Towards Understanding The Relationship Between Brain Disorders and the Gut Microbiome with Explainable Graph Neural Networks

Naafey Aamer[1*†], Muhammad Nabeel Asim[2,3†], Sebastian Vollmer[1,2], Andreas Dengel[1,2]

[1*]University of Kaiserslautern-Landau, Gottlieb-Daimler-Straße, Kaiserslautern, 67663, Germany.
[2]DFKI, Trippstadter Str. 122, Kaiserslautern, 67663, Germany.
[3]Intelligentx GmbH (intelligentx.com), Kaiserslautern, 67663, Germany.

*Corresponding author(s). E-mail(s): naafey.aamer@cs.rptu.de;
Contributing authors: Muhammad_Nabeel.Asim@dfki.de; sebastian.vollmer@dfki.de; andreas.dengel@dfki.de;
†These authors contributed equally to this work.

Abstract

The communication between the gut microbiome and the brain, known as the microbiome-gut-brain axis (MGBA), is emerging as a critical factor in neurological and psychiatric disorders. This communication involves complex pathways including neural, hormonal, and immune interactions that enable gut microbes to modulate brain function and behavior. However, the specific mechanisms through which gut microbes influence brain function remain poorly understood. Existing computational efforts to understand these mechanisms are simplistic or have limited scope. This works presents a comprehensive approach for understanding these mechanisms by elucidating the cascade of interactions that allows gut microbes to influence brain disorders. By using a large curated biomedical knowledge graph, we train **GNN-GBA**, an explainable graph neural network, to learn the complex biological interactions between the gut microbiome and the brain. GNN-GBA is then used to extract the mechanistic pathways through which the gut microbiome can influence brain disorders. The network successfully identified pathways for 103 brain disorders, and we show that these pathways are consistent with existing literature. We further provide an interactive dashboard (link) to explore thousands of potential mechanisms through which the gut microbiome can influence brain diseases. By shining light on the intricate mechanisms

of the gut-brain axis, this work paves the way for microbiome-led therapeutic interventions for neurological and psychiatric disorders.

Keywords: gut-brain axis, knowledge graphs, brain disorders, GNNs, explainability

1 Introduction

Brain disorders impose a staggering global burden, they are the leading cause of disability and the second leading cause of death worldwide [1]. As shown in Figure 1, these conditions are highly complex and fall into diverse categories, including developmental, immune-mediated, neurodegenerative, and psychiatric disorders [2]. Some of these common and highly recurring conditions have no treatment options like Alzheimer's disease, Parkinson's disease, autism spectrum disorders, epilepsy, and schizophrenia [3]. The mechanisms behind brain disorders are often multifactorial, reflecting the interplay of genetic, environmental, and, as recent studies suggest [4–9], microbial factors.

The relationship between brain disorders and these microbial factors is not fully understood [10], and it may be attributed to interactions between intestinal microbes and the central nervous system, which is known as the microbiome-gut-brain axis (MGBA). The MGBA is a communication network linking the gut and brain via neural, endocrine, immune and metabolic pathways [3] and a growing body of studies implicate it in neurological conditions, including Alzheimer's, Parkinson's, multiple sclerosis, autism spectrum disorder and even stroke [3, 11]. These findings suggest that the gut microbiome may be a key factor in neurodegeneration and neurodevelopment.

Central to gut-brain communication are gut metabolites, small bioactive chemicals generated during microbial metabolic processes of the digestive system [12]. These metabolites are critical messengers between the gut and the brain [12], binding to receptors on various cells in both systems to modulate key processes such as inflammation and neurotransmission [13, 14]. Beyond their role as messengers, these metabolites can influence metabolism and gene expression, resulting in functional mechanistic pathways between gut microbes and various diseases [15]. These pathways suggests that gut microbes regulate not only brain function but also non-neuronal cell activity in the nervous system, potentially causing brain disorders [16]. Without a clear understanding of these mechanistic pathways, our comprehension of gut microbes' role in disease remains incomplete, hindering the development of targeted therapeutic strategies.

Since the gut microbiome composition is influenced by diet, medications and other confounding factors[11], existing studies often struggle to take a global view of this intricate network of cause and effect, making it challenging to develop a comprehensive understanding of these complex gut-brain interactions. Traditional analytical methods typically examine one data modality at a time and tend to miss complex, multi-scale interactions. There is therefore a critical need for an integrative approach that can jointly analyzes diverse types of microbial, genetic, metabolic and phenotypic data.

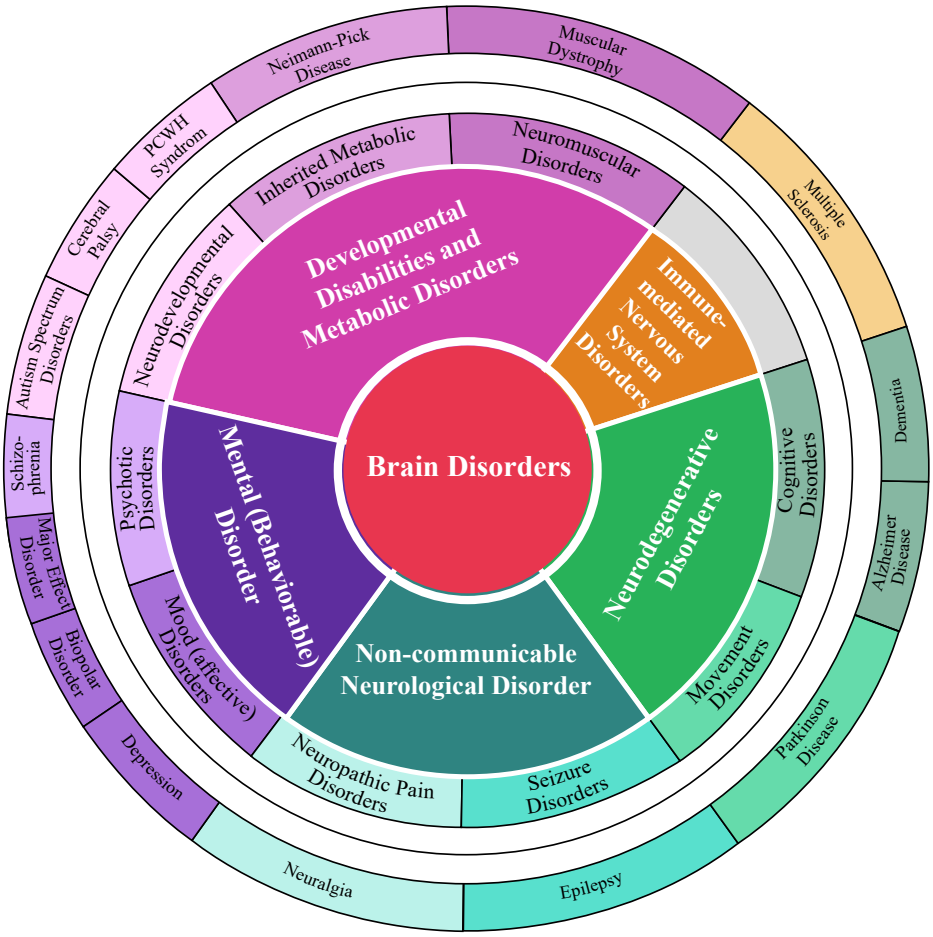

Fig. 1: Brain disorders classified into several categories and sub-categories.

Biomedical knowledge graphs offer a powerful solution for such integrative analysis [17]. These graphs are constructed by merging diverse data types into structured, machine-readable formats [18–20]. They are able to represent biomedical entities (genes, proteins, microbes, diseases, metabolites, etc.) as nodes and their relationships (e.g. molecular interactions, causal links, phenotypic associations) as edges [17]. To explore the MGBA, the inclusion of metabolites is particularly crucial, as they represent the functional output of microbial activity and serve as the mechanistic link between microbes and disease outcomes. Graph machine learning has been highlighted as a key emerging tool in biomedicine, with the potential to accelerate biomedical discovery [21]. Once, the graph is constructed, graph machine learning can be directly applied to it to capture complex interaction patterns in the MGBA.

This paper explores the mechanisms between brain disorders and the gut microbiome through knowledge graphs and advanced graph machine learning. Our contributions include: (1) we curate a biomedical knowledge graph (focused on the MGBA) from existing work [22], (2) train an explainable graph neural network (GNN-GBA) that learns the underlying biological interactions within this complex graph, (3) we use this network to systematically investigate 103 distinct brain disorders, identifying and validating mechanistic pathways through which specific gut microbes influence these neurological conditions; and (4) we provide an interactive dashboard to explore and visualize thousands of mechanistic pathways for 103 brain disorders (link). This approach not only reveals novel insights into how specific microbes might influence neurological conditions but also provides a generalizable framework for exploring other complex disease-microbiome interactions. The interactive dashboard promotes further investigation in this emerging field, offering a resource for future experimental validation and therapeutic development.

2 Related Work

Early studies often employed conventional machine learning on microbiome profiles – for instance, a genus-level random forest ranks microbial species by importance, but it does not explain through which biological pathway a given microbe influences a disease [23]. Such models can identify important microbial features for diseases (potential "biomarkers"), but they typically treat the microbiome as an independent high-dimensional feature vector, lacking explicit representation of mechanistic pathways. To incorporate network structure, researchers have turned to graph-based methods [24]. Since the gut-brain axis information can be efficiently represented using Knowledge Graphs (KGs), multiple works have aimed to construct them. MiKG was developed to identify potential associations between gut microbiota, neurotransmitters, and mental disorders by manually extracting relevant entities and relationships from scientific publications [25]. Additionally, established biomedical databases—such as MetaCyc [26], Reactome [27], gutMGene [28], and KEGG [29]—serve as valuable resources for KG construction, as they have collected diverse data on pathways, drugs, genes, and microbes. The Pre-/Probiotics Knowledge Graph (PPKG) integrates both scientific publications and existing biomedical databases to construct a comprehensive KG to store the relationship between the central nervous system and the enteric (gut) nervous system [30]. Beyond constructing KGs that encapsulate known relationships, there is growing interest in discovering novel MGBA pathways through predictive modeling and meta-search. Several graph based models have been proposed to predict microbe–disease links. For example, MGMLink leverages the gutMGene database to identify the shortest mechanistic pathways (i.e., gut-brain links) through breadth-first search (BFS) and template-based searches in a heterogeneous graph [31]. However, MGMLink uses node2vec [32] and TransE [33] as embedding methods which are static, precomputed, and shallow representations that do not learn global patterns within the knowledge graph, leaving a little room for comprehensive learning.

Other works employ graph neural networks (GNNs), which have shown the promise of interpretability by highlighting important microbial neighbors that drive a given

disease association [34][35]. While existing GNN-based methods like [35] and [36] have potential, they lack interpretability, and the data incorporated is upto two orders of magnitude smaller than the one used in this work. This results in limited generalizability and an inability to capture the complexity of microbe-brain interactions across diverse biological pathways. To address this, this work addresses this need by training a GNN over a large curated gut–brain-axis knowledge graph of over 3.5 million relationships, encompassing microbes, their metabolites, host targets, and neurological diseases. By training on this rich network, the model learn global interaction patterns that link microbes to brain pathology. To understand these patterns, this study also uses a graph interpretability method [37] that highlights relevant mechanistic pathways, effectively pointing on which intermediate nodes (specific metabolites, genes, or signaling molecules) are most critical for a predicted microbe–disease link.

3 Materials and Methods

This study develops a comprehensive computational framework to investigate the microbiome-gut-brain axis (MGBA) and its role in neurological disorders. The approach integrates knowledge graph construction, path mining algorithms, and graph neural network modeling to systematically map the complex relationships between gut microbes, metabolites, and brain diseases. Figure 3 illustrates the overall flow of the methodology.

3.1 Knowledge Graph Construction

To create the initial MGBA knowledge graph, [22]'s methodology is utilized. First, an ontology KG was built using the PheKnowLator [38] pipeline and combined with associations from the GutMGene database. PheKnowLator is a Python 3 library that enables construction of KGs that incorporate a wide variety of data and terminology sources, including ontologies such as the Mondo Disease Ontology (MONDO) [39], the Chemical Entities of Biological Interest Ontology (CHEBI) [40], and the Human Phenotype Ontology (HPO) [41]. The gutMGene database [28] consists of microbe-metabolite and microbe-gene assertions that occur in the host of either human or mouse. These relationships were manually extracted from over 360 PubMed publications and are based on validated methods such as RT-qPCR, high-performance liquid chromatography, and 16S rRNA sequencing[28].

To ensure relevance and reduce noise, the constructed graph was altered to remove redundant entities and extraneous ontologies (e.g., Plant Ontology, Food Ontology, Genotype, and Transcription Factors) that did not contribute meaningfully to the scope of this work. During this process, 1,502,361 edges and 196,148 nodes were removed. The resulting knowledge graph consists of **586,318** nodes spanning 16 distinct biomedical entity types (Table 1) and **3,573,936** edges covering 103 unique predicate types (Table 2). Our methodology resulted in sufficient pathways for exploring the MGBA for brain disorders, for example, Figure 2 shows the connectivity between "enterococcus avium ly1", a gut microbe, and "Autism".

It is important to note that metabolites —the critical messenger molecules between the gut and the brain— are primarily represented within the Chemical node category,

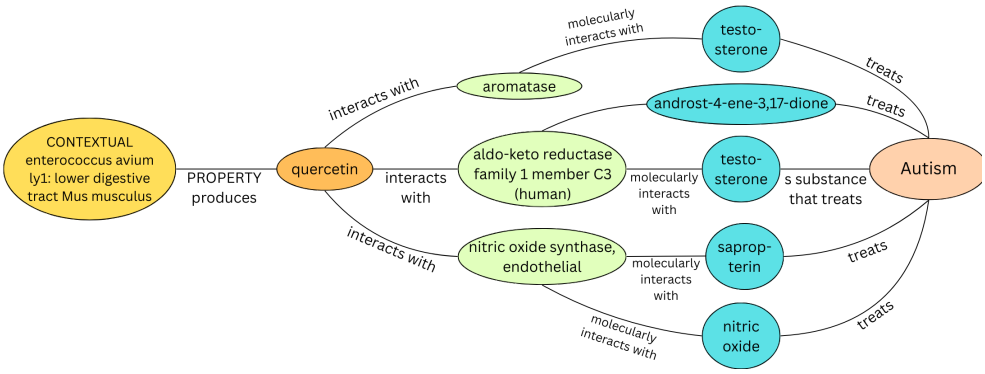

Fig. 2: A portion of knowledge graph with the detailed pathways from a microbe to a brain disorder.

which constitutes the largest node type in our graph (25.60%). This substantial representation of chemical entities, including short-chain fatty acids, neurotransmitter precursors, and bioactive peptides, enables us to trace metabolite-mediated mechanisms between gut microbes and neurological diseases. Furthermore, the relationships "molecularly interacts with," "causally influences," "causes or contributes to condition", and "is substance that treats" are particularly valuable for mapping the mechanistic pathways through which metabolites influence brain disorders.

3.2 Disease Selection And Path Mining

To get practical insights for brain disorders, it is necessary to ensure that sufficient interactions existed between brain disorders and the gut microbiome in the constructed knowledge graph. For that, the study initially identified 2,905 diseases associated with the brain. From this large set, the focus was on diseases with robust metabolite connections, as these are critical for understanding microbe-disease relationships. Only 138 diseases had more than 60 metabolite connections, and after grouping variants of the same disease (e.g., various Alzheimer's disease subtypes) and removing less brain-associated conditions, the final set of 103 neurological disorders were shortlisted for in-depth analysis. With these 103 diseases identified, paths between each disease and the 814 microbes in the knowledge graph were mined. For each disease-microbe pair, paths are searched, with the Networkx Python library [42], upto a maximum length of 5, capturing relevant connections while avoiding computational overhead. Table 3 shows the top 15 brain disorders with the most disease-microbe paths.

The path mining yielded substantial paths across all diseases, as shown in Table 3 for the top 15 diseases, dementia showed the highest connectivity with 2,029 paths connecting it to 288 different microbes. These comprehensive path mining results provide the foundation for this work's analysis, enabling the exploration of specific mechanisms through which gut microbes may influence brain disorders, with metabolites playing a crucial mediating role.

Table 1: Node Types and Counts in the Knowledge Graph

Node Type	Count	Percentage (%)
Chemical	150,080	25.60
SNP	145,156	24.76
Protein	96,196	16.41
GO_Term	43,870	7.48
Cell_Line	41,801	7.13
Gene	26,838	4.58
Disease	23,264	3.97
Pathway	16,395	2.80
Phenotype	16,291	2.78
Anatomy	14,181	2.42
Vaccine	6,271	1.07
Taxonomy	2,373	0.40
Cell_Type	2,368	0.40
Microbe	814	0.14
Chromosome	249	0.04
Environmental_Conditions	171	0.03
Total	**586318**	**100.00**

3.3 The GNN-GBA Architecture

To effectively model the complex relationships within the knowledge graph, GNN-GBA was trained for link prediction. It was implemented in PyTorch Geometric [43], a library that extends PyTorch [44] to handle graph-structured data efficiently.

Unlike traditional methods [32, 45], GNNs simultaneously captures both the local structure (direct connections) and global context (multi-hop relationships) of the biomedical entities in the graph. This is particularly crucial for understanding the gut-brain axis, where the relationships between microbes, metabolites, and brain disorders often involve complex, multi-step pathways rather than direct links.

GNN-GBA model was trained to predict the probability of each relationship between nodes in our knowledge graph. The implementation explicitly modeled the 103 different types of biological relationships in the graph. This relationship-aware modeling is essential for capturing the nuanced ways that microbes might influence brain disorder through metabolite-mediated mechanisms. Through the training process, the model learned to embed each entity (whether microbe, metabolite, disease, or other biomedical entity) in a high-dimensional space where the distance and direction between embeddings encode meaningful biological relationships. The key advantage of our approach over simpler alternatives (like [22]'s cosine similarity between node embeddings) is its ability to explicitly learn each relationship separately which enables it to differentiate between mechanistic and less relevant edges.

Table 2: 30 Most Frequent Relationships in the Knowledge Graph

Relationship	Count
molecularly interacts with	961,885
subClassOf	614,583
has phenotype	411,610
participates_in	366,750
is substance that treats	268,074
located in	179,064
causally influences	139,506
interacts with	84,804
only_in_taxon	82,784
part_of	82,267
causes or contributes to condition	80,171
has function	69,324
has_role	41,688
derives_from	32,166
has_gene_template	19,077
has gene product	18,718
has functional parent	17,174
has component	16,406
has part	11,807
is conjugate acid of	7,851
is conjugate base of	7,874
is disease model for	5,734
disease has basis in dysfunction of	4,418
inheres in	4,636
regulates (processual)	3,487
positively regulates	2,993
negatively regulates	2,989
disease has location	2,659
is enantiomer of	2,559
develops_from	1,863

On top of the GNN-GBA, an GNNExplainer [37] module is incorporated to provide comprehensive explanations capabilities. GNNExplainer [37] is a model explanation framework that identifies the pathways that most influence a specific interaction in the knowledge graph. By applying this explainer to the GNN-GBA, the most relevant paths connecting microbes to brain disorders can be extracted and visualized. For the identified disease-microbe paths, the explainer computed importance scores for each edge, which were aggregated using average pooling to rank pathways. This enables not only the prediction of interactions between microbes and brain disorders but also to elucidates the specific biological mechanisms mediating these relationships.

Table 3: The top 15 brain disorders with the most disease-microbe paths

Brain Disorder	Interacting Metabolites	Connected Microbes	Paths Found (Disease-Microbe)
dementia	70	288	2,029
Depression	373	274	1,808
Parkinson disease	183	272	1,724
autism	155	303	1,512
Alzheimer disease	104	286	1,455
Niemann-Pick disease	65	219	1,116
PCWH syndrome	65	219	1,111
neuralgia	80	266	1,071
multiple sclerosis	78	215	876
schizophrenia	133	183	847
bipolar disorder	200	254	790
epilepsy	172	234	789
major affective disorder	197	152	336
cerebral palsy	78	121	172
muscular dystrophy	65	88	312

The explanations produced by this module are particularly valuable in the biomedical domain, where understanding the reasoning behind predictions is essential for generating testable hypotheses and advancing scientific knowledge, especially for emerging fields such as the gut-brain axis.

4 Experimental Setup

To evaluate the performance of the Graph Neural Network, the knowledge graph was partitioned in a 80:10:10 ratio, resulting in 2,144,360 training samples, 714,788 validation samples, and 714,788 test samples. The validation set was used for early stopping and learning rate scheduling. Negative samples were generated through random negative sampling to create balanced datasets.

The architecture of GNN-GBA has three graph convolutional layers: two initial layers with 4 attention heads each, followed by a single-head output layer producing 128-dimensional embeddings. ReLU activation [46] and dropout [47] (p=0.2) were applied between layers during training. To model the heterogeneous biological relationships, the architecture incorporated learned embeddings for all 103 unique relation types, utilizing a DistMult [48] scoring function to compute predictions based on source embeddings, target embeddings, and relation representations. The model was trained using Adam optimization [49] (learning rate 0.0001, weight decay 5×10^4) with binary cross-entropy loss with hard negative sampling. Training proceeded for up to 500 epochs with early stopping (patience=15) based on validation AUC. The GNNExplainer [37] was integrated with the trained GNN-GBA, configured for model-level

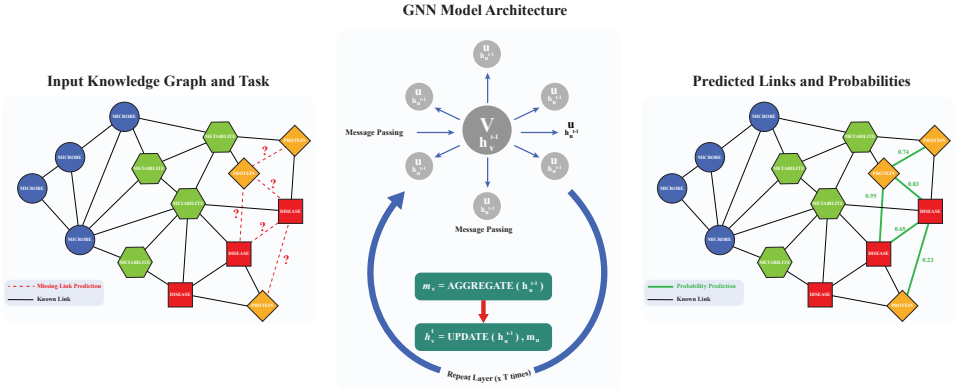

Fig. 3: Gut-brain KG is prepared by gutMGene database using PheKnowLator python framework. This KG is then fed to GNN-GBA which learns to predict new links.

explanations using object-based edge masking with 20 training epochs and learning rate 0.05 per explanation.

Three baseline methods combined static embeddings with machine learning classifiers. Node2Vec [32] generated 128-dimensional embeddings using walks of length 20, with 10 walks per node and context window 10, trained for 10 epochs. Edge features were constructed via Hadamard products of node embeddings and fed to Random Forests [50], XGBoost [51], and SVM [52] classifiers. Performance was evaluated using AUC-ROC, AUC-PRC, accuracy, precision, recall, and F1-score, computed both globally and stratified by relation type.

Table 4: Relation-Wise Performance Summary Statistics

Metric	Mean	Std Dev	Min	Median	Max
AUC	0.9719	0.0476	0.7438	0.9919	1.0000
AUPRC	0.9317	0.1121	0.4688	0.9809	1.0000
F1 Score	0.7022	0.3749	0.0000	0.9333	1.0000
Precision	0.8175	0.3532	0.0000	0.9776	1.0000
Recall	0.6631	0.3892	0.0000	0.8947	1.0000
Accuracy	0.8198	0.1961	0.4500	0.9342	1.0000

Total Relations: 103 — Total Samples: 357,394

5 Results

GNN-GBA demonstrated strong performance in predicting biological interactions within the constructed knowledge graph. As shown in Table 4, the model achieved robust relation-wise performance across 103 different relationship types, evaluated on 357,394 test samples, with a relation-wise mean of AUC of 0.9719 and mean AUPRC of 0.9317. However, the moderate mean F1 score of 0.7022, along with mean precision and recall values of 0.8175 and 0.6631 respectively, can be attributed to the class imbalance present in the knowledge graph. As illustrated in the predicate distribution, the top relationships dominate the graph structure, with "molecularly interacts with" accounting for 961,885 edges (26.9% of all edges), "subClassOf" with 614,821 edges (17.2%), and "has phenotype" with 411,610 edges (11.5%). In contrast, there are many rare relationships with fewer than 100 instances, such as "conduit for" (54 edges), "proximally connected to" (54 edges), and "in right side of" (55 edges). This imbalance explains why the model achieves excellent AUC scores (which are less sensitive to class imbalance) while showing more modest average relation-wise precision and recall metrics. The AUC metric effectively captures the model's ability to rank predictions correctly, whereas precision and recall are more affected by the under-representation of rare but significant relationships in the training data. Despite this challenge, the mean accuracy of 0.8198 validates the model's reliability in learning the underlying interaction patterns within the microbiome-gut-brain axis knowledge graph, particularly for the well-represented relationship types.

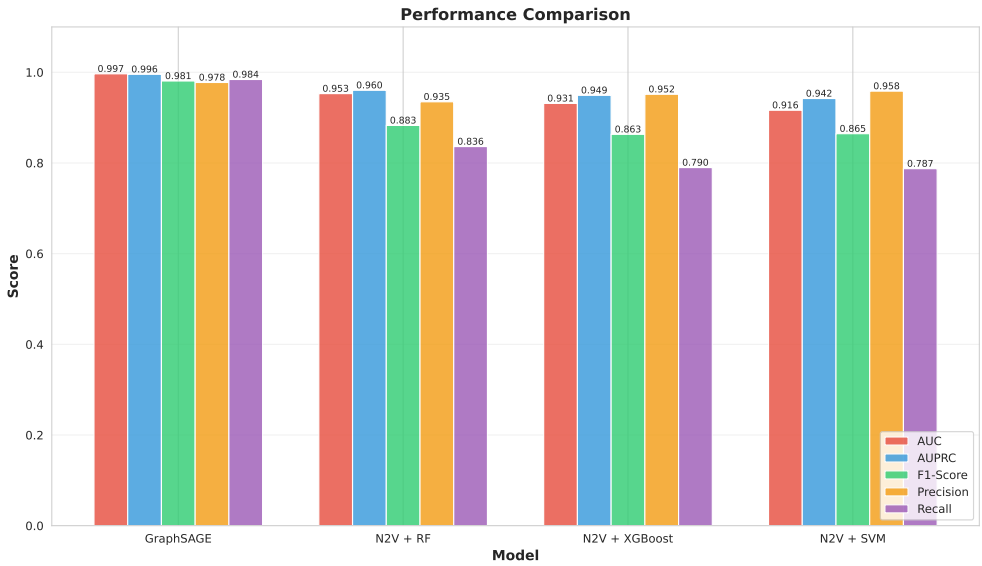

Fig. 4: Overall performance results

To validate the superiority of GNN-GBA, we compared its performance against several baseline methods including Node2Vec combined with Random Forest (N2V + RF), XGBoost (N2V + XGBoost), and Support Vector Machine (N2V + SVM). Figure 4 presents the ROC curves for all methods, demonstrating GNN-GBA's substantially outperforming the baselines. Figure 5 provides a comprehensive performance comparison across multiple metrics. These results demonstrate that GNN-GBA's can effectively capture both local structure and global context through its message-passing mechanisms.

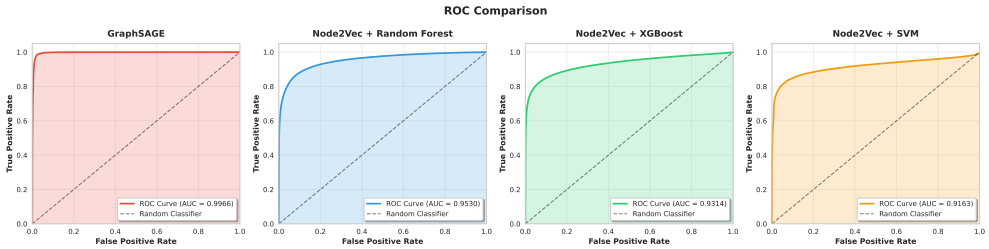

Fig. 5: AUROC Comparison with baselines methods

Using the trained GNN-GBA with GNNExplainer, we identified mechanistic pathways connecting gut microbes to brain disorders. Figure 7 illustrates the top-ranked pathways for five major brain disorders: Autism, Parkinson's Disease, Alzheimer's Disease, Major Affective Disorder, and Schizophrenia. Each pathway reveals a multi-hop cascade of interactions beginning with a specific gut microbe, proceeding through metabolite and molecular interactions, and ultimately connecting to the target disease. When the top-ranked pathways for multiple diseases were merged and analyzed, interesting hub structures emerged, as visualized in Figure 6. These hub structures reveal shared mechanistic nodes that connect multiple diseases to various gut microbes, suggesting common pathways through which the microbiome influences neurological health. The presence of these hub structures also validates our approach, as they align with known biological principles where key metabolites and enzymes often participate in multiple interconnected pathways. The GNNExplainer successfully identified these convergence points, demonstrating its ability to extract biologically meaningful patterns from the complex knowledge graph structure.

5.1 Brain Disorders and the Gut Microbiome

While the model's interaction prediction performance is notable, the goal is to explore the relationship of brain disorders with the gut microbiome. For each disorder, numerous potential microbe-disease pathways through our methodology described in Section 3.2 were identified. Figure 7 illustrates the top-ranked pathway for 5 common disorders as determined by GNNExplainer. Below, each of these pathways' mechanistic plausibility is verified from literature to show that practical significance of our results.

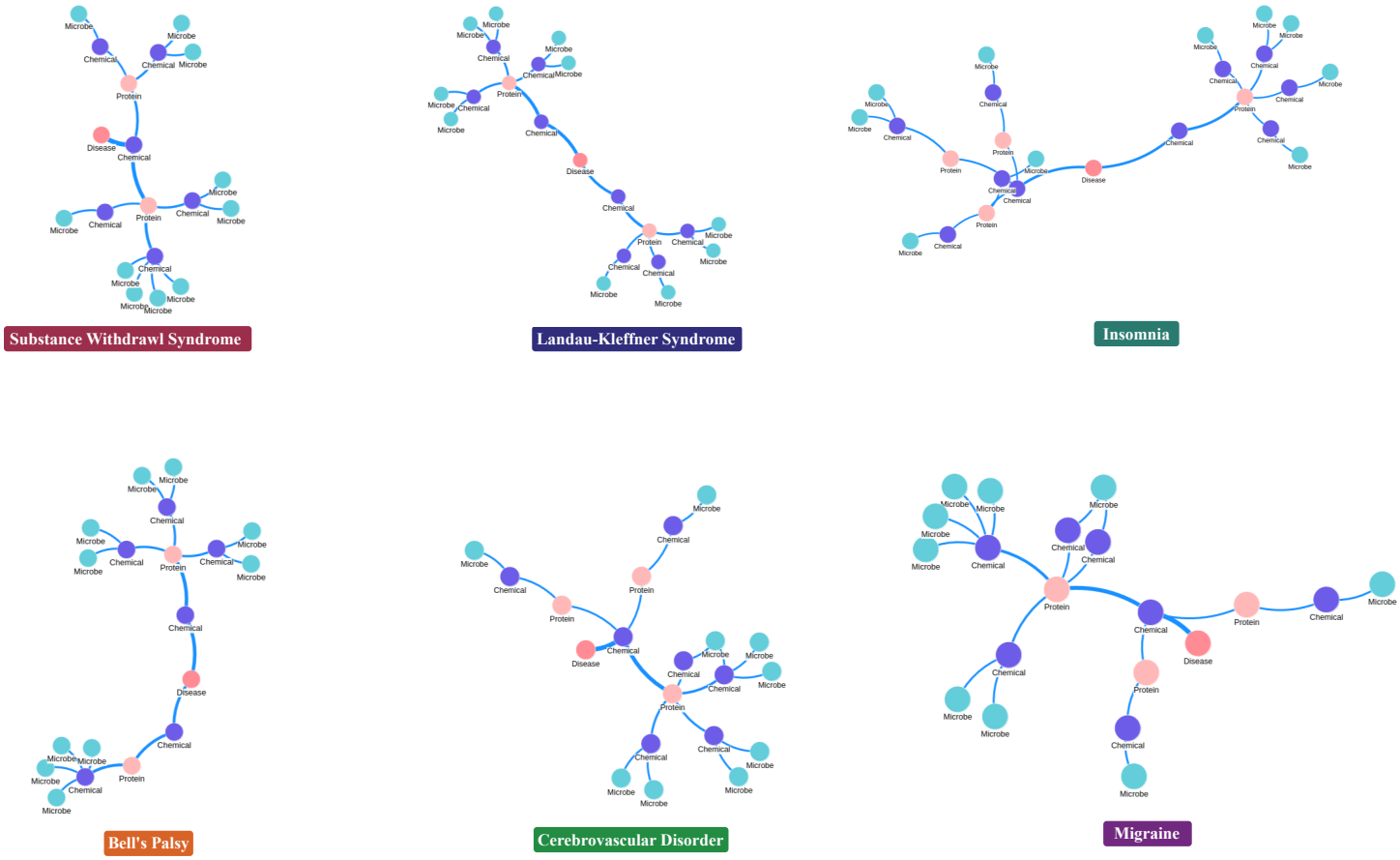

Fig. 6: Merged top paths reveal hub structures

5.1.1 Autism

The top pathway connecting microbes to autism (from 1,512 identified paths) involves Enterococcus Avium. Enterococcus avium (E. Avium) is a common bacterium found in the intestinal tracts of humans and animals [53]. It is a part of the gut microbiome, and is considered a commensal organism in the gut, meaning it usually lives there without causing harm [53]. E. Avium in the gut metabolizes Rutin (found in many plants, fruits and vegetables) to produce Quercetin, which is then absorbed through the intestine [54]. Quercetin is a member of the flavonoids family and has numerous health benefits [54]. But, Quercetin is also an AKR1C3 inhibitor [55], an enzyme that is crucial to testosterone production [56]. Testosterone has a strong and complex relationship with autism [57–59], and is an emerging field of study. Hence, E. Avium can possibly interact with Autism through this pathway.

Fig. 7: Mechanistic pathways for the brain related diseases like Autism, Parkinson's Disease, Alzheimer's Disease, Major Affective Disorder, and Schizophrenia.

5.1.2 Major Affective Disorder

The top pathway connecting microbes to major affective disorder (from 336 identified paths) involves Mitsuokella multacida. Mitsuokella multacida is a anaerobic bacterium found in the lower digestive tract of humans [60] that is crucial to a healthy digestive system, Mitsuokella multacida helps Unlock nutrients from plant foods (via phytate degradation) and Promotes gut and metabolic health (via propionate production). [60]. While Mitsuokella multacida itself does not directly produce creatine, it is involved in arginine metabolism [61], which is a precursor for creatine synthesis [62]. Creatine is primarily synthesized in the liver from arginine, glycine, and methionine [62]. Studies suggest that creatine supplementation shows promise as a potential therapy for major affective disorders [63]. Creatine plays a crucial role in brain energy metabolism, and disruptions in this process have been linked to mood disorders [63]. Research indicates that creatine may enhance the effectiveness of standard antidepressants such as selective serotonin reuptake inhibitors (SSRIs) [63]. This pathway suggests a biologically plausible mechanistic relationship between Mitsuokella multacida and major affective disorder through indirect influence on creatine metabolism, and warrants further investigation.

5.1.3 Alzheimer's Disease

The top pathway connecting microbes to Alzheimer's disease (from 1,455 identified paths) involves Bacillus subtilis. This bacterial species is found in the lower digestive tract of Mus musculus and is part of the gut microbiome, contributing to the overall microbial diversity of the digestive system [64]. Bacillus subtilis produces tannase, an enzyme that can effectively hydrolyze tannins, releasing gallic acid as a major end product [64]. Gallic acid is a naturally occurring polyphenol with antioxidant and anti-inflammatory properties that can interact with Poly(ADP-ribose) polymerase 1 (PARP1) and potentially inhibit its activity [65]. PARP1 is a key enzyme involved in DNA repair and other cellular processes, which molecularly interacts with nicotinamide [65]. Nicotinamide inhibits PARP1 activity by interacting with the enzyme's catalytic site, leading to reduced ADP-ribosylation transferase activity [65]. Nicotinamide, a form of vitamin B3, has shown promise in preclinical studies for Alzheimer's disease, particularly in improving cognitive function and reducing the accumulation of amyloid plaques [66]. Studies in mouse models demonstrate that nicotinamide compounds can improve cognitive function, reduce neuroinflammation, decrease DNA damage, and enhance mitochondrial function, which is often impaired in Alzheimer's disease [67]. This pathway provides a biologically plausible mechanistic connection through which Bacillus subtilis may influence Alzheimer's disease pathology, and warrants further investigation.

5.1.4 Schizophrenia

The top pathway connecting microbes to schizophrenia (from 847 identified paths) involves Clostridium XIVa. This is a bacterial group that resides in the lower digestive tract, comprising gram-positive, anaerobic bacteria that significantly contributes to gut health and maintaines [68]. Clostridium XIVa is associated with the production of eicosapentaenoic acid (EPA) [69], an omega-3 fatty acid with therapeutic properties [67][70][71]. EPA is known to influence cell membrane composition and function, which is particularly relevant to neurological disorders [66]. Studies have shown that EPA supplementation may improve symptoms in individuals with schizophrenia, particularly when added to standard antipsychotic treatment [72]. The "membrane hypothesis" of schizophrenia suggests that abnormalities in cell membrane composition, including changes in omega-3 fatty acids, may contribute to the pathophysiology of the disorder [73] [66]. EPA can correct these membrane abnormalities, potentially improving neuronal function and neurotransmitter signaling [66]. This pathway provides a biologically plausible mechanistic connection through which Clostridium XIVa might influence schizophrenia pathology via EPA metabolism, and warrants further investigation.

5.1.5 Parkinson's Disease

The top pathway connecting microbes to Parkinson's disease (from 1,724 identified paths) involves Escherichia coli. This bacterium is commonly found in the gut of humans and warm-blooded animals, with most strains being harmless or even beneficial, contributing to digestion, vitamin production, and protecting against harmful

germs [74]. E. coli has been shown to possess enzymatic activity capable of metabolizing chlorogenic acid (CGA), a common polyphenol found in plants including coffee and green tea [75]. Studies have demonstrated that E. coli can utilize enzymes like esterase to break down CGA, releasing CGA and quinic acid, allowing for the absorption of these components in the intestines [76][77]. Studies show that he products of the metabolism of chlorogenic acid interact with NAD(P)H dehydrogenase [quinone] 1 (NQO1) by inhibiting its activity, reducing the enzyme's effectiveness [78, 79]. NQO1 is a crucial enzyme encoded by the NQO1 gene that plays a vital role in protecting against oxidative stress and inflammation [80]. Research suggests that dysregulation of NQO1 activity is linked to various neurological disorders, including Parkinson's disease [81]. Impaired NQO1 function may contribute to abnormal neurotransmitter release, increased oxidative stress, and cellular damage characteristic of Parkinson's disease [81]. This pathway provides a biologically plausible mechanistic pathway through which E. coli might influence Parkinson's disease pathology, and warrants further investigation.

6 Discussion

These pathways reveal specific mechanisms through which gut microbes may influence brain disorders. Our computationally derived mechanistic pathways align with existing literature while providing new insights into the microbiome-gut-brain axis and its interaction with brain disorders. The diversity of identified pathways across different disorders suggests condition-specific microbial influences, potentially opening avenues for targeted therapeutic approaches. The top paths for 103 distinct diseases are visualized in the GutBrainExplorer. It has an easy-to-use interface that allows researchers to select diseases from a comprehensive list and visualize the predicted pathways as interactive network graphs. These graphs display the step-by-step connections from microbes through metabolites and proteins to target diseases.

This work presents a novel approach to understanding the relationship between brain disorders and the gut microbiome using explainable graph neural networks. By integrating diverse biomedical data into a knowledge graph and applying advanced graph learning techniques, we have identified specific metabolite-mediated pathways connecting gut microbes to brain disorders. These pathways have been validated through literature and are ready for experimental validation, offering an opportunity to accelerate the development of microbe-based therapies. Moreover, these detailed pathways suggest a clear path toward developing diet recommender systems to alleviate symptoms of neurological disorders with a high global burden. Future work can entail adding dietary components to the knowledge graph and using GNN-GBA to identify dietary compounds that can modulate disease symptoms through the gut microbiome.

- **Data/Materials availability** All data used in this study is publicly available. The GutBrainExplorer dashboard is publicly available at: https://sds-genetic-interaction-analysis.opendfki.de/gut_brain/

References

[1] Feigin, V.L., *et al.*: The global burden of neurological disorders: translating evidence into policy. The Lancet. Neurology **19**(3), 255–265 (2020) https://doi.org/10.1016/S1474-4422(19)30411-9

[2] Thakur, K.T., Albanese, E., Giannakopoulos, P., *et al.*: Neurological disorders. In: Patel, V., Chisholm, D., Dua, T., *et al.*(eds.) Mental, Neurological, and Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). The International Bank for Reconstruction and Development / The World Bank, Washington (DC) (2016). Chap. 5. Available from: https://www.ncbi.nlm.nih.gov/books/NBK361950/. https://doi.org/10.1596/978-1-4648-0426-7_ch5

[3] Nakhal, M.M., *et al.*: The microbiota-gut-brain axis and neurological disorders: A comprehensive review. Life **14**(10), 1234 (2024) https://doi.org/10.3390/life14101234

[4] Ullah, H., Arbab, S., Tian, Y., Liu, C.Q., Chen, Y., Qijie, L., Khan, M.I.U., Hassan, I.U., Li, K.: The gut microbiota-brain axis in neurological disorder. Frontiers in Neuroscience **17**, 1225875 (2023) https://doi.org/10.3389/fnins.2023.1225875

[5] Loh, J.S., Mak, W.Q., Tan, L.K.S., *et al.*: Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduction and Targeted Therapy **9**, 37 (2024) https://doi.org/10.1038/s41392-024-01743-1

[6] Friedland, R.P., Chapman, M.R.: The role of microbial amyloid in neurodegeneration. PLoS Pathogens **13**(12), 1006654 (2017) https://doi.org/10.1371/journal.ppat.1006654

[7] Sani, G., Manchia, M., Simonetti, A., Janiri, D., Paribello, P., Pinna, F., Carpiniello, B.: The role of gut microbiota in the high-risk construct of severe mental disorders: A mini review. Frontiers in Psychiatry **11**, 585769 (2021) https://doi.org/10.3389/fpsyt.2020.585769

[8] Park, J., Kim, C.H.: Regulation of common neurological disorders by gut microbial metabolites. Experimental & Molecular Medicine **53**, 1821–1833 (2021) https://doi.org/10.1038/s12276-021-00703-x

[9] Lotz, S.K., Blackhurst, B.M., Reagin, K.L., Funk, K.E.: Microbial infections are a risk factor for neurodegenerative diseases. Frontiers in Cellular Neuroscience **15**, 691136 (2021) https://doi.org/10.3389/fncel.2021.691136

[10] Almeida, C., Oliveira, R., Soares, R., Barata, P.: Influence of gut microbiota dysbiosis on brain function: a systematic review. Porto biomedical journal **5**(2), 059 (2020) https://doi.org/10.1097/j.pbj.0000000000000059

[11] Cryan, J.F., *et al.*: The gut microbiome in neurological disorders. The Lancet.

Neurology **19**(2), 179–194 (2020) https://doi.org/10.1016/S1474-4422(19)30356-4

[12] Perino, A., Schoonjans, K.: Metabolic messengers: bile acids. Nature Metabolism **4**(4), 416–423 (2022) https://doi.org/10.1038/s42255-022-00559-z

[13] Dalile, B., Van Oudenhove, L., Vervliet, B., Verbeke, K.: The role of short-chain fatty acids in microbiota–gut–brain communication. Nat. Rev. Gastroenterol. Hepatol. **16**(8), 461–478 (2019) https://doi.org/10.1038/s41575-019-0157-3

[14] Carabotti, M., Scirocco, A., Maselli, M.A., Severi, C.: The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann. Gastroenterol. **28**(2), 203–209 (2015). PMCID: PMC4367209

[15] Wallen, Z.D., Demirkan, A., Twa, G., Cohen, G., Dean, M.N., Standaert, D.G., Sampson, T.R., Payami, H.: Metagenomics of parkinson's disease implicates the gut microbiome in multiple disease mechanisms. Nat. Commun. **13**(1), 6958 (2022) https://doi.org/10.1038/s41467-022-34667-x

[16] Loh, J.S., Mak, W.Q., Tan, L.K.S., Ng, C.X., Chan, H.H., Yeow, S.H., Foo, J.B., Ong, Y.S., How, C.W., Khaw, K.Y.: Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. Frontiers in Neuroscience **17**, 10384867 (2023) https://doi.org/10.3389/fnins.2023.10384867

[17] Nicholson, D.N., Greene, C.S.: Constructing knowledge graphs and their biomedical applications. Computational and Structural Biotechnology Journal **18**, 1414–1428 (2020) https://doi.org/10.1016/j.csbj.2020.05.017

[18] Chandak, P., Huang, K., Zitnik, M.: Building a knowledge graph to enable precision medicine. Scientific Data **10**, 67 (2023) https://doi.org/10.1038/s41597-023-01960-3

[19] Zhang, Y., Sui, X., Pan, F., Yu, K., Li, K., Tian, S., Erdengasileng, A., Han, Q., Wang, W., Wang, J., Wang, J., Sun, D., Chung, H., Zhou, J., Zhou, E., Lee, B., Zhang, P., Qiu, X., Zhao, T., Zhang, J.: A comprehensive large scale biomedical knowledge graph for ai powered data driven biomedical research. bioRxiv: The Preprint Server for Biology (2025) https://doi.org/10.1101/2023.10.13.562216

[20] Alshahrani, M., *et al.*: Combining biomedical knowledge graphs and text to improve predictions for drug-target interactions and drug-indications. PeerJ **10**, 13061 (2022) https://doi.org/10.7717/peerj.13061

[21] Li, M.M., Huang, K., Zitnik, M.: Graph representation learning in biomedicine and healthcare. Nature Biomedical Engineering **6**, 1353–1369 (2022) https://doi.org/10.1038/s41551-022-00942-x

[22] Santangelo, B.E., Bada, M., Hunter, L.E., *et al.*: Hypothesizing mechanistic links

between microbes and disease using knowledge graphs. Scientific Reports **15**, 6905 (2025) https://doi.org/10.1038/s41598-025-91230-6

[23] Su, Q., Liu, Q., Lau, R.I., *et al.*: Faecal microbiome-based machine learning for multi-class disease diagnosis. Nature Communications **13**(1), 6818 (2022) https://doi.org/10.1038/s41467-022-34405-3

[24] Mayers, M., Tu, R., Steinecke, D., Li, T.S., Queralt-Rosinach, N., Su, A.I.: Design and application of a knowledge network for automatic prioritization of drug mechanisms. Bioinformatics **38**(10), 2880–2891 (2022) https://doi.org/10.1093/bioinformatics/btac205

[25] Liu, T., Pan, X., Wang, X., Feenstra, K.A., Heringa, J., Huang, Z.: Predicting the relationships between gut microbiota and mental disorders with knowledge graphs. Health Information Science and Systems **9**(1), 3 (2020) https://doi.org/10.1007/s13755-020-00128-2

[26] Karp, P.D., Riley, M., Paley, S.M., Pellegrini-Toole, A.: The metacyc database. Nucleic Acids Research **30**(1), 59–61 (2002) https://doi.org/10.1093/nar/30.1.59

[27] Croft, D., O'Kelly, G., Wu, G., Haw, R., Gillespie, M., Matthews, L., Caudy, M., Garapati, P., Gopinath, G., Jassal, B., Jupe, S., Kalatskaya, I., Mahajan, S., May, B., Ndegwa, N., Schmidt, E., Shamovsky, V., Yung, C., Birney, E., Hermjakob, H., D'Eustachio, P., Stein, L.: Reactome: a database of reactions, pathways and biological processes. Nucleic Acids Research **39**(suppl_1), 691–697 (2010) https://doi.org/10.1093/nar/gkq1018

[28] Cheng, L., *et al.*: gutmgene: a comprehensive database for target genes of gut microbes and microbial metabolites. Nucleic Acids Research **50**(D1), 795–800 (2022) https://doi.org/10.1093/nar/gkab786

[29] Kanehisa, M., Goto, S., Sato, Y., Kawashima, M., Furumichi, M., Tanabe, M.: Data, information, knowledge and principle: back to metabolism in kegg. Nucleic Acids Research **42**(Database issue), 199–205 (2014) https://doi.org/10.1093/nar/gkt1076

[30] Liu, T., Lan, G., Feenstra, K.A., Huang, Z., Heringa, J.: Towards a knowledge graph for pre-/probiotics and microbiota–gut–brain axis diseases. Scientific Reports **12**(1), 18977 (2022) https://doi.org/10.1038/s41598-022-21735-x

[31] Santangelo, B., Bada, M., Hunter, L., Lozupone, C.: Hypothesizing mechanistic links between microbes and disease using knowledge graphs. bioRxiv (2023) https://doi.org/10.1101/2023.12.01.569645 . Preprint

[32] Grover, A., Leskovec, J.: node2vec: Scalable Feature Learning for Networks (2016). https://arxiv.org/abs/1607.00653

[33] Bordes, A., Usunier, N., Garcia-Duran, A., Weston, J., Yakhnenko, O.: Translating embeddings for modeling multi-relational data. In: Advances in Neural Information Processing Systems, vol. 26. Curran Associates, Inc., ??? (2013). https://papers.nips.cc/paper_files/paper/2013/file/1cecc7a77928ca8133fa24680a88d2f9-Paper.pdf

[34] Feng, J., Wu, S., Yang, H., Ai, C., Qiao, J., Xu, J., Guo, F.: Microbe-bridged disease-metabolite associations identification by heterogeneous graph fusion. Briefings in Bioinformatics **23**(6), 423 (2022) https://doi.org/10.1093/bib/bbac423

[35] Lu, P., Li, L.: MGDHGS: Gene-bridged metabolite-disease relationships prediction via graphsage and self-attention mechanism. Computational Biology and Chemistry **108**, 108036 (2024) https://doi.org/10.1016/j.compbiolchem.2024.108036

[36] Jiang, C., Feng, J., Shan, B., Chen, Q., Yang, J., Wang, G., Peng, X., Li, X.: Predicting microbe-disease associations via graph neural network and contrastive learning. Frontiers in Microbiology **15**, 1483983 (2024) https://doi.org/10.3389/fmicb.2024.1483983

[37] Ying, R., Bourgeois, D., You, J., Zitnik, M., Leskovec, J.: GNNExplainer: Generating Explanations for Graph Neural Networks (2019)

[38] Callahan, T.J., Tripodi, I.J., Hunter, L.E., Baumgartner, W.A.: A framework for automated construction of heterogeneous large-scale biomedical knowledge graphs. bioRxiv (2020) https://doi.org/10.1101/2020.04.30.071407

[39] Vasilevsky, N.A., *et al.*: Mondo: Unifying diseases for the world, by the world. medRxiv (2022) https://doi.org/10.1101/2022.04.13.22273750

[40] Degtyarenko, K., Matos, P., Ennis, M., Hastings, J., Zbinden, M., McNaught, A., Alcántara, R., Darsow, M., Guedj, M., Ashburner, M.: Chebi: a database and ontology for chemical entities of biological interest. Nucleic Acids Research **36**(suppl_1), 344–350 (2008) https://doi.org/10.1093/nar/gkm791

[41] Gargano, M.A., *et al.*: The human phenotype ontology in 2024: phenotypes around the world. Nucleic Acids Research **52**(D1), 1333–1346 (2024) https://doi.org/10.1093/nar/gkad1005

[42] Hagberg, A., Swart, P., S Chult, D.: Exploring network structure, dynamics, and function using NetworkX (2008)

[43] Fey, M., Lenssen, J.E.: Fast graph representation learning with pytorch geometric. ICLR Workshop on Representation Learning on Graphs and Manifolds (2019)

[44] Paszke, A., Gross, S., Massa, F., Lerer, A., Bradbury, J., Chanan, G., Killeen, T.,

Lin, Z., Gimelshein, N., Antiga, L., Desmaison, A., Kopf, A., Yang, E., DeVito, Z., Raison, M., Tejani, A., Chilamkurthy, S., Steiner, B., Fang, L., Bai, J., Chintala, S.: Pytorch: An imperative style, high-performance deep learning library. In: Advances in Neural Information Processing Systems 32, pp. 8024–8035. Curran Associates, Inc., ??? (2019). http://papers.neurips.cc/paper/9015-pytorch-an-imperative-style-high-performance-deep-learning-library.pdf

[45] Perozzi, B., Al-Rfou, R., Skiena, S.: Deepwalk: online learning of social representations. In: Proceedings of the 20th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining. KDD '14, pp. 701–710. ACM, ??? (2014). https://doi.org/10.1145/2623330.2623732 . http://dx.doi.org/10.1145/2623330.2623732

[46] Agarap, A.F.: Deep Learning using Rectified Linear Units (ReLU) (2019). https://arxiv.org/abs/1803.08375

[47] Srivastava, N., Hinton, G., Krizhevsky, A., Sutskever, I., Salakhutdinov, R.: Dropout: a simple way to prevent neural networks from overfitting. J. Mach. Learn. Res. **15**(1), 1929–1958 (2014)

[48] Yang, B., Yih, W.-t., He, X., Gao, J., Deng, L.: Embedding Entities and Relations for Learning and Inference in Knowledge Bases (2015). https://arxiv.org/abs/1412.6575

[49] Kingma, D.P., Ba, J.: Adam: A Method for Stochastic Optimization (2017). https://arxiv.org/abs/1412.6980

[50] Breiman, L.: Random forests. Machine Learning **45**(1), 5–32 (2001) https://doi.org/10.1023/A:1010933404324

[51] Chen, T., Guestrin, C.: Xgboost: A scalable tree boosting system. In: Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining. KDD '16, pp. 785–794. ACM, ??? (2016). https://doi.org/10.1145/2939672.2939785 . http://dx.doi.org/10.1145/2939672.2939785

[52] Cortes, C., Vapnik, V.: Support-vector networks. Machine Learning **20**(3), 273–297 (1995) https://doi.org/10.1007/BF00994018

[53] Silva, N., Igrejas, G., Gonçalves, A., *et al.*: Commensal gut bacteria: distribution of enterococcus species and prevalence of escherichia coli phylogenetic groups in animals and humans in portugal. Ann Microbiol **62**, 449–459 (2012) https://doi.org/10.1007/s13213-011-0308-4

[54] Shin, N.R., *et al.*: Isolation and characterization of human intestinal enterococcus avium efel009 converting rutin to quercetin. Letters in applied microbiology **62**(1), 68–74 (2016) https://doi.org/10.1111/lam.12512

[55] Skarydová, L., *et al.*: Akr1c3 as a potential target for the inhibitory effect of dietary flavonoids. Chemico-biological interactions **178**(1-3), 138–144 (2009) https://doi.org/10.1016/j.cbi.2008.10.015

[56] Penning, T.M.: 4.08 - aldo-keto reductases*. In: McQueen, C.A. (ed.) Comprehensive Toxicology (Second Edition), Second edition edn., pp. 149–167. Elsevier, Oxford (2010). https://doi.org/10.1016/B978-0-08-046884-6.00408-5 . https://www.sciencedirect.com/science/article/pii/B9780080468846004085

[57] Tan, D.W., Maybery, M.T., Clarke, M.W., Di Lorenzo, R., Evans, M.O., Mancinone, M., Panos, C., Whitehouse, A.J.O.: No relationship between autistic traits and salivary testosterone concentrations in men from the general population. PloS one **13**(6), 0198779 (2018) https://doi.org/10.1371/journal.pone.0198779

[58] Dooley, N., Ruigrok, A., Holt, R., Allison, C., Tsompanidis, A., Waldman, J., Auyeung, B., Lombardo, M.V., Baron-Cohen, S.: Is there an association between prenatal testosterone and autistic traits in adolescents? Psychoneuroendocrinology **136**, 105623 (2022) https://doi.org/10.1016/j.psyneuen.2021.105623

[59] Muscatello, R.A., Rafatjoo, E., Mirpuri, K.K., *et al.*: Salivary testosterone in male and female youth with and without autism spectrum disorder: considerations of development, sex, and diagnosis. Molecular Autism **13**, 37 (2022) https://doi.org/10.1186/s13229-022-00515-4

[60] De Vos, W.M., *et al.*: Phytate metabolism is mediated by microbial cross-feeding in the gut microbiota. Nature microbiology **9**(7), 1812–1827 (2024) https://doi.org/10.1038/s41564-024-01698-7

[61] Dai, Z.-L., *et al.*: Utilization of amino acids by bacteria from the pig small intestine. Amino acids **39**(5), 1201–1215 (2010) https://doi.org/10.1007/s00726-010-0556-9

[62] Jahangir, E., Vita, J.A., Handy, D., Holbrook, M., Palmisano, J., Beal, R., Loscalzo, J., Eberhardt, R.T.: The effect of l-arginine and creatine on vascular function and homocysteine metabolism. Vascular medicine **14**(3), 239–248 (2009) https://doi.org/10.1177/1358863X08100834

[63] Juneja, K., Bhuchakra, H.P., Sadhukhan, S., Mehta, I., Niharika, A., Thareja, S., Nimmakayala, T., Sahu, S.: Creatine supplementation in depression: A review of mechanisms, efficacy, clinical outcomes, and future directions. Cureus **16**(10), 71638 (2024) https://doi.org/10.7759/cureus.71638

[64] Govindarajan, R.K., Mathivanan, K., Khanongnuch, C., Srinivasan, R., Unban, K., Charli Deepak, A., Al Farraj, D.A., Mohammed Alarjani, K., Al Qahtany, F.S.: Tannin acyl-hydrolase production by bacillus subtilis kms2-2: Purification, characterization, and cytotoxicity studies. Journal of King Saud University - Science **33**(3), 101359 (2021) https://doi.org/10.1016/j.jksus.2021.101359

[65] Salech, F., Ponce, D.P., Paula-Lima, A.C., SanMartin, C.D., Behrens, M.I.: Nicotinamide, a poly [adp-ribose] polymerase 1 (parp-1) inhibitor, as an adjunctive therapy for the treatment of alzheimer's disease. Frontiers in Aging Neuroscience **12**, 255 (2020) https://doi.org/10.3389/fnagi.2020.00255

[66] Puri, B., Richardson, A.J., Horrobin, D.F., *et al.*: Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalisation of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. International Journal of Clinical Practice **54**(1), 57–63 (2000)

[67] Aronson, W.J., Glaspy, J.A., Reddy, S.T., Reese, D., Heber, D., Bagga, D.: Modulation of omega-3/omega-6 polyunsaturated ratios with dietary fish oils in men with prostate cancer. Urology **58**(2), 283–288 (2001)

[68] Lopetuso, L.R., Scaldaferri, F., Petito, V., *et al.*: Commensal clostridia: leading players in the maintenance of gut homeostasis. Gut Pathogens **5**, 23 (2013) https://doi.org/10.1186/1757-4749-5-23

[69] Hagihara, M., *et al.*: Clostridium butyricum-induced ω-3 fatty acid 18-hepe elicits anti-influenza virus pneumonia effects through interferon-λ upregulation. Cell Reports **41**(11), 111755 (2022) https://doi.org/10.1016/j.celrep.2022.111755

[70] Amiano, P., Machon, M., Dorronsoro, M., *et al.*: Intake of total omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid and risk of coronary heart disease in the spanish EPIC cohort study. Nutrition, Metabolism and Cardiovascular Diseases **24**(3), 321–327 (2014)

[71] Angerer, P., Schacky, C.: n-3 polyunsaturated fatty acids and the cardiovascular system. Current Opinion in Lipidology **11**(1), 57–63 (2000)

[72] Peet, M.: Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. Prostaglandins, Leukotrienes and Essential Fatty Acids **69**(6), 477–485 (2003) https://doi.org/10.1016/j.plefa.2003.08.020 . Recent Advances of Membran e Pathology in Schizophrenia

[73] Horrobin, D.F., *et al.*: The membrane hypothesis of schizophrenia. Schizophrenia Research **13**(3), 195–207 (1994) https://doi.org/10.1016/0920-9964(94)90043-4

[74] World Health Organization: E. coli (2018). https://www.who.int/news-room/fact-sheets/detail/e-coli

[75] Raimondi, S., Anighoro, A., Quartieri, A., Amaretti, A., Tomás-Barberán, F.A., Rastelli, G., Rossi, M.: Role of bifidobacteria in the hydrolysis of chlorogenic acid. MicrobiologyOpen **4**(1), 41–52 (2015) https://doi.org/10.1002/mbo3.219

[76] Nguyen, V., Taine, E.G., Meng, D., Cui, T., Tan, W.: Chlorogenic acid: A systematic review on the biological functions, mechanistic actions, and therapeutic potentials. Nutrients **16**(7), 924 (2024) https://doi.org/10.3390/nu16070924

[77] Hu, M., Chen, J., Wang, H., Wang, L., Gao, S., Zhou, Z., Zhou, J.: Efficient biosynthesis of chlorogenic acid in escherichia coli by optimization of precursors metabolic flow and reduction of an unknown byproduct. ACS Sustainable Chemistry & Engineering **13** (2025) https://doi.org/10.1021/acssuschemeng.4c08395

[78] Wang, S., Li, Y., Huang, D., Chen, S., Xia, Y., Zhu, S.: The inhibitory mechanism of chlorogenic acid and its acylated derivatives on α-amylase and α-glucosidase. Food Chemistry **372**, 131334 (2022) https://doi.org/10.1016/j.foodchem.2021.131334

[79] Wang, L., Pan, X., Jiang, L., Chu, Y., Gao, S., Jiang, X., Zhang, Y., Chen, Y., Luo, S., Peng, C.: The biological activity mechanism of chlorogenic acid and its applications in food industry: A review. Frontiers in Nutrition **9**, 943911 (2022) https://doi.org/10.3389/fnut.2022.943911

[80] NCBI: NQO1 NAD(P)H quinone dehydrogenase 1 [Homo sapiens (human)]. NCBI Gene Database. Gene ID: 1728, updated on 3-May-2025 (2025). https://www.ncbi.nlm.nih.gov/gene/1728 Accessed 2025-05-09

[81] Luo, S., *et al.*: Akt phosphorylates nqo1 and triggers its degradation, abolishing its antioxidative activities in parkinson's disease. The Journal of Neuroscience **39**(37), 7291–7305 (2019) https://doi.org/10.1523/JNEUROSCI.0625-19.2019