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Integrated RNA-Sequencing Profiling and Molecular Docking to Identify Key Genes, pathways and Drug Targets for Frontotemporal Dementia

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ABSTRACT: Frontotemporal dementia (FTD) is a neurodegenerative disease marked by progressive degeneration of the brain's frontal and temporal lobes, resulting in behavioral and cognitive impairments. There are no current disease-modifying therapies for FTD. This study analyzed RNA sequencing datasets to identify differentially expressed genes (DEGs) and dysregulated molecular pathways contributing to FTD pathogenesis. Protein-protein interaction network analysis revealed key genes-RPL13A, MED1, MRTO4, RPL12, EIF3G, EIF5A, CDH1, IGF1, CD44, and SOD1-with strong centrality in disease pathways. Molecular docking studies demonstrated significant binding affinities of phytochemicals to FTD-associated proteins. Notably the phytochemical epigallocatechin gallate shows binding affinity with more than one FTD proteins: 4UG0, 8FKR, 4V6X, 6YBS, 3CPF, 7WRQ and 1UUH with docking score of -8, -6.7, -7, -6, -7.7, -6.9 and -7.2 kcal/mol respectively. The hesperetin shows binding free energy of -9.4 kcal/mol with 1RJK. The phytochemical hesperetin, luteolin, naringenin, apigenin and epicatechin shows significant binding towards 1RJK with the binding free energy of -9.4, -9.3, -9.2, -9.1 and -8.5 kcal/mol respectively. Toxicity predictions identified epicatechin as a favorable drug candidate, demonstrating low toxicity and a benign safety profile. Our findings highlight the power of omics-driven and computational approaches to identify novel therapeutic agents for FTD.

1. INTRODUCTION

FTD is a significant cause of early-onset dementia, particularly affecting individuals between the ages of 45 and 64. Progressive frontal and temporal lobes neurodegeneration resulting in significant alterations in behavioral patterns, personality traits, and language abilities. The global prevalence of FTD is estimated to be 15 to 22 cases per 100,000 individuals within this age group [1]. Genetic mutations play a crucial role in FTD, with mutations in genes such as MAPT, GRN, and C9orf72 being significant contributors [2]. This accumulation causes misfolded proteins and cell dysfunction which can lead to neurodegeneration. There are also distinguishing features between FTD and other forms of dementia. FTD typically begins with behavior or language impairment which worsens gradually over time instead of memory. Characteristics of FTD symptoms are: personality shifts. Language disturbances, impaired decision making, memory impairment in later stages of the illness [3].

In recent years, new molecular approaches have increased our knowledge of diseases. Among these approaches, genome and whole transcriptome wide sequencing in postmortem FTD brain and/or blood has allowed the identification of differentially expressed genes/pathways implicated in the pathogenesis of FTD. The translational genomics work over the years increased the knowledge of neurodegenerative diseases, including FTD [4]. These discoveries allow new diagnostic approaches to implement treatment strategies to get better prognosis and quality of life for FTD patients [5]. Today, in the FTD patient population treatment strategies only offer symptomatic improvement of symptoms. In the light of those findings, many studies

reported repeatedly on the impact of molecular markers for patients' prognosis, as well as treatment outcome prediction. Through Whole transcriptome-Wide Association Studies and bioinformatics the expression differences in some genes and protein-protein interactions can potentially be targeted with new medications [6–8].

Integrative approaches generate essential insight into the mechanisms of FTD molecular and underpin efforts toward personalized medicine in which therapy based on genetically determined profile of an individual. These strategies are critical for design of rational therapeutic approaches and their successful clinical outcomes. There is already experimental therapy approaches for attenuation of tau phosphorylation and aggregation, for restoration of progranulin levels by gene therapy or delivery of recombinant proteins, and for repression of hexanucleotide repeat expansions in C9orf72 gene with antisense oligonucleotides under development [9]. Parallel advances in high-throughput transcriptomics, proteomics, and metabolomics are facilitating the discovery of markers enabling early diagnosis, and the assessment of therapeutic outcomes. Furthermore, the integration of longitudinal multi-omics data with machine learning algorithms enhances the capacity to stratify patient subgroups and predict individual trajectories, ultimately supporting the implementation of precision medicine paradigms in FTD [10]. The present study aims to identify genes significantly associated with FTD through RNA-seq analysis, using RNA-seq pipeline to uncover DEGs, elucidate their important roles in FTD pathways, and assess their potential key genes as therapeutic targets. By incorporating various computational approaches, the study enables an in-depth RNA-seq analysis, docking, ADME and toxicity analysis to provide molecular insights into the FTD disease's mechanisms and highlighting promising strategies for FTD targeted treatment.

2. MATERIALS AND METHODS

2.1 RNA Sequencing Analysis

Transcriptomic samples were downloaded from NCBI GEO Database for two dataset GSE230519 and GSE219279, from that 12 samples were chosen for further study (6 FTD patients and 6 non-FTD patients) namely SRR24299742, SRR299743, SRR299744, SRR24299737, SRR24299738, SRR24299753, SRR22512064, SRR22512065, SRR22512066, SRR22512075, SRR22512076, SRR22512086. The datasets were imported into the Galaxy Server using the tool faster download and extract reads in FASTQ format from NCBI SRA [11]. Read quality was assessed through FastQC, which provides comprehensive quality reports for RNA-seq data. Using HISAT2 sequence reads were aligned to the hg38 reference human genome, a high-speed and sensitive alignment tool. Gene expression levels were measured from the resulting BAM files using FeatureCounts. Differentially expressed features from the count table were determined using the tool DESeq2. ShinyGO is a convenient user-friendly web-based tool to perform enrichment analysis of gene functions. It helps to understand the biological significance of genes by identifying their biological processes, pathways, or functions that are overrepresented [12]. It was used to interpret differentially expressed genes by highlighting key pathways and cellular activities that are involved in FTD.

2.2 Protein-protein interaction (PPI) network

The web-based database STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) a network with PPI has been constructed using string [13]. The relationship between genotypes, biologic systems, and gene expression is visualized via the Cytoscape software [14]. In this study, the scale-free topology of the network resulted in higher scores for central nodes. PPI network was built for 91 genes using STRING with a threshold of >0.900. Module detection was performed in Cytoscape using the MCODE plugin, yielding a single gene module consisting of 6 nodes and 15 edges. Cluster-based filtering identified ten hub genes, namely RPL13A, MED1, MRTO4, RPL12, EIF3G, EIF5A, CDH1, IGF1, CD44, and SOD1. Following hub gene identification through PPI analysis, the corresponding protein products were selected for molecular docking studies with phytochemicals, enabling the exploration of phytochemical-based therapeutic targets for FTD.

2.3 Molecular Docking

Molecular docking is a computational technique to predict the preferential orientation of two molecules to form a stable complex [15-18]. Molecular docking evaluation were done to assess the interaction between phytochemicals and FTD-associated target proteins. In the current study, molecular docking was performed using PyRx software [19]. The three-dimensional structure of the FTD target proteins (**Table 1**) was obtained from the protein data bank (PDB) [20]. The protein structure was prepared for docking by removing the remaining chains except one chain were removed and cleaned using Chimera. Furthermore, the direct interaction between the ligand and the protein are disrupted by water molecules, and their influence on altering protein- ligand binding is avoided when they are eliminated [21-22]. The ligand-binding search space was

defined by generating a receptor grid box, with grid sizes and spacing adjustment created on the binding pocket characteristics. Phytochemical substances that exhibit antioxidative, anti-amyloidogenic, anti-inflammatory, and anti-apoptotic effects could serve as valuable resources in the pursuit of drug candidates for dementia. Plant-based compounds may provide effective treatments for dementia with reduced side effects. In total ten phytochemicals resveratrol, secoisolariciresinol, apigenin, luteolin, quercetin, epicatechin, epigallocatechin gallate, hesperetin, naringenin and genistein are sourced and retrieved from the pubchem database were docked against the binding sites of FTD target proteins [23].

2.4 Toxicity prediction

The ProTox-III web server was utilized to assess multiple toxicity endpoints, such as mutagenicity, immunotoxicity, cytotoxicity, hepatotoxicity, and oral toxicity, together with corresponding adverse outcome pathways (AOPs) and toxicity targets. The toxicity profile for the ten phytochemicals were predicted using the ProTox 3.0 server [24].

2.5 Pharmacokinetic property prediction

The pharmacokinetic properties of the chosen ten phytochemical compounds were evaluated using the SwissADME tool, which provides insights into key drug-likeness factors [25]. This analysis included predictions of gastrointestinal absorption, blood-brain barrier penetration, and potential P-glycoprotein interactions. Analyzing these attributes is essential for determining the compound's potential for oral bioavailability, metabolic processes, and the risk of drug-drug interactions, all of which are vital considerations during the initial phases of drug development.

3. RESULTS AND DISCUSSION

3.1 FTD RNA Seq analysis

To gain a preliminary insight into the molecular mechanisms underlying FTD, a total of 2 RNA-Seq dataset (GSE230519 and GSE219279) were chosen, out of which 12 samples (6 cases and 6 controls) were selected for analysis. The corresponding Sequence Read Archive (SRA) identifiers are SRR24299742, SRR24299743, SRR24299744, SRR24299737, SRR24299738, SRR24299753, SRR22512064, SRR22512065, SRR22512066, SRR22512075, SRR22512076, and SRR22512086 (Figure. 1-2). Analysis of differential gene expression identified a total of 26,971 significantly expressed genes, of which up-regulated and down-regulated genes of 17,287 and 9,684, respectively. Among the 17,287 differentially expressed genes 148 significantly expressed genes were filtered for upregulated and 61 significantly expressed down regulated genes were filtered based on the (p -value of < 0.05 and $\log_2$ fold change of $\geq \pm 1.5$). Subsequent string PPI interaction network analysis identified 91 nodes, and Cytoscape's MCODE plugin detected six nodes comprising 15 edges. Further prioritization using the CytoHubba plugin identified ten key hub genes potentially associated with FTD pathogenesis: RPL13A, MED1, MRTO4, RPL12, EIF3G, EIF5A, CDH1, IGF1, CD44, and SOD1. The heatmap sample-to-sample cluster analysis derived from normalized counts, allowing evaluation of the similarity and divergence among gene expression profiles in FTD samples. The dark blue areas on the heatmap represent a shorter distance between samples, suggesting a higher degree of similarity between the controls and cases (Figure 3-4). This clustering method emphasizes the gene expression profile with functionally significant patterns, which aids the principal component analysis by pinpointing essential section that account for the most differences and are pertinent for predicting FTD outcomes. Based on the criteria, p -value less than 0.05 and $\log$ FC greater than or equal to ± 1.5 , out of 26971 genes, 148 significantly up-regulated genes and 61 significantly down-regulated genes were chosen. Using Gene card, the names for both upregulated genes and downregulated genes were identified.



Figure 1: Principal component plot of the control vs case for upregulated and downregulated gene for FTD samples.

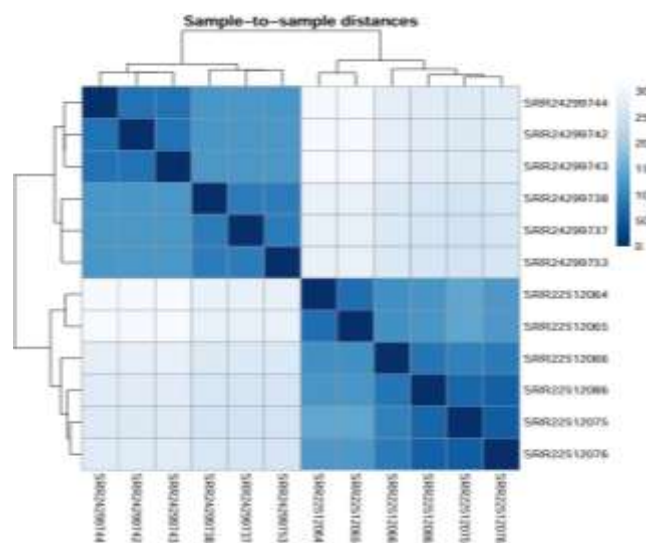


Figure 2: Heatmap of the sample to sample distance of FTD.

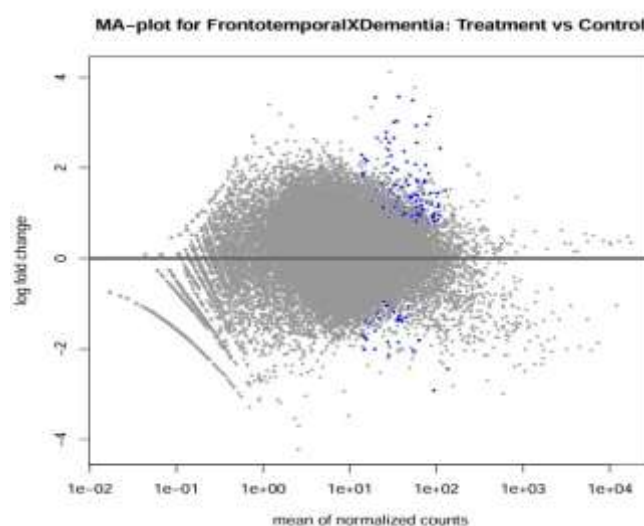


Figure 3: MA Plot for FTD (treatment vs control) for up-regulated and down-regulated genes.

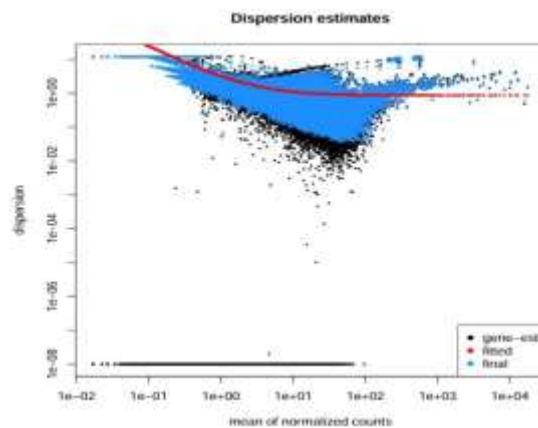


Figure 4: Dispersion estimates for up-regulated and down-regulated genes for FTD.

3.2 PPI network analysis

The PPI network was designed, where each and every node characterized the protein, and edges indicated the interactions between the proteins. The core network, composed of upregulated genes, comprised 6 nodes and 15 edges. In the STRING database context, the PPI network coefficient is commonly used to evaluate the strength and confidence of interactions among proteins. Post-STRING analysis, the hub genes was identified through the MCODE plugin of cytoscape. The clustering and scoring parameters for differentially expressed genes (DEGs) were set as follows: MCODE score of cluster 1 is 6.000, with degree cut-off = 2, node score cut-off = 0.2, k-score = 2, and max depth = 100, comprising of 6 nodes and 15 edges. MCODE score of cluster 2 is 4.000 with the same parameter settings, comprising of 4 nodes and 6 edges. MCODE score of cluster 3 is 3.333, with degree cut-off=2, node score cut-off=0.2, k-score=2, and max. depth=100, comprising of 4 nodes and 5 edges (Figure 5-7). With cytohubba plugin the 10 hub node genes RPL13A, MED1, MRT04, RPL12, EIF3G, EIF5A, CDH1, IGF1, CD44 and SOD1 were identified (Figure 8).

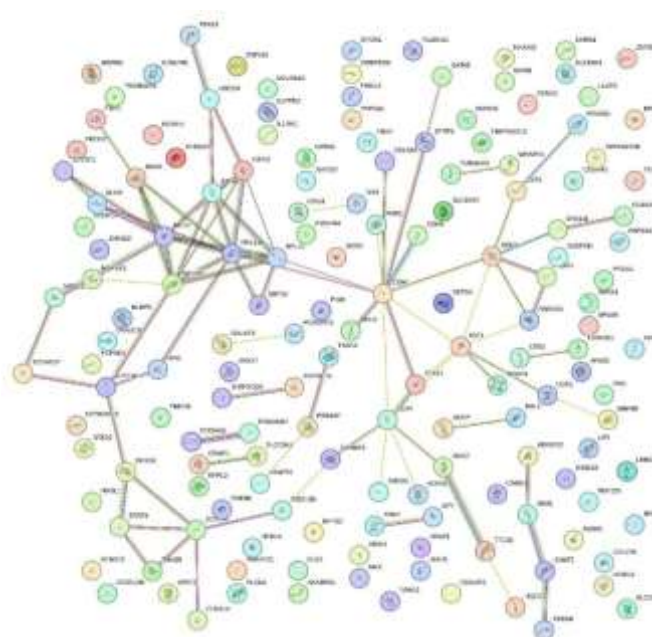


Figure 5: PPI network backbone of identified upregulated genes consisted of 9 nodes and 15 edges using string db.

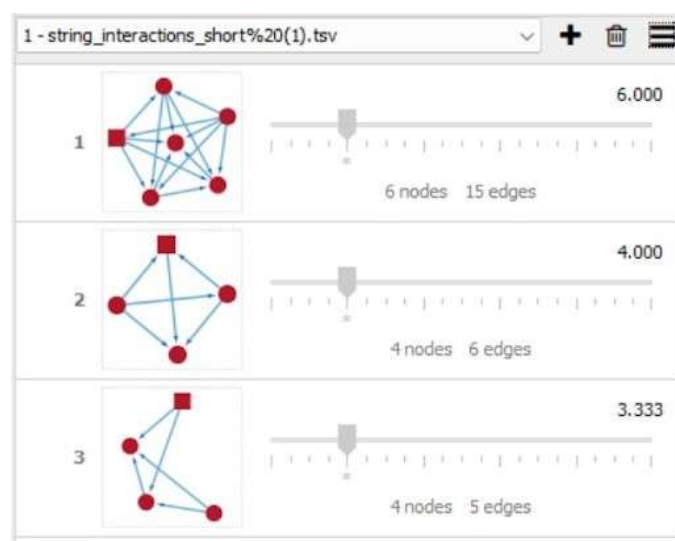


Figure 6: MCODE plugin was used to identify the nodes and edges of FTD genes.



Figure 7: Key genes were identified using PPI network.

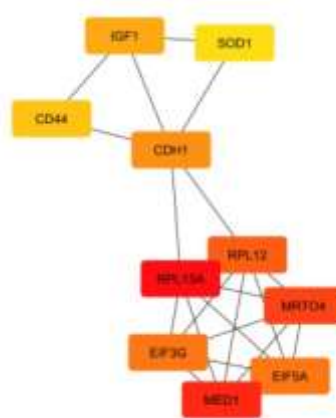


Figure 8: Top 10 hub genes of FTD were inferred using cytohubba.

3.3 Pathway Analysis of DEGs

Gene ontology enrichment study revealed that the DEGs were significantly enriched in several important biological processes associated to protein synthesis, transport and metabolism. DEGs of FTD involved in the pathways of cytoplasmic translation, ribonucleoprotein complex biogenesis, peptide metabolic process, intracellular protein transport, cellular amide metabolic process, intracellular transport, protein transport, establishment of protein localization, establishment of localization in cell and cellular localization (Figure 9).

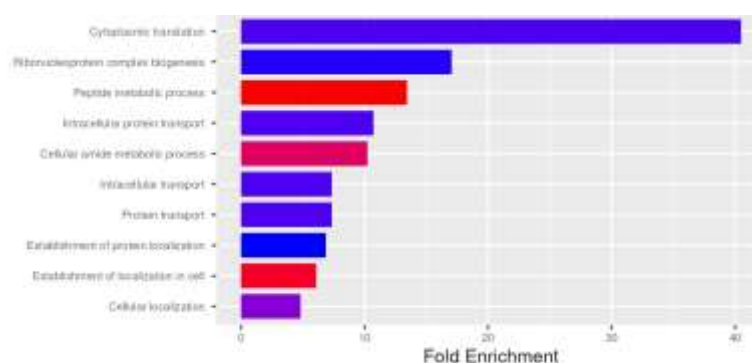


Figure 9: Enrichment analysis of biological pathways for 10 hub genes of FTD using ShinyGO.

3.4 FTD- phytochemical complex docking analysis

In the current study, ten phytochemicals were docked against the binding pocket of FTD target proteins (**Table 1**). The phytochemical compound genistein shows better interaction with the protein MED1, with a docking score of -10.3 kcal/mol. Similarly, luteolin (-9.3 kcal/mol), hesperetin (-9.4 kcal/mol), naringenin (-9.2 kcal/mol) apigenin (-9.1 kcal/mol) also demonstrated high binding potential to 1RJK. The ten FTD-phytochemical complexes that has highest binding affinity score: RPL13A-epigallocatechin gallate complex, MED1-genistein complex, MRDO4-epigallocatechin gallate complex, RPL12-epigallocatechin gallate complex, EIF3G-epigallocatechin gallate complex, EIF5A-epigallocatechin gallate complex, CDH1-quercetin complex, IGF1-epigallocatechin gallate complex, CD44-epigallocatechin gallate complex, SOD1-luteolin complex (**Table 2**). Also, it shows strong interactions via hydrogen bonds, van der Waals, and pi-pi interactions, which were demonstrated by the BIOVIA discovery studio visualizer (Figure 10-12).

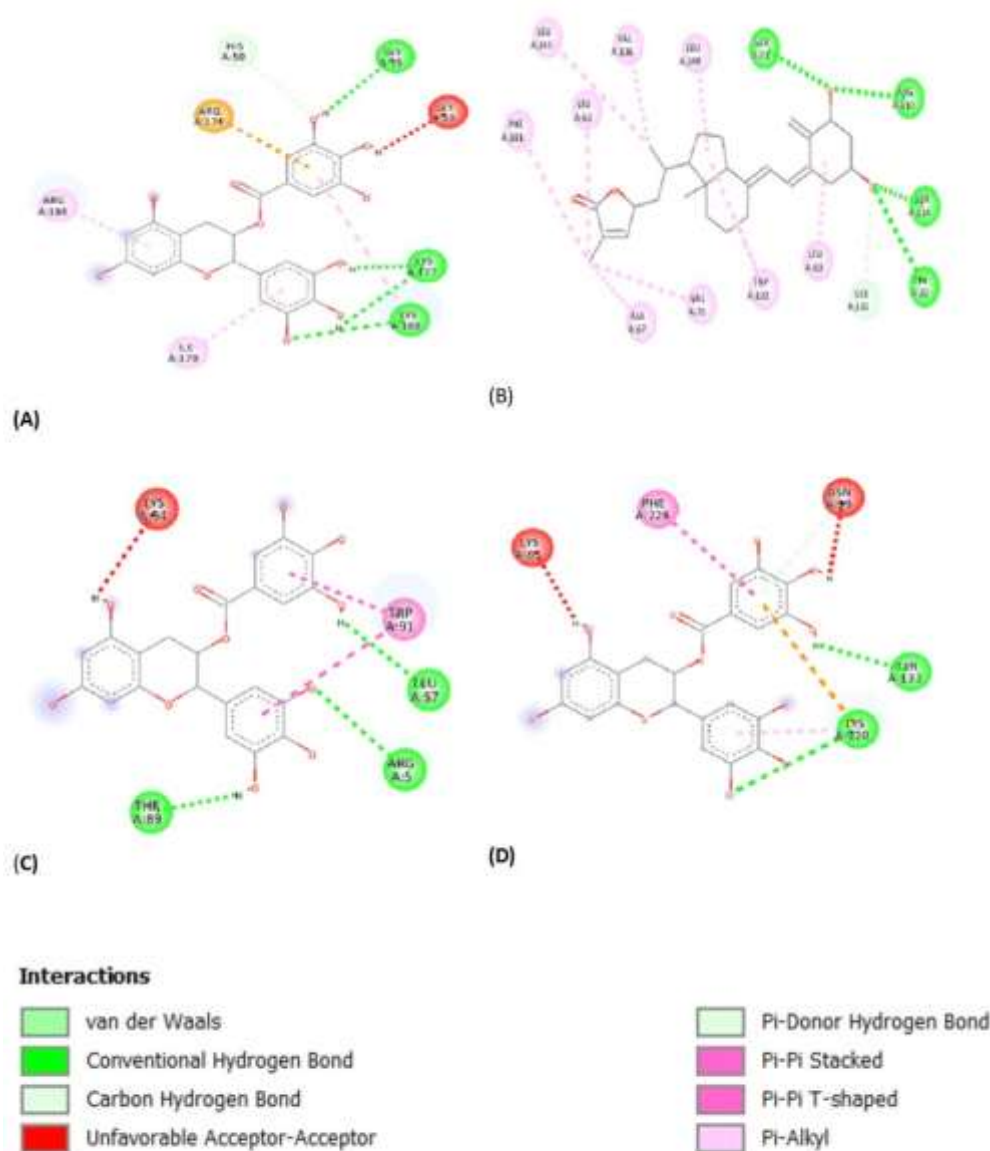


Figure 10: Docking results of (A) 4UG0 - Epigallocatechin gallate complex, (B) 1RJK – Genistein complex, (C) 8FKR - Epigallocatechin gallate complex, (D) 4V6X -Epigallocatechin gallate complex.

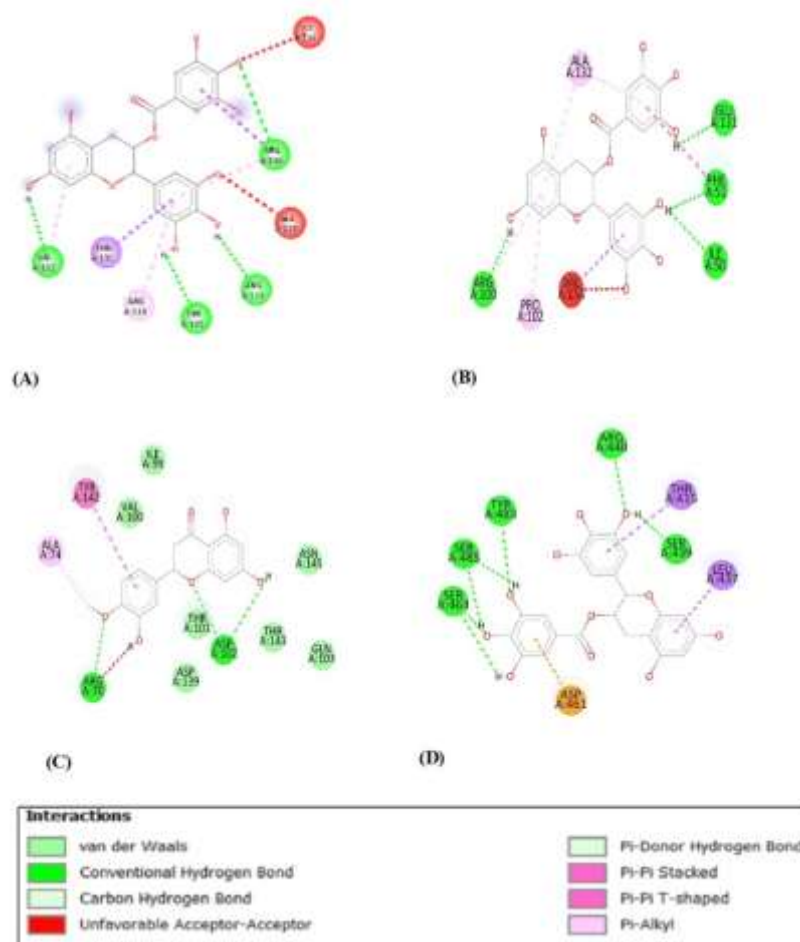


Figure 11: Docking results of (A) 6YBS - Epigallocatechin gallate complex, (B) 3CPF- Epigallocatechin gallate complex, (C) 6ZTB - Quercetin complex, (D) 7WRQ - Epigallocatechin gallate complex.

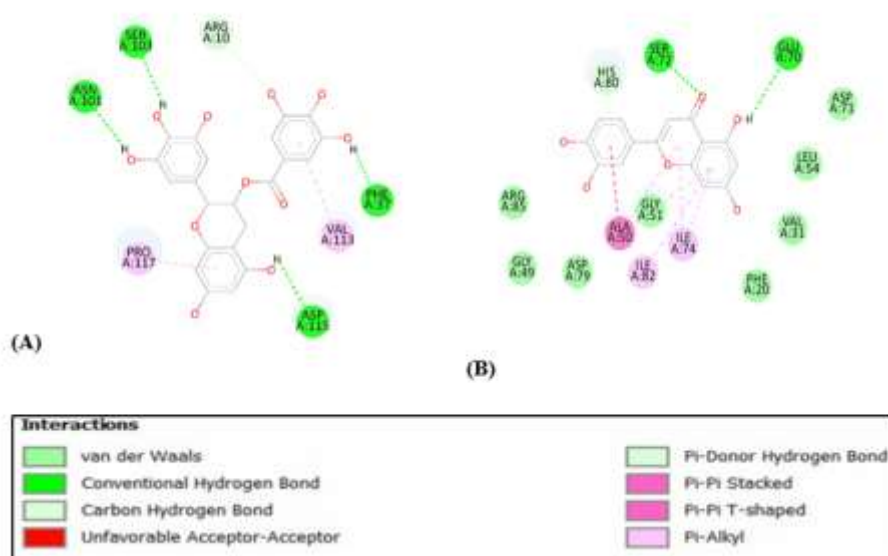


Figure 12: Docking results of (A) 1UUH - Epigallocatechin gallate complex, (B) 7CJW - Luteolin complex.

3.5 Phytochemical toxicity profile

One of the main stages of the drug discovery steps is the prediction of the toxicity of small molecules. For the present study, ten phytochemicals were selected for toxicity prediction by ProTox-III. It is applied to predict some of the toxic outcomes with hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, carcinogenicity, immunotoxicity, mutagenicity, projected toxicity class, and LD50. The phytochemicals had predicted toxicity categories as follows: Class 4 resveratrol and secoisolariciresinol LD50 1560 mg/kg, and 2000 mg/kg respectively, Class 5 apigenin and luteolin LD50 2500 mg/kg and 3919 respectively, Class 3 quercetin LD50 of 159, Class 6 epicatechin LD50 10000 mg/kg, class 4 epigallocatechin gallate, hesperetin and naringenin LD50 of 1000 mg/kg, 2000 mg/kg and 2000 mg/kg, class 5 genistein LD50 of 2500 mg/kg (**Table 3**). Epicatechin is the lead compound that reveals a less toxicological level and inactive organ toxicity, which can be used as a drug target for FTD hub proteins.

3.6 Pharmacokinetic property prediction

To facilitate and enhance the efficiency of the drug design process SwissADME was used to predict the ADME properties of the ten phytochemicals. The ADME parameters like pharmacokinetic profile, drug-likeness and therapeutic understanding, courtesy of the selected phytochemicals. The molecular weights of these compounds ranged from 228.24 g/mol for Resveratrol to 458.37 g/mol for epigallocatechin gallate. The consensus Log P_o/p (a measure of lipophilicity and a key factor in membrane transport) ranged from 0.85 for epicatechin to 2.48 for resveratrol, suggesting that most compounds are moderately lipophilic, a property favorable for oral bioavailability. Of these, noteworthy was that resveratrol was able to effectively penetrate the blood-brain barrier (BBB) which is significant when considering drugs that focus on treating neurodegenerative disorders like FTD. Although a number of compounds showed the necessary good lipophilicity, not crossing the BBB can potentially make the administration to central nervous system challenging without the help of carriers (**Table 4**).

3.7 Discussion

For molecular characterization of underlying mechanisms in FTD, extensive differential gene expression analysis was conducted comparing patient and control samples. After processing the data using the limma-voom pipeline, a volcano plot was developed. Initially resulting in 26,971 DEGs were found. We filtered genes on a log fold change ≥ 1.5 and a p-value < 0.05 to get 209 significant DEGs (148 upregulated and 61 downregulated) for the enrichment and network analyses. Through ShinyGO enrichment analysis of the DEGs, genes were enriched in progresses, like cytoplasmic translation, ribonucleoprotein complex biogenesis and intracellular transport. The high enrichment in cytoplasmic translation and ribonucleoprotein complex formation suggesting increased protein production that could be the answer to higher intracellular activity or stress. It is logical to predict that the increase in cytoplasmic translation might contribute to protein buildup which could in FTD be paradoxical as increased production could trigger proteostasis dysregulation [26]. In order to investigate the PPIs of the DEGs, a PPI network was constructed using the STRING database. Of the 148 DEGs, there were 9 nodes and 15 edges in the network, which reflects interactions between DEGs and could give us a closer idea about how these are acting in tandem. Network clustering was conducted with the MCODE plugin in Cytoscape that yielded three significant modules with cluster 1 (MCODE = 6.000), consisting of 6 nodes and 15 edges with dense interconnectivity (figure 3). Cluster 2 (MCODE = 4.000) also seemed to play an important part of the network as there were 4 nodes and 6 edges (figure 3). Furthermore, in cluster 3 (MCODE = 3.333) there were 4 nodes and 5 edges. Analysis of the clusters, there were ten hub genes in the PPI network: RPL13A, MED1, MRTO4, RPL12, EIF3G, EIF5A, CDH1, IGF1, CD44 and SOD1. The key gene CD44 is a cell surface glycoprotein linked with immune cell adhesion and migration. It's upregulated in neurodegenerative conditions and contributes to microglial activation and synaptic dysfunction in FTD [27]. The key gene SOD1 mutations lead to oxidative stress and protein misfolding, contributing to neurodegeneration. Some ALS patients with SOD1 mutations exhibit cognitive and behavioral changes consistent with FTD [28]. Previous study suggest that IGF1 dysregulation may exacerbate tau pathology and neuroinflammation [29]. Molecular docking studies aimed to evaluate the interactions and binding affinities across different target FTD proteins. Genistein revealed the strongest interaction towards the protein MED1, with docking scores of -10.3 kcal/mol. Similarly, Apigenin, Naringenin, Luteolin and Hesperetin showed better binding to MED1 with docking scores ranging from -9.1 to -9.4 kcal/mol. The ten complexes were RPL13A-epigallocatechin gallate complex, MED1-genistein complex, MRDO4-epigallocatechin gallate complex, RPL12-epigallocatechin gallate complex, EIF3G-epigallocatechin gallate complex, EIF5A-epigallocatechin gallate complex, CDH1-quercetin complex, IGF1-epigallocatechin gallate complex, CD44-epigallocatechin gallate complex, SOD1-luteolin complex of FTD target proteins-phytochemical with the highest binding affinity score were found. The phytochemical

epicatechin was identified as a lead compound owing to its low toxicological profile, favorable docking interaction towards MED1 with docking score -8.5 kcal/mol. This suggests its potential as a safer therapeutic drug target with promising efficacy. The physicochemical properties, ADME parameters, pharmacokinetic profiles and drug-likeness of all ten phytochemicals were assessed using SwissADME, providing insights into their overall suitability as therapeutic candidates. The phytochemical epigallocatechin gallate and resveratrol indicates strong potential to form complexes with FTD. The integration of gene expression analysis, PPI network construction, and molecular docking provides a multifaceted understanding of the molecular mechanisms driving FTD. This illustrates the potency of an integrated transcriptomic-to-target pipeline for rational therapeutic discovery in FTD.

4. CONCLUSION

Our study provides a comprehensive understanding of FTD by applying RNA seq analysis, PPI network construction, and molecular docking. Analysis of gene expression data from 12 patients initially identified 26,971 DEGs, which were further refined to 209 high-confidence DEGs. The Enrichment analysis using ShinyGO revealed that differentially expressed genes are primarily associated with protein synthesis, metabolic process, and intracellular transport. The activation of these pathways indicates an adaptive cellular response to managing the intracellular changes. The PPI network study emphasized hub genes including RPL13A, MED1, MRTO4, RPL12, EIF3G, EIF5A, CDH1, IGF1, CD44 and SOD1, which are closely interconnected clusters, enlightening the complex molecular interactions in FTD. Molecular docking revealed phytochemicals with potential therapeutic effects against hub proteins, epicatechin as a lead candidate due to its low toxicity and resveratrol and epigallocatechin gallate is a prominent drug for FTD, have less toxicity level, and have strong binding affinity to FTD target proteins. Based on the outcomes of this study, a systematic framework of pharmacophore design rules can be formulated to support the development of inhibitors against FTD.

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AUTHOR CONTRIBUTIONS

J. Jino Blessy: Conceptualization, Writing-review and editing.

Jessita Jesudas: Material preparation, data collection, experiment and analysis, writing-review and editing.

Latha. S: Material preparation, data collection, experiment and analysis, Writing-review and editing.

M. Harish: Material preparation, data collection, experiment and analysis, writing-review and editing.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the author(s).

ETHICS STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

All data generated and used during the current study are from publically available resources, i.e., NCBI Gene Expression Omnibus (GEO) with accession numbers cited in the manuscript; Protein Data Bank (PDB) for protein structure and PubChem for ligand structure.

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