trials. Another earlier study demonstrated that, through bioinformatic analysis, this study sought to identify important genes and possible inhibitory medications linked to ameloblastoma cell invasion and proliferation. After analyzing a gene profile database and finding 204 upregulated genes, the researchers focused on cell invasion and proliferation pathways. Significant overexpression was observed in SLC6A3, SOX10, and LRP5, which was negatively correlated with overall survival. The positive expression of SLC6A3 and LRP5 was confirmed by immunohistochemical analysis [5, 9]. Our dataset (321 nodes, 1028 edges) sufficed for benchmarking but offers a simplified MEK pathway view. Using a bipartite graph may miss directional signaling or timing, risking bias. Future work will incorporate multi-omics data and dynamic graphs to enhance biological accuracy.

The discovery of parthenolide and vorinostat as possible inhibitory medications for these genes raises the possibility of using them to create novel treatment approaches for ameloblastoma. With an emphasis on the MEK signaling pathway [2, 4]. This study compares three well-known Graph Neural Network (GNN) architectures for predicting drug-gene associations in ameloblastoma: Graph Convolutional Network (GCN), Graph Attention Network (GAT), and graphSAGE. With the lowest minimum validation loss (0.8653) among the models tested, the GAT architecture showed the best validation performance. This implies that the attention mechanism is especially good at capturing intricate and diverse interactions in biological graphs and dynamically weights the significance of nearby nodes. The GCN model, on the other hand, produced competitive results with less computational overhead, making it an appropriate choice for situations where simplicity and scalability are crucial. GraphSAGE demonstrated the most balanced training-validation loss ratio (0.9949) and strong generalization

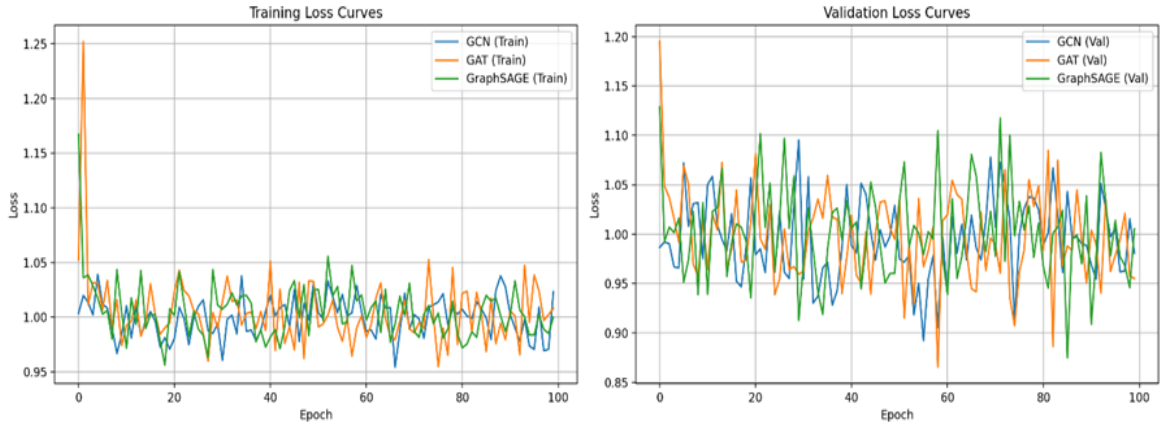

Figure -1 illustrates three Graph Neural Network (GNN) models GraphSAGE, GCN, and GAT showing training and validation loss over 100 epochs. As seen in the training loss plots, all models exhibit a sharp initial decrease, with GCN and GraphSAGE achieving smooth convergence around 1.0, while GAT displays minor oscillations before stabilizing similarly. The validation loss curves, however, display greater variability; GAT ultimately achieves the lowest validation loss (≈0.8653), indicating better generalization. Despite some fluctuations, GraphSAGE and GCN perform similarly. Overall, the close alignment of training and validation curves reflects the models' learning and overfitting tendency; GAT excels in peak validation performance, GraphSAGE demonstrates stability, and GCN provides consistent results with less variance.

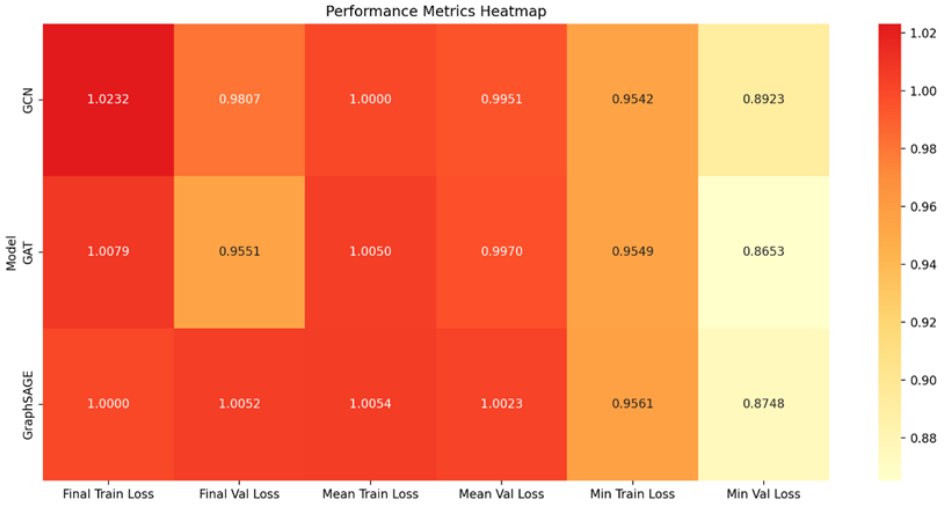

Figure 2. Shows a Comparison of the Three Graph Neural Network models. GCN, GAT, and GraphSAGE in a heatmap based on six loss metrics. GAT outperforms others with the lowest final and validation losses (0.9551 and 0.8653), showing better generalization. GraphSAGE, with a minimum validation loss of 0.8748, shows good potential and balanced performance. GCN has the highest final training loss (1.0232), indicating a poorer fit. Lighter yellow hues mean lower losses; darker red indicates higher losses. The heatmap shows GCN as a simple but useful baseline, GraphSAGE as reliable, and GAT as the best overall.

Table 2. Shows a Comparison of the Accuracy of the Results

Metric	GCN	GAT	GraphSAGE
Final Training Loss	1.0232	1.0079	1.0000
Final Validation Loss	0.9807	0.9551	1.0052
Mean Training Loss	1.0000	1.0050	1.0054
Mean Validation Loss	0.9951	0.9970	1.0023
Minimum Training Loss	0.9542	0.9549	0.9561
Minimum Validation Loss	0.8923	0.8653	0.8748
Train/Validation Loss Ratio	1.0433	1.0553	0.9949

performance. It draws attention to its possible use in inductive tasks, such as drug repurposing or evolving biological networks, where new nodes are added after training (Figures 1, 2, 3) (Table 2).

Notwithstanding these revelations, a few restrictions [15–17] Should be taken into account. First, the graph structure of this study was static and undirected, which may not adequately represent biological processes that are directional or temporal, such as transcriptional regulation or drug activation cascades. Secondly, the node features were restricted to binary encodings that differentiated genes from drug targets, leaving out potentially useful biochemical, structural, or pathway-specific characteristics.

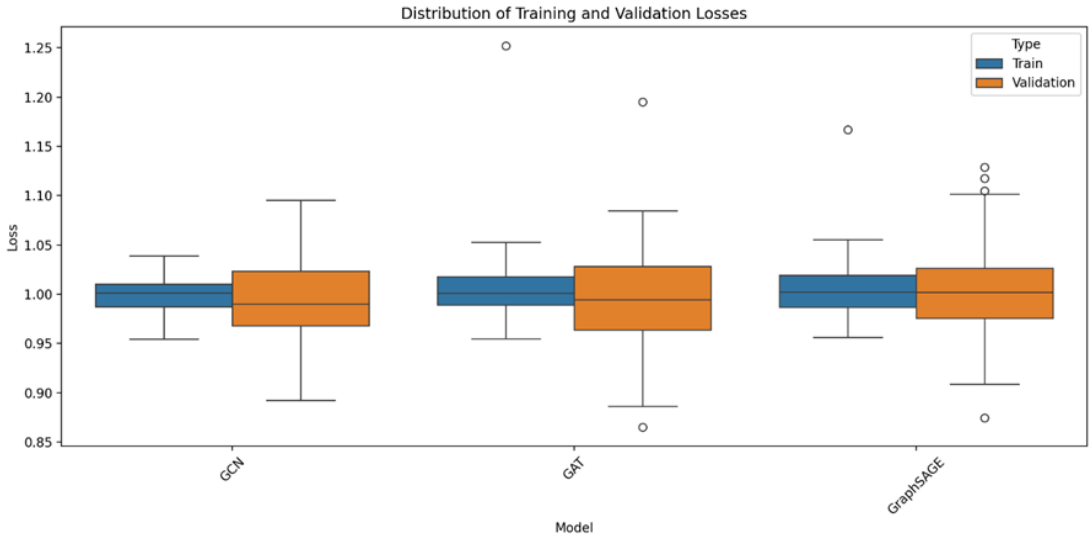

Figure 3. Shows the Boxplot that Visually Compares the Training and Validation Loss Distributions Across Three Different Graph Neural Network Models: GraphSAGE, GCN (Graph Convolutional Network), and GAT (Graph Attention Network). Among these, GCN stands out for having the most stable and tightly clustered loss distribution, indicating consistent performance during training and validation. In contrast, both GAT and GraphSAGE show greater variability in their validation loss, with several outliers, which suggests fluctuations in their validation performance and potential sensitivity to different data samples or hyperparameter settings.

Third, the models' direct clinical translation was limited because they were trained using artificial reconstruction targets rather than actual drug response labels or biological efficacy results [10, 18, 19].

We mainly used mean squared error as the loss criterion for evaluation. This gauges regression performance but doesn't account for biological significance or the influence of functional pathways [12, 13]. Moreover, k-fold cross-validation would produce more reliable model performance estimates; overfitting analysis was limited to a simple train/validation split. Future research should include richer node and edge features, such as molecular docking scores, expression levels, mutation status, and chemical fingerprints, to overcome these constraints and improve translational relevance. Time-dependent or causal relationships within signaling pathways may also be easier to model using directed or dynamic graphs. The learning process may be further improved by incorporating biological priors, such as protein interaction subnetworks or pathway ontologies [20, 21].

Furthermore, incorporating classification tasks (such as toxicity profiles or drug efficacy labels) or multi-task learning frameworks into the training objective, beyond reconstruction loss, may enhance the models' biological interpretability and usefulness. Performance improvements may also be obtained by investigating more complex GNN architectures, such as multi-modal fusion networks, edge-aware GNNs, or Graph Transformers. Finally, the clinical relevance of these computational models would be strengthened by experimental validation of the top-ranked drug-gene predictions or external validation on independent datasets.

Over 100 epochs, the three GNN models exhibited competitive learning behavior, each displaying unique traits regarding generalization balance, minimum loss, and convergence stability [21, 22].

Reliable generalization with little overfitting is demonstrated by the Graph Convolutional Network's (GCN) smooth convergence, which maintained a train/validation loss ratio of 1.0433 with a final training loss of roughly 1.0232 and a minimum validation loss of 0.8923. With a minimum validation loss of 0.8653 and a final validation loss of roughly 0.9551, the Graph Attention Network (GAT) demonstrated how well attention mechanisms capture changes in node importance. However, its marginally higher train/validation ratio of 1.0553 suggests some overfitting, possibly due to attention feature redundancy or overparameterization. However, with mean training and validation losses that were nearly equal, GraphSAGE showed the most balanced train/validation loss ratio, at about 0.9949. Particularly for inductive tasks where new nodes, like novel drugs or targets, must be integrated after training, its robustness is demonstrated by its consistent performance across epochs and a minimum validation loss of 0.8748. GCN's isotropic message passing may limit its efficacy in heterogeneous or edge-weighted graphs, despite being computationally efficient. On the other hand, GAT utilizes adaptive edge weighting through attention to enhance expressiveness, albeit at the expense of increased memory and training time [23].

Large-scale and dynamic biological graphs can benefit from GraphSAGE's neighborhood sampling strategy, which balances scalability and performance. There are many chances for therapeutic advancements if the MEK pathway is targeted for treating ameloblastoma. Key focus areas to decrease tumor recurrence and improve efficacy include creating targeted therapies using MEK inhibitors and investigating combination strategies with other treatment modalities [24]. Furthermore, understanding how MEK/ERK signaling works in ameloblastoma and identifying potential biomarkers can aid in early diagnosis and improve treatment outcomes. Clinical trials that evaluate the efficacy and safety of these inhibitors will also be crucial in developing treatment plans for patients with severe forms of the illness. To maximize treatment results, looking into how the tumor microenvironment affects therapeutic responses is essential [25–27]. Our findings suggest that GNN models can support precision oncology by aiding in drug repurposing (e.g., FDA-approved agents such as parthenolide or vorinostat) and biomarker discovery to stratify patients based on MEK activity. Embedding these into clinical trials could accelerate the development of personalized treatments for ameloblastoma.

Our findings show that the best GAT model can prioritize MEK inhibitors, such as trametinib and cobimetinib, for BRAF V600E–positive ameloblastoma patients, where MEK/BRAF inhibition has shown promise. The graph-based framework also enables drug repurposing, allowing for the quick screening of FDA-approved compounds, such as parthenolide and vorinostat, as potential inhibitors. Clinically, it serves as a precision oncology tool, helping oncologists stratify patients based on MEK activity and guide personalized therapy. Transitioning from computation to the clinic requires in vitro validation, correlation with mutation/biomarker profiles, and integration into clinical trials. Despite challenges such as heterogeneity and resistance, these predictions provide a rational foundation for developing targeted therapies in ameloblastoma. The GNN framework supports treatment stratification by identifying patients likely to benefit from MEK inhibition, such as those with BRAF-positive cases. It also guides preclinical validation by prioritizing top drug–gene associations for testing in ameloblastoma cell lines and trial design. A limitation of this study is that validation was performed using an 80/20 train–validation split, which may not fully capture dataset variability. Future work will utilize k-fold cross-validation and external test sets to provide more reliable performance estimates. Although GAT had the lowest validation loss, differences among GNN architectures were modest and not statistically tested. These variations shouldn't be over-interpreted as biologically significant but as architectural trends. Future work will include statistical comparisons and external biological validation to assess significance.

However, obstacles such as tumor heterogeneity, mechanisms of MEK inhibitor resistance, and a lack of preclinical models could hinder advancement. Concerns about the side effects and safety characteristics of MEK inhibitors must be carefully considered. There is an urgent need for more thorough information regarding the MEK

pathway in ameloblastoma, and regulatory obstacles may delay the application of research findings in clinical settings. Addressing these constraints is essential to developing robust clinical guidelines that can enhance treatment approaches and improve patient outcomes.

In conclusion, investigating the MEK/ERK signaling pathway in ameloblastoma presents a promising avenue for developing more effective therapies for this complex tumor type. An increasing understanding of the molecular processes underlying ameloblastoma and the role of the MEK pathway may lead to the creation of targeted treatments that benefit patients, particularly those with aggressive or recurrent forms of the disease. Tumor heterogeneity, the development of treatment resistance, and the limitations of preclinical models remain significant challenges. Addressing these issues through comprehensive research will be essential for translating lab results into effective clinical treatments. By identifying biomarkers and understanding the tumor microenvironment, researchers can tailor treatments for each patient, enhancing efficacy while minimizing side effects. To fully realize the potential of MEK pathway inhibitors in treating ameloblastoma, a multidisciplinary strategy that integrates molecular biology, clinical trials, and pharmacogenomics will be imperative moving forward. By focusing on these areas, we can aim to improve the quality of life and survival rates for patients affected by this challenging cancer.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

None.

References

1. Correa-Arzate L, Portilla-Robertson J, Ramírez-Jarquín JO, Jacinto-Alemán LF, Mejía-Velázquez CP, Villanueva-Sánchez FG, et al. Lrp5, slc6a3, and sox10 expression in conventional ameloblastoma. Genes (Basel). 2023;14(8). https://doi.org/10.3390/genes14081524.
2. Zhao Z, Xiong G, Wang C, Cao W. From pathogenesis to precision medicine: Transformative advances in research and treatment of ameloblastoma. Cancer Lett. 2025;612:217448. https://doi.org/10.1016/j.canlet.2025.217448.
3. Zhong LP, Zhang ZY, Zhu HG, Fu HH, He Y. Clinical management of peripheral ameloblastoma. J Craniofac Surg. 2011;22(5):1929-32. https://doi.org/10.1097/SCS.0b013e318210bcc7.
4. Ebeling M, Scheurer M, Sakkas A, Pietzka S, Schramm A, Wilde F. Braf inhibitors in braf v600e-mutated ameloblastoma: Systematic review of rare cases in the literature. Med Oncol. 2023;40(6):163. https://doi.org/10.1007/s12032-023-01993-z.
5. Bayat Z, Mirzaeian A, Taherkhani A. Potential biomarkers and signaling pathways associated with the pathogenesis of primary ameloblastoma: A systems biology approach. Int J Dent. 2022;2022:3316313. https://doi.org/10.1155/2022/3316313.
6. Chujan S, Vajeethaveesin N, Satayavivad J, Kitkumthorn N. Identification of molecular mechanisms of ameloblastoma and drug repositioning by integration of bioinformatics analysis and molecular docking simulation. Bioinform Biol Insights. 2024;18:11779322241256459. https://doi.org/10.1177/11779322241256459.
7. Brunet M, Khalifa E, Italiano A. Enabling precision medicine for rare head and neck tumors: The example of braf/mek targeting in patients with metastatic ameloblastoma. Front Oncol. 2019;9:1204. https://doi.org/10.3389/fonc.2019.01204.
8. Oh KY. Treatment options for advanced ameloblastoma in the era of precision medicine: A brief review. Oral Oncol. 2023;146:106585. https://doi.org/10.1016/j.oraloncology.2023.106585.
9. Zhang Z, Peng Y, Dang J, Liu X, Zhu D, Zhang Y, et al. Identification of key biomarkers related to epithelial-mesenchymal transition and immune infiltration in ameloblastoma using integrated bioinformatics analysis. Oral Dis. 2023;29(4):1657-67. https://doi.org/10.1111/odi.14173.
10. Xie Y, Zhang Y, Gong M, Tang Z, Han C. Mgat: Multi-view graph attention networks. Neural Netw. 2020;132:180-9. https://doi.org/10.1016/j.neunet.2020.08.021.
11. Itoh TD, Kubo T, Ikeda K. Multi-level attention pooling for graph neural networks: Unifying graph representations with multiple localities. Neural Netw. 2022;145:356-73. https://doi.org/10.1016/j.neunet.2021.11.001.
12. Lai B, Xu J. Accurate protein function prediction via graph attention networks with predicted structure information. Brief Bioinform. 2022;23(1). https://doi.org/10.1093/bib/bbab502.
13. Zhang F, Hu W, Liu Y. Gcmm: Graph convolution network based on multimodal attention mechanism for drug repurposing. BMC Bioinformatics. 2022;23(1):372. https://doi.org/10.1186/s12859-022-04911-8.
14. Skuta C, Popr M, Muller T, Jindrich J, Kahle M, Sedlak D, et al. Probes &drugs portal: An interactive, open data resource for chemical biology. Nat Methods. 2017;14(8):759-60. https://doi.org/10.1038/nmeth.4365.
15. Öztürk H, Özgür A, Ozkirimli E. Deepdta: Deep drug-target binding affinity prediction. Bioinformatics. 2018;34(17):i821-i9. https://doi.org/10.1093/bioinformatics/bty593.
16. Zhao Q, Zhao H, Zheng K, Wang J. Hyperattentiondti: Improving drug-protein interaction prediction by sequence-based deep learning with attention mechanism. Bioinformatics. 2022;38(3):655-62. https://doi.org/10.1093/bioinformatics/btab715.
17. You Y, Lai X, Pan Y, Zheng H, Vera J, Liu S, et al. Artificial intelligence in cancer target identification and drug discovery. Signal Transduct Target Ther. 2022;7(1):156. https://doi.org/10.1038/s41392-022-00994-0.
18. Long Y, Wu M, Liu Y, Kwoh CK, Luo J, Li X. Ensembling graph attention networks for human microbe-drug association prediction. Bioinformatics. 2020;36(Suppl_2):i779-i86. https://doi.org/10.1093/bioinformatics/btaa891.
19. Kim J, Seo H, Naseem MT, Lee CS. Pathological-gait recognition using spatiotemporal graph convolutional networks and attention model. Sensors (Basel). 2022;22(13). https://doi.org/10.3390/s22134863.
20. Inoue Y, Lee H, Fu T, Luna A. drGT: Attention-Guided Gene Assessment of Drug Response Utilizing a Drug-Cell-Gene Heterogeneous Network. ArXiv. 2025 Aug 27:arXiv-2405.
21. Yu H, Li K, Dong W, Song S, Gao C, Shi J. Attention-based cross domain graph neural network for prediction of drug-drug interactions. Brief Bioinform. 2023;24(4). https://doi.org/10.1093/bib/bbad155.

22. Wang J, Liu X, Shen S, Deng L, Liu H. Deepdds: Deep graph neural network with attention mechanism to predict synergistic drug combinations. Brief Bioinform. 2022;23(1). https://doi.org/10.1093/bib/bbab390.
23. Zhang Y, Lei X, Pan Y, Wu FX. Drug repositioning with graphsage and clustering constraints based on drug and disease networks. Front Pharmacol. 2022;13:872785. https://doi.org/10.3389/fphar.2022.872785.
24. Huang P, Yan R, Zhang X, Wang L, Ke X, Qu Y. Activating wnt/β-catenin signaling pathway for disease therapy: Challenges and opportunities. Pharmacol Ther. 2019;196:79-90. https://doi.org/10.1016/j.pharmthera.2018.11.008.
25. Niu Z, Gao X, Xia Z, Zhao S, Sun H, Wang H, et al. Prediction of small molecule drug-mirna associations based on gnns and cnns. Front Genet. 2023;14:1201934. https://doi.org/10.3389/fgene.2023.1201934.
26. Zhong Y, Peng Y, Lin Y, Chen D, Zhang H, Zheng W, et al. Modilm: Towards better complex diseases classification using a novel multi-omics data integration learning model. BMC Med Inform Decis Mak. 2023;23(1):82. https://doi.org/10.1186/s12911-023-02173-9.
27. Przybyszewski J, Malawski M, Lichołai S. Graphtar: Applying word2vec and graph neural networks to mirna target prediction. BMC Bioinformatics. 2023;24. https://doi.org/10.1186/s12859-023-05564-x.