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Common molecular and pathophysiological underpinnings of delirium and Alzheimer's disease: molecular signatures and therapeutic indications

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Abstract

Background Delirium and Alzheimer's disease (AD) are common causes of cognitive dysfunction among older adults. These neurodegenerative diseases share a common and complex relationship, and can occur individually or concurrently, increasing the chance of permanent mental dysfunction. However, the common molecular pathophysiology, key proteomic biomarkers, and functional pathways are largely unknown, whereby delirium is superimposed on AD and dementia.

Methods We employed an integrated bioinformatics and system biology analysis approach to decipher such common key proteomic signatures, pathophysiological links between delirium and AD by analyzing the gene expression data of AD-affected human brain samples and comparing them with delirium-associated proteins. The present study identified the common drug target hub-proteins examining the protein–protein interaction (PPI) and gene regulatory network analysis. The functional enrichment and pathway analysis was conducted to reveal the common pathophysiological relationship. Finally, the molecular docking and dynamic simulation was used to computationally identify and validate the potential drug target and repurposable drugs for delirium and AD.

Results We detected 99 shared differentially expressed genes (sDEGs) associated with AD and delirium. The sDEGs-set enrichment analysis detected the transmission across chemical synapses, neurodegeneration pathways, neuroinflammation and glutamatergic signaling pathway, oxidative stress, and BDNF signaling pathway as the most significant signaling pathways shared by delirium and AD. The disease-sDEGs interaction analysis highlighted the other disease risk factors with delirium and AD development and progression. Among the sDEGs of delirium and AD, the top 10 hub-proteins including ALB, APP, BDNF, CREB1, DLG4, GAD1, GAD2, GFAP, GRIN2B and GRIN2A were found by the PPI network analysis. Based on the maximum molecular docking binding affinities and molecular dynamic simulation (100 ns) results, the ALB and GAD2 were found as prominent drug target proteins when tacrine and donepezil were identified as potential drug candidates for delirium and AD.

Conclusion The study outlined the common key biomolecules and biological pathways shared by delirium and AD. The computationally reported potential drug molecules need a deeper investigation including clinical trials

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to validate their effectiveness. The outcomes from this study will help to understand the typical pathophysiological relationship between delirium and AD and flag future therapeutic development research for delirium.

Keywords Delirium, Alzheimer's disease, Common signaling pathways, Essential drug targets, Drug repurposing, Molecular docking simulation

Background

Delirium among older adults results in a higher economic burden for the family and caregivers and increases cognitive and physical dysfunctions [1, 2]. Due to mysterious and multifactorial properties, more than half of this neurologically complicated condition remains undiagnosed in intensive care units (ICU) [3–5]. This is mainly caused by inconsistency in delirium's definition and subsequent identification, and its complex molecular pathophysiology [6]. Delirium is triggered by multiple potential factors and causes, including the predisposing of older persons and potential frailty [7], pre-diagnosed cognitive impairment [8, 9], any psychological illness [10, 11], use of alcohol, and associated malnutrition [12, 13] other precipitating factors including chronic and acute medical conditions, severe diseases, trauma, major surgery and stress, and medications [4, 14]. The molecular pathophysiological mechanism of delirium involves different important signaling pathways and biological mechanisms. The oxidative stress-associated medical condition, hypoxia, is also considered a driver of delirium [15, 16]. Severe systemic cytokines-derived inflammation and peripheral neuroinflammation are widely reported and described as influencers and triggers of delirium [17, 18]. The functional disruption of brain neurotransmitter systems, including the dopamine, acetylcholine (ACh), and GABA associate pathways, and cholinergic synapses neurodegeneration, are closely connected with delirium [19, 20].

AD is an elusive neurodegenerative disease characterized by chronic and persistent cognitive impairment and is considered one of the major causes of dementia [21]. The molecular pathophysiology of AD reveals a wide range of neurobiological functions, including amyloid plaques, neurofibrillary tangles, neuroinflammation, oxidative stress, and damage to cholinergic neurons [22, 23]. The chemical synapse-associated pathways, notably axonal dystrophy, loss of pre-synaptic terminal loss, and dendritic spines loss, lead to the primary stage of AD, introducing memory dysfunction [24–26].

Both neurodegenerative diseases, delirium, and AD, have a complex interrelationship among their pathophysiological mechanisms in which they can act interactively, independently, and simultaneously [27]. Delirium has been treated as a vulnerability marker for AD which can alter the potential neuronal injury that leads to AD. The risk of incident dementia is considerably increased by delirium, frequently misdiagnosed or confused with AD. Studies suggest that 22%-89% of patients with dementia experience delirium during critical medical events [28]. The outcomes of studies examining delirium-related biomarkers in people with AD have been mixed. However, there are associations between delirium and AD-associated biomarkers, suggesting that the underlying AD pathology might impact the development of delirium [29, 30]. Moreover, AD patients with delirium are at greater risk of suffering negative consequences, including death or being admitted to a nursing home and experiencing hastened cognitive loss [31]. Glucose utilization and insulin signaling are significantly decreased in AD patients [32, 33], which are also linked with delirium [34, 35].

This introduction indicates a complex and mysterious relationship between the etiology of delirium and AD. Even though a few weakly powered genetic investigations have been carried out, no persistent potential genes linked to delirium risk have been found [35–37]. To better understand the underlying pathophysiology of both diseases, we consider that conducting an in-depth investigation is necessary to decipher the common biomarkers and signaling pathways shared by both diseases. In addition, the conjugial nature of these two neurological diseases increases the challenge of developing successful treatments for both. Although very few drugs are being prescribed or treating the symptoms of AD [21], no specific drugs are being considered for delirium treatment, despite ongoing research [38–41].

We have carried out an integrated bioinformatics and system biology analysis to explore the typical potential molecular relationship between delirium and AD, exploring the common molecular signatures and pathways and the repurposable drug investigation for delirium and AD. The study was designed to capture the delirium pathophysiology associated with AD and dementia. The study also sought to elucidate the typical pathophysiological association between delirium and AD/dementia. The outcomes of this study were hypothesized to generate evidence for more profound knowledge and understanding of delirium and AD as well as better therapeutic development, especially for delirium.

Materials and methods

We used delirium-associated proteins and AD-related proteins from different independent sources, to identify the common proteomic biomarker candidates. Then, a network-based analysis approach was used to decipher the pathophysiological processes and their regulators. The entire study diagram has been presented in Fig. 1.

Data sources and descriptions

Due to a lack of delirium-gene expression data, the current study searched for delirium-associated gene expression data. For this study, the delirium-associated protein dataset was collected through a systematic literature review (SLR) (please see the Supplementary File 1 for details about the SLR) and the Comparative Toxicogenomics Database (CTD, http://ctdbase.org/) [42], a widely used database for investigating chemical genes or proteins relationships. In our study, we searched the proteins from CTD against delirium. Combining these two protein datasets, we have compiled a delirium-associated total protein seed dataset containing 524 unique gene encoded proteins (Table 1).

The AD-associated gene expression transcriptomic dataset was downloaded from the National Center for Biotechnology Information Gene Expression Omnibus (NCBI-GEO) data repository. The AD-associated microarray dataset (GSE36980 [45]) contained 80 samples of human postmortem brains, of which 33 samples were from AD-affected brains, and others were from non-AD brains collected from the area of the frontal cortex, temporal cortex, and hippocampus of brains.

Identification of differentially expressed genes (DEGs) between AD and control samples

We used the well-established linear model method for microarray data (LIMMA) [46] to identify AD-associated DEGs. The conventional LIMMA procedure employs an empirical Bayes estimation procedure to 'moderate' the ordinary t-test statistic by adjusting the sample variance using the distribution of all standard deviations. The *p*-values were adjusted using the

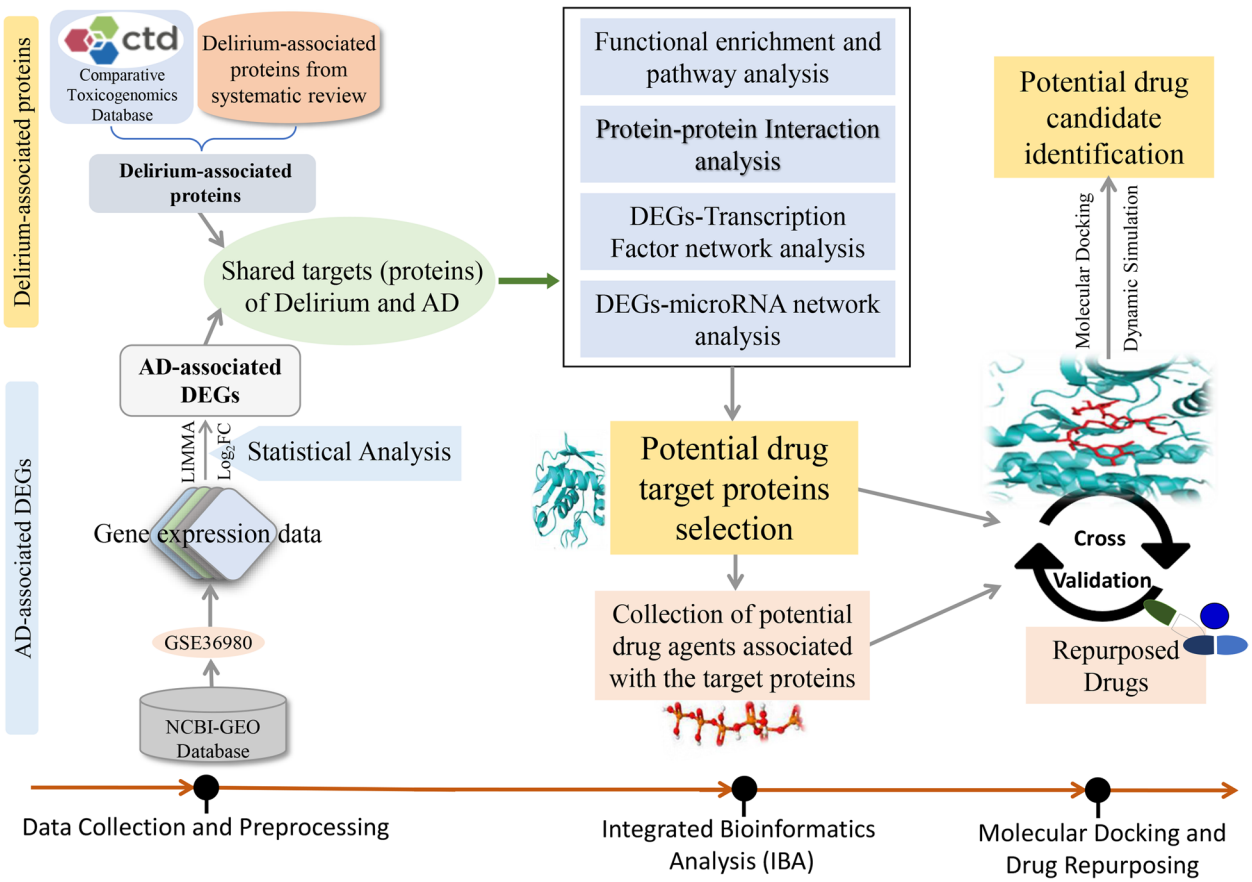


Fig. 1 This study's pipeline and flow diagram. The diagram illustrates the data collection process, integrated bioinformatics analysis, and the computational cross-validation of protein targets and repurposable drugs conjugates. This involves using molecular docking and dynamic simulation to identify the best lead pairs

Table 1 Description of delirium and AD-associated genomic datasets

Diseases	Data Sources	Databases	Period	# of collected gene encoded proteins	# of selected encoded proteins
Delirium	Through a SLR following PRISMA guidelines [43]	PubMed, Scopus, and EBSCOhost (CINAHL, Medline) databases	1st January 2000, to 31st December 2023	$A = 189$ unique genes were collected from 78 included studies	The final combined dataset, $P_D = (AUB)$
	Database search	Comparative Toxicogenomics Database (CTD) [42]	Accessed on 13 June 2023	$B = 350$ unique genes were collected having inference score > 40 [44]	
AD	Gene expression data (GSE36980) [45]	NCBI-GEO	Published in 2014	The dataset contained the expression data of 27,925 probes	Only the significant DEGs were included

Benjamini and Hochberg approach to control the multiple testing false discovery rate (FDR) [47]. Statistical significance was considered by an adjusted P-value < 0.05 and the $|\log_2(FC)| > 0.5$ (where FC means average fold change value) to identify the significant DEGs. The statistical tests were performed and implemented by the NCBI-GEO2R web tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/, accessed on 22 June 2023).

In this statistical test, the k^{th} gene (*where* $k = 1,2, \ldots, 27{,}925$) was considered as DEG altering between the AD and non-AD groups if the adjusted P_k-value < 0.05 with the $|\log_2({}_aFC_k)| > 0.5$ after controlling the FDR at 5% level or else, it was an equally expressed gene (EEG). If the k^{th} gene's adjusted P_k-value were less than 0.05 and $\log2({}_aFC_k) > 0.5$ and $\log2({}_aFC_k) < -0.5$, the gene was classified as either up- or down-regulated DEG, respectively. Here, the ${}_aFC_k$ represents the average normalized fold change value of the k^{th} gene's expression arrays concerning AD and non-AD samples which can be defined as ${}_aFC_k = \bar{x}_k/\bar{y}_k$ (where $\bar{x}_k and\ \bar{y}_k$ is the average value of the normalized expression array count of the k^{th} gene in AD and non-AD samples). For instance, if the $\bar{x}_k$=8 in the AD sample and $\bar{y}_k = 2$, then the ${}_aFC_k = 4$, indicating that the k^{th} gene is fourfold upregulated in AD compared to non-AD conditions and vice versa for downregulated genes.

Identification of shared DEGs (sDEGs) between AD and delirium

First, we collected DEGs between delirium and control samples from the literature. Suppose we denoted the delirium-associated DEGs encoded protein dataset by P_D and the AD-associated DEGs encoded protein dataset by Q_{AD}. Then we selected the shared DEGs (sDEGs) encoded protein dataset between delirium and AD by $Z = (P_D \cap Q_{AD})$ which has been used as the final combined analytical dataset for this study.

sDEGs-set enrichment (GSE) and annotation analysis

Gene ontology enrichment and functional signaling pathway analysis were conducted to identify the significant biological and molecular functions. The gene set enrichment and ontology analysis were performed using g:GOSt embedded in g:Profiler web server. The significant signaling pathways were retrieved from four databases including BioCarta, WikiPathways, KEGG, and Reactome. The significant signaling pathways and ontology terms were considered based on the adjusted P-value < 0.05 and the Benjamini and Hochberg [47] procedure for controlling FDR.

Identification of common key genes associated with delirium and AD

It is a common practice to investigate key proteins using protein–protein interaction (PPI) network analysis [48, 49]. In the current study, the STRING, a protein interactome database [50] was used to build the PPI network of the sDEGs encoded proteins between delirium and AD. The highly representative key common proteins, also known as hub-proteins, were retrieved using a topological investigation based on dual-metric measurement degree and betweenness on the PPI network using the Cytoscape [51]. ClueGO, a plug-in Cytoscape was used to create a network of functions for GO enrichment analysis utilizing the key hub genes under the statistical significance of P-value < 0.05.

Pre- and post-transcriptional gene regulatory network analysis

In this study, we have identified the pre- and post-transcriptional gene regulatory factors-microRNA (miRNA) and the transcriptional factor (TF) analyzing the interaction networks among the shared hub-genes encoded proteins and miRNAs and TFs, respectively. The interaction network of TFs and shared hub-DEGs was constructed using the JASPAR [52] TF database as well as the TarBase

V8.0 and miRTarBase [53, 54] miRNAs databases were utilized to construct the miRNA-hub-DEGs interaction network. The Network Analyst [55] online server revealed all the regulatory networks. Dual-metric measurement degree and betweenness were implemented in network analysis and visualization.

Disease-gene interaction analysis

The disease multimorbidity association of the sDEGs was investigated using the disease-gene interaction network. To discover this, the DisGeNET database [56, 57] was utilized and then Cytoscape was used to analyze the network under the dual-metric topological measurement condition degree and betweenness to capture the important and significant disease interactions with the hub-DEGs. The significant diseases were also highlighted which are highly comorbid with delirium and AD.

Drug repurposing and molecular docking

Since we observed the internal pathophysiological relationship, we attempted to identify the potential repurposable drugs against delirium and AD using computational molecular docking analysis. The FDA-approved drugs that are used for neurological treatment (like AD) have been retrieved from the online drug-repositioning tool and database Connectivity Map (CMap) [58] (Supplementary File 2). The drug repurposing database was used to search the drug molecules against hub-proteins. Only the top-ranked associated repurposable drug molecules were collected for the docking analysis with our hub-proteins. Then we performed molecular docking analysis between the top-ranked repurposable drug molecules and target proteins as *in-silico* validation. The binding affinity of the repurposable drugs with the top key common hub-proteins and TFs was investigated by a molecular docking simulation study. The 3D structures of the drug target key hub-proteins, TF proteins, and repurposable drugs were downloaded from the Protein Data Bank (PDB) [59] and SWISS-MODEL [60], a homology modeling-based database as well as from PubChem database [61]. The 3D drug target proteins were visualized and preprocessed by removing the co-crystal ligands and water molecules using Discovery Studio Visualizer 2019 [55], Swiss PDB Viewer Software, and MGLTools Software [62]. The energy minimization of the drug compounds was performed by applying the MMFF94 force field [63]. Molecular docking analysis was performed using AutoDockTools 4.2 [64] and AutoDock Vina [65]. For the drug-protein interaction, the highest docking score with the best-fit posture was considered to select the best repurposable drug for delirium as well as AD.

Molecular Dynamic (MD) simulations

The MD simulation was employed to explore the dynamic nature of the top-ranked protein-drug complex by using the YASARA Dynamics software [66], and the AMBER14 force field [67]. The simulation included the top four protein-drug complexes, ALB-Donepezil, ALB-Tacrine, GAD2-Donepezil, and GAD2-Tacrine from molecular docking analysis. The hydrogen bonding network of the target protein-drug complex was optimized and solvated using a TIP3P [68] water model in a simulation cell before simulation. Given a solvent density of 0.9971 gL-1, periodic boundary conditions were maintained. The ALB-Donepezil, ALB-Tacrine, GAD2-Donepezil, and GAD2-Tacrine complex contained 115,942, 114,258, 158,429, and 159,893 atoms respectively at the initial energy minimization process using the simulated annealing method with the steepest gradient approach (5000 cycles). Under physiological circumstances (298 K, pH 7.4, 0.9% NaCl) [69], every simulation was run with a repeated time-step method [70] utilizing a time-step interval of 2.50 fs. The linear constraint solver (LINCS) [71] algorithm was used to limit all bond lengths and SETTLE [72] was used for water molecules. The root-mean-squared deviation (RMSD) and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) binding free energy was calculated for up to 100 ns MD simulation under the Berendsen thermostat [73] and constant pressure. The analysis was performed using the default script of YASARA macro and SciDAVis software available at http://scidavis.sourceforge.net/. The MM-PBSA binding free energy was calculated by the following equation [74], using YASARA built-in macros using AMBER 14 as a force field, with larger positive energies indicating better binding [75],

$$\text{Binding free Energy} = E_{\text{potReceptor}} + E_{\text{solvReceptor}} + E_{\text{potLigand}} + E_{\text{solvLigand}} - E_{\text{potComplex}} - E_{\text{solvComplex}}$$

Results

Identification of DEGs between AD and control samples

The statistical analysis revealed a total of 2257 DEGs (i.e., 534 up-regulated and 1723 down-regulated genes) with their official gene symbol identified from the gene expression data analysis. The significant upregulated and downregulated genes and their mean expression difference (AD vs. non-AD) plot are shown in Fig. 2A and B respectively.

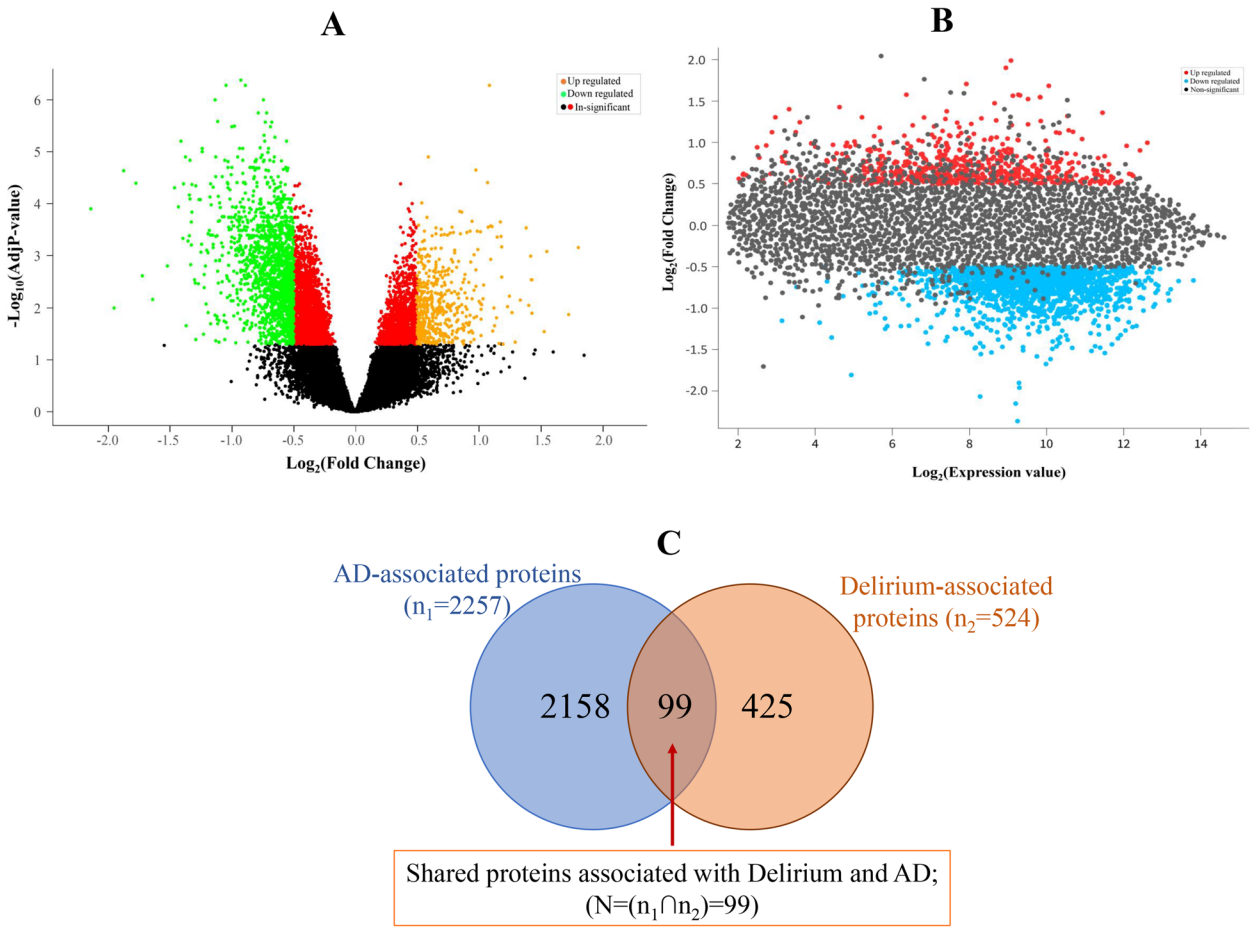


Fig. 2 Selection of shared DEGs (sDEGs) between AD and delirium**. A** The volcano plot denotes the DEGs associated with the AD. The green dots represent significantly downregulated genes, and the orange dots are for upregulated genes. **B** The mean-difference plot of their expression in AD and Non-AD samples. The red color dots are significantly upregulated and the blue color dots show the downregulated genes. **C** The Ven diagram shows the datasets that have been collected from different diseases and then combined. The common genes, $N = 99$, have been utilized in this study for further downstream analysis

Identification of DEGs between delirium and control samples

A total of 189 unique delirium-associated genes and their encoded proteins were found from 78 included studies (Table 1) in the comprehensive SLR. Under the cutoff inference score (> 40), the CTD database revealed a total of 350 delirium-associated gene encoded proteins. Then, the two protein datasets from separate sources (SLR and CDT database) were combined (mathematical union) to create an integrated delirium-associated protein dataset with 524 unique proteins (Table 1).

Identification of sDEGs between AD and delirium

A total of 99 common shared DEGs (sDEGs) between delirium and AD were identified as displayed in Fig. 2C. The distribution of up and downregulated genes with the delirium-associated genes shows that a total of 79 downregulated genes and 20 upregulated genes were common between delirium and AD (Table 2). The shared genes and their encoded proteins were utilized to identify the common regulatory biomolecules and common pathophysiological relationships between delirium and AD in the downstream analysis.

sDEGs set enrichment analysis with GO-terms and pathways

Based on the statistical significance criteria (AdjP-value < 0.05) under the controlled FDR, the top significant functional pathways and enriched GO shared by the common genes of delirium and AD are shown in Fig. 3. The bubble plots in Fig. 3A and B have been constructed from g:GOSt server, representing the top significant GO terms (Fig. 3A) and the functional pathways (Fig. 3B). The analysis revealed the significant GO terms including the biological process (BP) molecular functions (MF)

Table 2 The common shared proteins between delirium and AD

Delirium and AD-associated common genes (*N*=94)	AD-associated up regulated genes (*n*=20)	AD-associated down regulated genes (*n*=79)
	ABCC2, ABCC3, AGT, ALB, CALCA, CASP8, CCL5, CP, EDN1, FSTL1, GFAP, GJA1, GNAI2, IL12A, MICA, MUC1, NR0B2, NUPR1, SLC47A2, VCAM1	ACHE, ALDOA, AP1S1, APP, ASNS, ATP1A1, BACE1, BDNF, BNIP3, CACNA1C, CADM3, CAMK2D, CAMKK2, CDK5, CFL1, CHRM1, CHRM2, CHRM4, CHRNB2, CREB1, CREM, CX3CL1, CYCS, DLG4, DRD1, ENO1, FNDC4, GABRA1, GABRA4, GABRB2, GABRB3, GABRG2, GAD1, GAD2, GAP43, GOT2, GRIN2A, GRIN2B, GSR, HAPLN1, HOMER1, HRH1, HSP90AA1, HSPA8, HTR2A, H2AFZ, INSIG2, MAN1A1, MAP2, MAPK1, MAPK8, MTOR, NPY, NREP, NSF, ODC1, PDYN, PER2, PID1, PLCB1, PPIA, PRKCB, PTEN, RGS4, RTN4R, SLC17A6, SLC17A7, SLC1A1, SLC2A3, SMPD1, SNCA, STX1A, SYN1, SYP, TAC1, THY1, VEGFA, VGF, VLDLR

Note: The official gene symbols are presented here

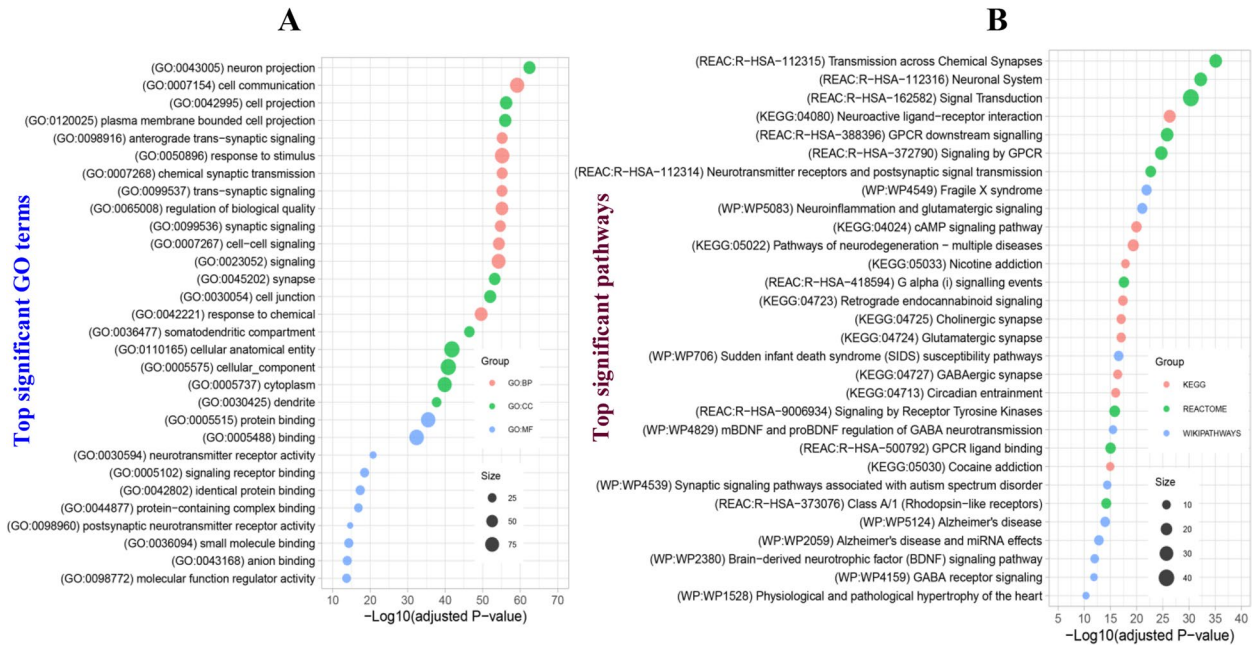


Fig. 3 The sDEGs-set enrichment analysis results with GO-terms and pathways, **A** represents the top significant GO terms and **B** shows the significant functional pathways, respectively that were retrieved from the g:GOSt server. The GO and pathway terms and IDs have been added to the y-axis and the x-axis represents the -log10(AdjP-value). The figure legend size indicates the number of enriched genes in a particular GO term and pathway

and cellular components (CC). The most significant GO terms are represented in Fig. 3A. According to the GO enrichment analysis, the chemical synaptic transmission, cell communication, memory, anterograde trans-synaptic signaling, response to stimulus, protein-binding activity, neurotransmitter receptor activities, and other synoptic signaling activities are highly enriched and are significant GO terms commonly shared by delirium and AD-associated genes (Fig. 3A).

The entire neurotransmission system along with the different signaling pathways were highly enriched pathways among the common genes of delirium and AD. The enriched functional pathways commonly linked with delirium and AD that have been identified, are mostly associated with the nervous system and their signaling synapse mechanism as well as the chemical reaction of receptors with ligand chemical molecules (Fig. 3). For example, among the most significant enriched pathways shared by delirium and AD, the transmission across chemical synapses, pathways of neurodegeneration-multiple diseases, signal transduction, neuroinflammation, and glutamatergic signaling pathway, brain-derived neurotrophic factor (BDNF) signaling pathway, fragile-X syndrome, oxidative stress, and hypoxia associated pathways are the most important. The detailed analysis output of GSE and functional pathway analysis has been provided in Supplementary File 3.

PPI network analysis of sDEGs

The PPI network of the sDEGs-encoded proteins revealed the most highly connected shared key proteins which are also known as drug-targeted hub-proteins. Among the signature proteins, three key proteins (ALB, AGT and GFAP) were AD-associated upregulated, and the others were found downregulated. The top 10 hub-proteins including ALB, APP, BDNF, CREB1, DLG4, GAD1, GAD2, GFAP, GRIN2B and GRIN2A were found in the PPI network (Fig. 4) and utilized for further downstream analysis.

Figure 4 demonstrated that the two upregulated and five downregulated gene-encoded proteins were not interconnected with any other proteins in the network (Fig. 4). With the PPI network, we observed the engagement and association of the signature proteins with delirium and AD. The ClueGO-derived GO network also revealed the association of mental dysfunction-related pathways and biological function which were consistent with the overall GSE analysis (Supplementary Fig. 1).

The sDEGs regulatory network analysis

The common sDEGs-TFs and DEGs-miRNAs interaction network is presented in Fig. 5. The gene-TFs regulatory network showed the key regulatory TF including the FOXC1, GATA2, and FOXL1. The highly connected

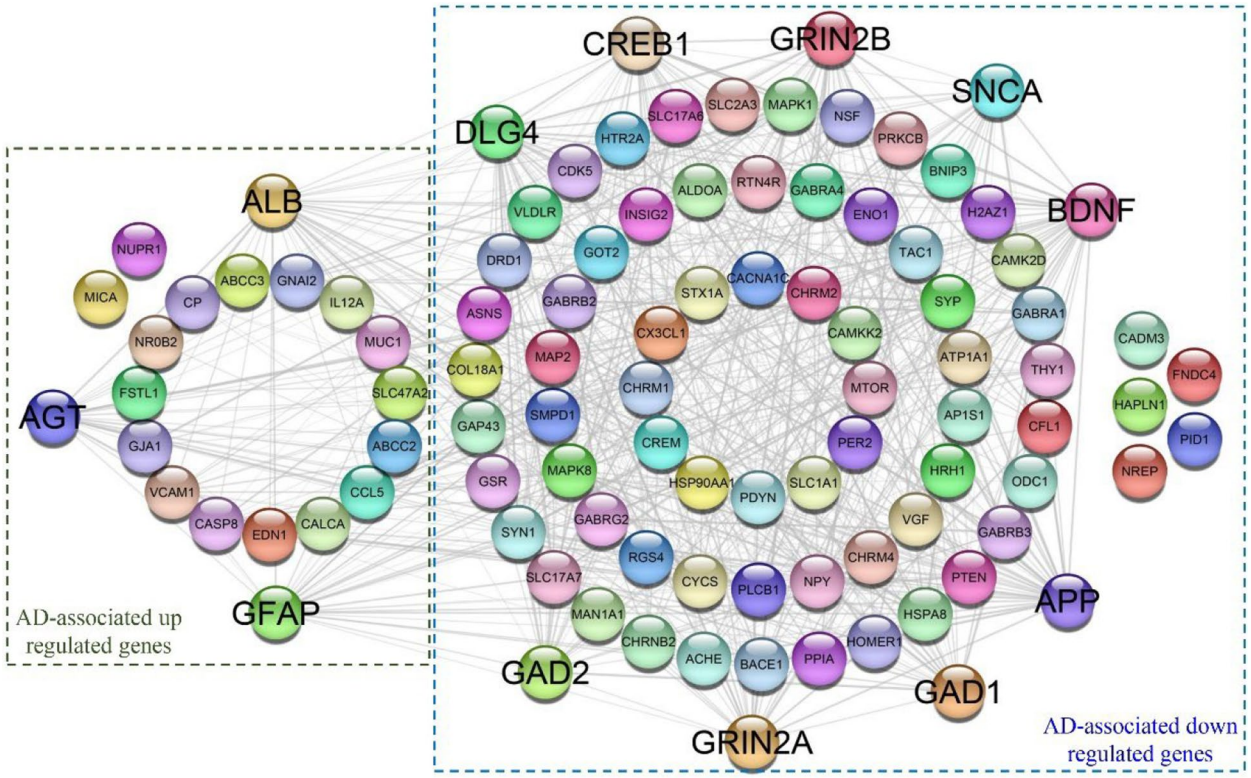


Fig. 4 The PPI network of sDEGs-encoded proteins shared by delirium and AD. The hub-proteins were shown with large node names. The AD-associated up and downregulated genes are indicated separately in the figure

TFs are represented in Fig. 5A with the green diamond nodes. The common DEGs-miRNA network analysis revealed the potential key miRNAs namely, miR-16-5p, miR-1-3p, and miR-34a-5p (Fig. 5B).

Disease-gene network fetched the key neurological disorders associated with the shared DEGs

The interaction network analysis revealed the associated diseases with the common hub-genes associated with delirium and AD. The interaction network is displayed in Fig. 6. Most importantly Alzheimer's disease 2, dementia, cognitive disorders, Parkinson's disease and disorders, and brain diseases were the most significant diseases associated with common hub-genes (Fig. 6). The disease interaction and the association indicate that neurological complications and disorders are highly comorbid with delirium and AD development.

The hub-proteins guided drug discovery

In this part the top 10 common hub-DEGs encoded hub-proteins and 3 key TFs (total = 13) proteins for molecular docking simulation were considered. The 3D-structure of the 10 hub-proteins including ALB, BDNF, GRIN2B, CREB1, APP, DLG4, GFAP, GAD1, GRIN2A and GAD2 were collected from the PDB database using the codes 7VR0, 1BND, 7EU8, 5ZKO, 1AAP, 6SPV, 6A9P, 3VP6, 5H8Q, and 2OKK respectively. The 3D structure of GATA2 TF-protein was also downloaded from the PDB database using the code 5O9B whereas the other two 3D structures of TFs FOXC1 and FOXL1 were collected from the SWISS-MODEL using UniProt with IDs Q12948 and Q12952. The 3D structure of eight FDA-approved neurological drugs was collected from the PubChem database and used for molecular docking against the drug receptor proteins associated with delirium and AD. Based on the binding affinity scores (kcal/mol) between the receptor proteins and the drug agents, the top repurposable drug molecules and the most effective drug targets were confirmed. The affinity scores were ordered and plotted in a heatmap against the receptor proteins in Fig. 7. In our investigation, the ALB and GAD2 were found as leading and prominent drug target receptor proteins associated with delirium and AD where donepezil (with ALB: -8.8 kcal/mol and with GAD2: -9.0 kcal/mol) and tacrine (with ALB: -8.0 kcal/mol) showed the maximum binding affinity scores with the two target proteins compared to others lead components (Fig. 7). The docking analysis revealed that most of the drug agents performed well with

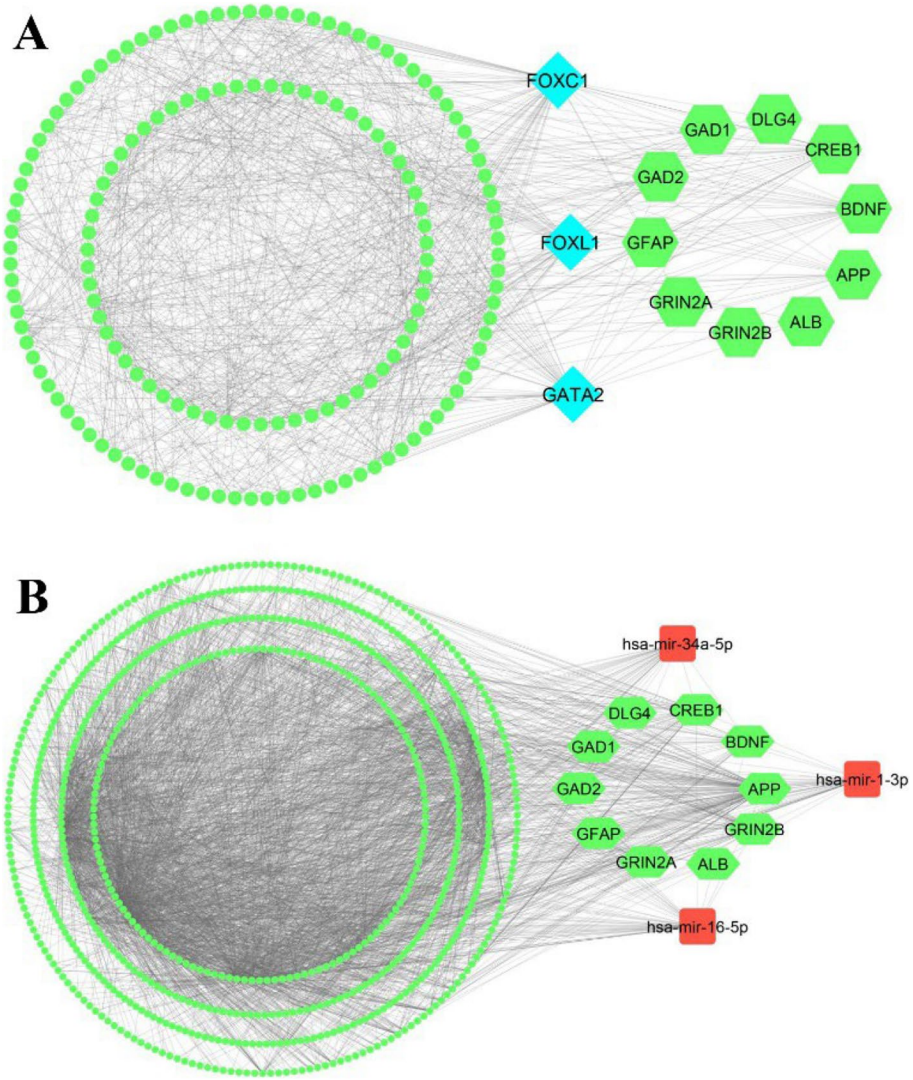


Fig. 5 The gene regulatory network analysis of (**A**) shared DEGs-TFs, (**B**) shared DEGs -miRNA. The red color square-shaped and green color diamond-shaped nodes represent the miRNAs and TFs respectively and other nodes represent the common DEGs

the target proteins which resulted in the GRIN2B protein also docking well with citicoline (-7.5 kcal/mol) and tacrine (-7.6 kcal/mol) drug molecules. The details docking score matrix is provided in Supplementary File 4.

Table 3 represents the gist of the molecular docking interaction summary of our top drug target proteins (ALB and GAD2) with the prominent drug candidates (Tacrine and Donepezil) scoring maximum binding affinity. The best docking pose (3D) of the drug molecule, the interaction complex (2D), and the adjacent interacting residues along with the bond and distance (Å) are reported in Table 3. The interaction pose of the target receptor and drug molecule indicates that the drug molecule fits on the target protein's pocket with significant binding affinities.

MD simulation

The complex stability analysis through MD simulation between the top-ranked drug target and drug molecules showed significant stability between the initial drug target and complex moving variation over the 100 ns MD-PBSA simulation. Fig. 8A shows the calculated RMSD for all four protein-drug complexes ALB-Donepezil, ALB-Tacrine, GAD2-Donepezil, and GAD2-Tacrine.

The system provided an average RMSD of 2.185 Å (Range: 0.428 Å to 3.148 Å), 2.255 Å (Range: 0.449 Å to 3.177 Å), 7.540 Å (Range: 0.483 Å to 8.434 Å) and 7.590 Å (Range: 0.504 Å to 8.727 Å) for the ALB-Donepezil, ALB-Tacrine, GAD2-Donepezil and GAD2-Tacrine respectively. The GAD2 complex structures fluctuated for the drug molecules up to 15 ns and became stable during

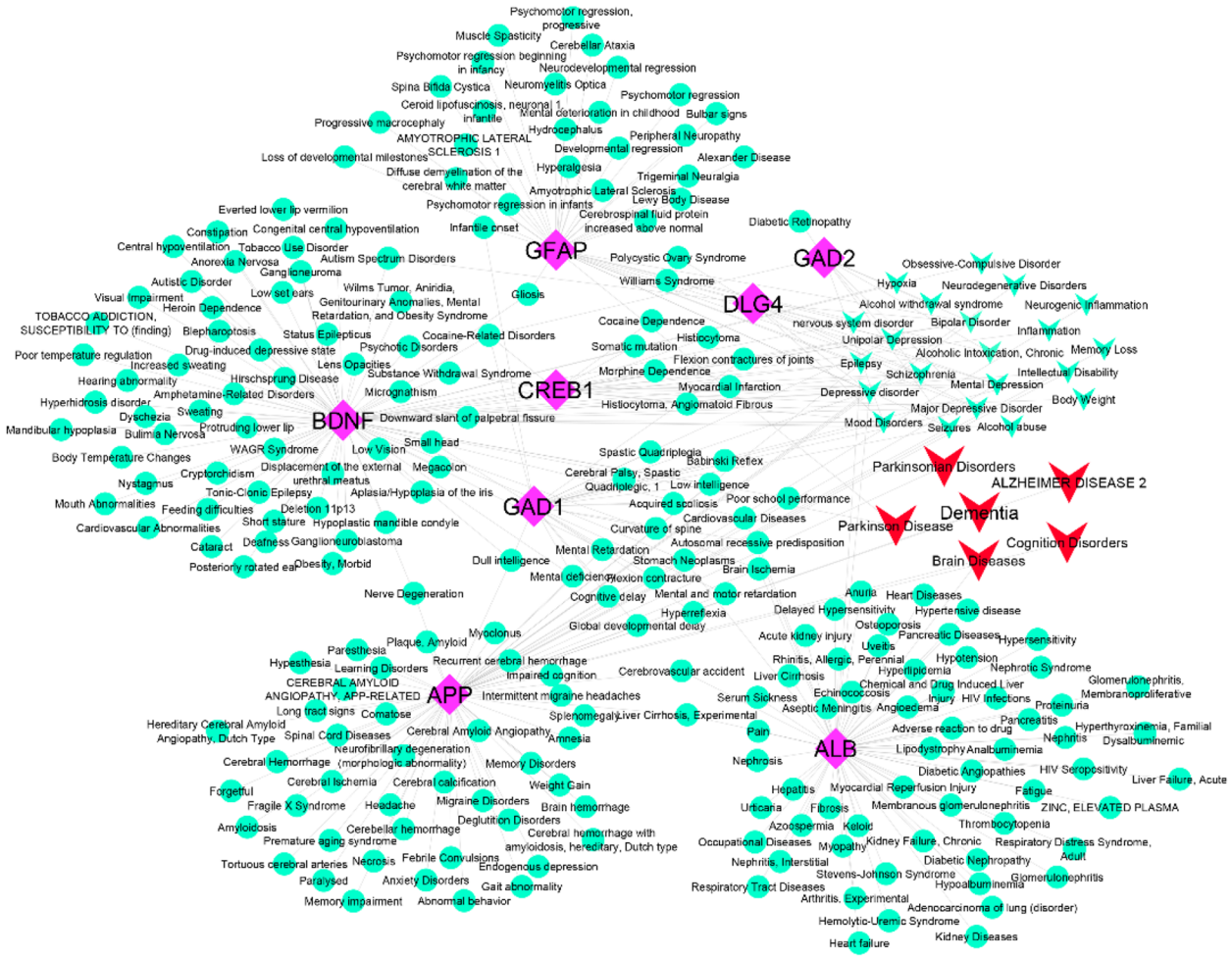


Fig. 6 The disease-gene interaction network represents the significant comorbidities associated with delirium and AD development. The hub-proteins are pink diamond-shaped nodes. The highly significant comorbidities are in V-shaped nodes. The most critical diseases are marked by red colored V-shaped

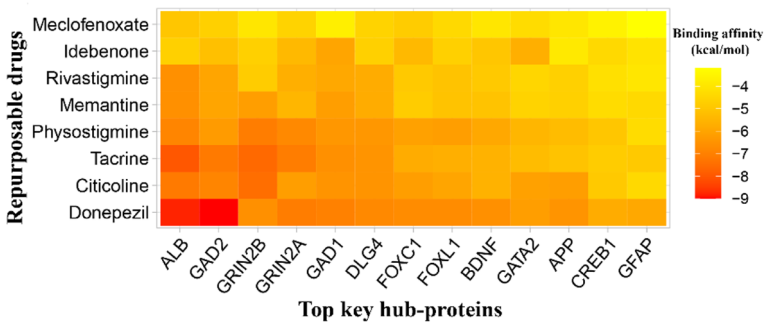
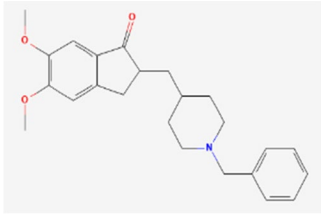
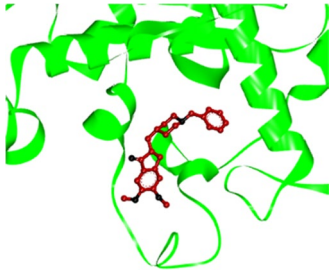
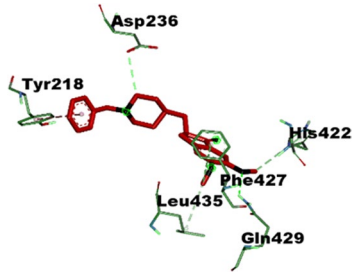
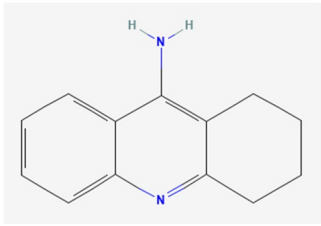
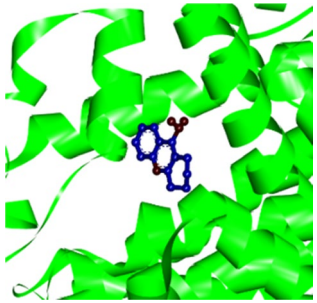
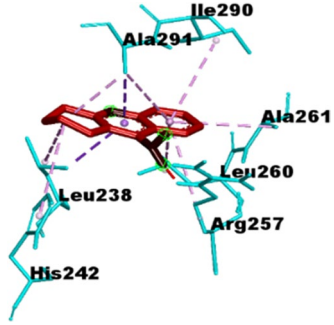
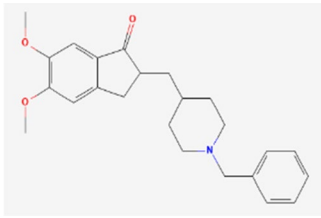
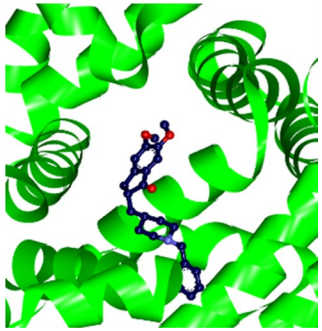
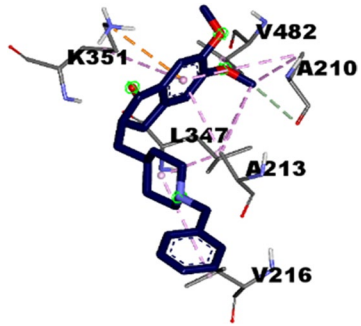


Fig. 7 AutoDock Vina findings for molecular docking simulation analysis between the key drug target hub-proteins encoded from hub-DEGs and the TFs. The redder color in the heatmap indicates the stronger binding affinity between the drug target proteins and the drug molecules. The repurposable drugs used for neurological treatments are on the Y-axis and the drug target proteins are represented on the X-axis. The top-scored repurposable medicines and the drug targets are presented in red color

Table 3 The interacting characteristics and outcomes of the top-ranked drug molecules and drug target key proteins. The Hydrogen Bond (HB), Electrostatic Bond (EB), and Hydrophobic Bond (HpB) are presented in the 4th column along with their bond distance in the last column

Potential Target Proteins	2D Drug Structure and Binding Affinity (kcal/mol)	3D Pose View of Interaction Complex	Target-ligand Interaction Complex	Interacting Residues	Bond Types	Distance (Å)
 GAD2	 Donepezil (-9.0 kcal/mol)			GLN429 ASP236 TYR218 LEU435 HIS422 PHE427	HB HB HpB HpB HpB HpB	2.30 3.57 4.80 4.01 4.78 5.15
GAD2	Donepezil (-9.0 kcal/mol)					
 ALB	 Tacrine (-8.0 kcal/mol)			LEU238 ALA291 LEU238 ALA291 HIS242 ARG257 LEU260 ALA261 ILE290 ALA291	HpB HpB HpB HpB HpB HpB HpB HpB HpB	3.96 3.74 4.99 3.86 4.89 5.21 4.76 4.99 4.59 5.13
ALB	Tacrine (-8.0 kcal/mol)					
 ALB	 Donepezil (-8.8 kcal/mol)			ALA210 LYS351 ALA210 ALA213 ALA213 VAL216 LEU347 VAL482 ALA210 ALA213 LYS351	HB EL HpB HpB HpB HpB HpB HpB HpB HpB HpB	3.46 4.14 3.72 3.99 4.34 5.40 4.25 4.33 5.40 3.89 4.48
ALB	Donepezil (-8.8 kcal/mol)					

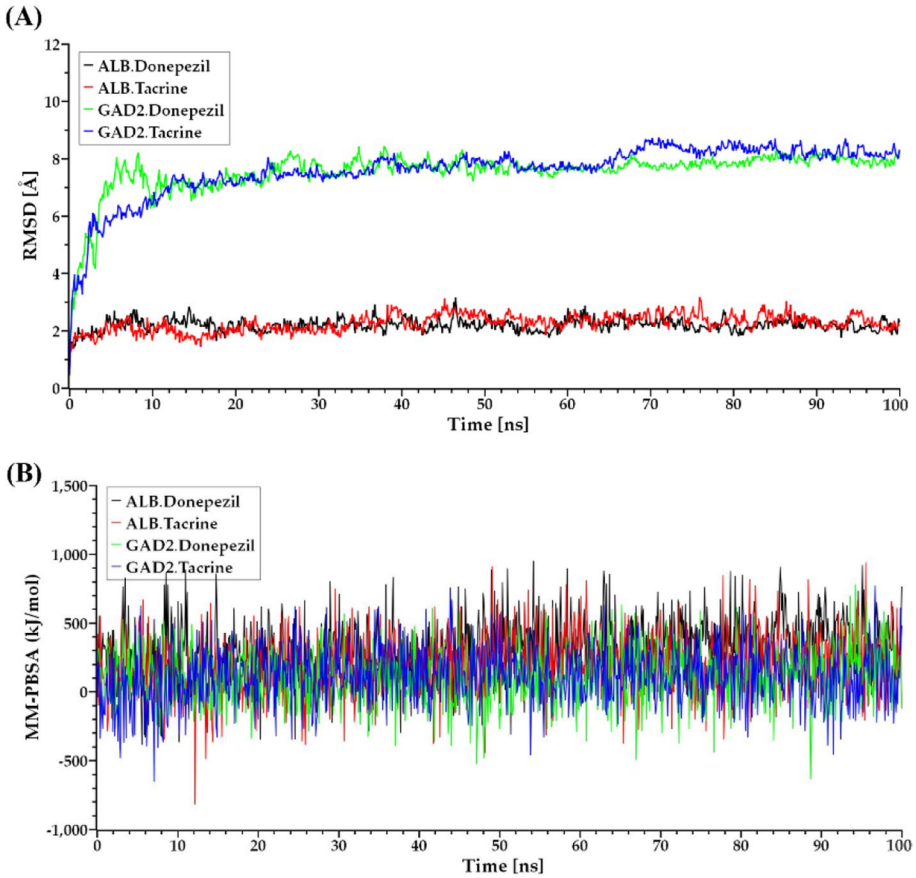


Fig. 8 **A** The RMSD (in Å) plot of backbone atoms (C, C and N) for every single docked complex over the MD simulation. **B** The MM-PBSA analysis computed binding free energy for every complex during the simulation which indicates the alteration of binding stability. The positive values indicate better binding. In both figures, black, red, green, and blue lines are for ALB-Donepezil, ALB-Tacrine, GAD2-Donepezil and GAD2-Tacrine complex respectively

the remaining simulation. The RMSD plot indicates that the ALB complexes were more stable with the reported drugs during the entire simulation than GAD2. The MM-PBSA binding energy for four complexes shows the average binding energy 307.061 kJ/mol, 192.694 kJ/mol, 105.350 kJ/mol, and 111.743 kJ/mol for ALB-Donepezil, ALB-Tacrine, GAD2-Donepezil, and GAD2-Tacrine complex respectively (Fig. 8B).

Discussion

This study has focused on deciphering the interactions and pathophysiological pathways shared by the shared key proteomic biomarkers between delirium and AD. The significant AD-associated DEGs were compared with the delirium-associated genes to identify the common genomic signatures and found 99 common genes between the two conditions. Among the common genes shared by delirium and AD, it was observed that the common genes are differentially expressed in AD where 20 genes were upregulated and 79 were downregulated.

The shared functional pathways between the two diseases show the epidemiological and internal pathophysiological relationship between them. For instance, transmission across chemical synapses is one of the most important and significant pathways shared by the common genes for transferring chemical neurotransmitters across the neurons [76]. One neuron can quickly and efficiently stimulate or inhibit the neuronal activity of another neuron via chemical synapses. The neurodegeneration pathways caused by multiple diseases play a significant role in enhancing the progression of memory loss and ultimately developing distinct brain-dysfunctional diseases like AD, dementia, and Parkinson's disease [77]. As the common genes of delirium and AD were significantly enriched in this pathway, it indicates that delirium is also associated with permanent cognitive and/or motor dysfunction, supported by different studies [27, 78]. Another significant shared pathway was the neuroinflammation and glutamatergic signaling pathway. Neuroinflammation is considered the primary process

that triggers delirium under any critical medical condition. The neuronal and synaptic dysfunction is changed due to the neuroinflammatory, which is after the abnormal neurobehavioral and mental disorder symptoms [79, 80]. The common genes also enriched the BDNF signaling pathway, which plays a vital role in the pathogenesis of neurodegenerative diseases by accelerating TrkB-mediated neuronal events [81]. Oxidative stress is a significant mechanism linked to chronic inflammation and age-related disorders that may also be connected to delirium pathogenesis [82]. Among the other important pathways, the glutamatergic signaling in the central nervous system, and cholinergic functional pathways are crucial pathways associated with delirium and AD development [83]. Studies show that anesthesia drugs during surgery can directly act on the central cholinergic system which leads to postoperative delirium and mental dysfunction [84]. Drugs used for anesthesia could be one of the major factors for postoperative delirium [85, 86] and it demands rigorous research to decipher the molecular interaction of the drug molecules with the delirium-associated target proteins. The pathway indicates the interrelationship of neuronal activity, cognitive impairment, and conditions like AD and dementia. Investigating these pathways enhances the influence of delirium on chronic brain diseases.

The PPI network analysis of sDEGs-encoded proteins revealed the top key hub-proteins where most of them came from the down-regulated genes. Among the top ten hub-proteins, the *ALB* and *GFAP* were upregulated from an AD perspective and others were downregulated. The expression profiles of the common genes between delirium and AD indicate that delirium superimposed on AD might also be triggered by the downregulated genes associated with delirium. Among the key hub-genes, albumin (*ALB*) is considered a potential biomarker to diagnose delirium among surgical patients [87]. The studies support that lower albumin levels are highly associated with delirium development postoperatively [88–91]. The astrocyte-expressed glial fibrillary acidic protein (*GFAP*) [92], is used to identify astrocytosis in cases of neurodegeneration and is associated with traumatic brain injury that might involve mental illness like AD. Among the other key downregulated hub-genes, *BDNF, GRIN2B,* and *CREB1* are highly connected with the other genes. The increased protein level of BDNF is associated with delirium diagnosis and quick recovery from postoperative delirium [93–95] whereas it has been found in lower levels among AD patients [96]. Studies suggested that genetic variation of the *GRIN2B* gene might be associated with the molecular mechanism of AD [97, 98] and its molecular variations may offer a crucial tip for understanding the molecular causes of AD [99]. The GSE analysis of the common genes revealed the cMAP-signaling pathway, mainly enhanced by *CREB1* genes associated with mental depression [100]. The pathway enrichment analysis of the hub-genes using ClueGo revealed the important pathways, namely BDNF-TrkB signaling pathway, NMDA glutamate receptor activity, synaptic signaling pathways, fragile X syndrome, cocaine addiction, and amphetamine addiction (Supplementary Fig. 1). The pathways are aligned with the overall GSE analysis results. The top significant hub-genes play a substantial role in delirium development and AD. The genes might influence higher delirium occurrence with the concurrence of critical medical conditions of AD-affected patients. Therefore, the hub-genes can serve as a potential biomarker to diagnose delirium and could be treated as a potential therapeutic target for drug development.

The gene regulatory network (GRN) analysis detected some key transcription factors (TFs), namely FOXC1, GATA2, and FOXL1, as the transcriptional regulators of shared key genes as well as key miRNAs, notably miR-16-5p, miR-1-3p, and miR-34a-5p as the post-transcriptional regulators. Neuroinflammation and neuronal death are linked to the FOXC1 TF whereas, neurodegenerative consequences including Alzheimer's disease, dementia, and Parkinson's disease are strongly correlated with neuroinflammation [101–103]. The key TF GATA2 is associated with the Neuroglobin (NGB) gene expression when the neural disease (like AD) is connected with the expression level of the NGB gene [104]. The results suggest that FOXL1, a transcriptional repressor regulates the development of the central nervous system in Zebra fish [105] and is also associated with AD [106] as reported in previous studies. The miR-16-5p miRNA plays a significant role in neuronal cell apoptosis in AD [107, 108]. The miR-1-3p is directly involved in Fas Apoptotic Inhibitory Molecule (FAIM) expression which is closely associated with the physiological and pathological processes of Alzheimer's and Parkinson's diseases [109]. Different clinical and molecular studies suggested that the plasma level of miR-34a-5p miRNA is being considered as an early biomarker [110, 111], which also decreases oxidative stress and apoptosis condition by inhibiting β-amyloid (Aβ)-induced neurotoxicity in AD [112]. The EGR1 TF regulates the AChE expression contributing to cholinergic function alteration in AD development [113] which may contribute to delirium as well. The SP1 is known as a pro-inflammatory TF that regulates the AD causal genes including amyloid precursor protein (APP) and β-secretase (BACE1) gene expression [114, 115]. Besides the TF, the miR-103 and miR-107 are directly associated with neurodegenerative diseases like AD and neurodegeneration-associated pathways which play an important role in delirium as well [116, 117]. Since the regulatory

molecules are associated with the common hub-genes of delirium and AD their functionalities are directly involved with neurological complications and pathophysiology and they might have close connectivity with delirium occurrence and development.

The disease-gene interaction network revealed the comorbidities associated with delirium and AD. The common genes associated with diseases contain mental dysfunctions and disorder-related complications that might influence delirium and AD development, or they could boost medical complications in patients with delirium and AD. The comorbidity analysis revealed alcoholic intoxication which could lead to delirium. The results are consistent with the GSE and ClueGO GO group analysis results including cocaine and nicotine addiction pathways. Studies suggested that the alcohol withdrawal/alteration could result in delirium [118–120] where the key hub-genes may have been involved.

Repurposable drugs are considered a great source of treatment in any emergency. In this aspect, the FDA-approved neurological drugs especially used for AD treatment were retrieved from the CMap database. The computational molecular docking simulation study was implemented to investigate the drug target properties of our proposed drug target proteins which might be investigated further for more effective therapeutic development against delirium and AD. The docking analysis revealed that the drug molecules significantly interact with the target protein pockets. Among the drug target proteins, ALB and GAD2 were found to be highly interacting drug targets compared to others. Tacrine and donepezil showed the highest binding affinity scores which indicate the primary properties of drug candidate molecules. Tacrine was approved by the FDA as one of the first drugs to treat AD [121] although it has been prescribed with limitations for easing AD symptoms [122, 123]. Studies suggest that tacrine-related drugs could be a potential source for AD treatment [124]. Tacrine also showed effective improvement in treatment of cholinergic delirium [125]. On the other hand, donepezil, an acetylcholinesterase (AChE) inhibitor has already been investigated as a drug for neurological or psychiatric complications including delirium and AD [126, 127]. Studies supported that the donepezil showed strong significant binding affinity with AChE which triggers the cholinergic pathways on AD therapeutics [128–130]. Clinical improvement was investigated by using the donepezil for the Alzheimer dementia patients [131]. Research indicates that donepezil has being investigated as a potential medication for treating delirium [132, 133]. Donepezil medication also improved the critical condition of dementia patients and reduced the delirium development [134]. The computational analysis in this study revealed consistent findings about donepezil as a prominent therapeutic candidate which will influence the therapeutic development for delirium as well. The 100 ns MD-based simulation revealed the stability of the reported protein-drug complexes suggesting significant structural consistency according to the physical law [135]. Based on the prominent properties of our proposed drug molecules, further clinical and pharmacological research is needed for effective therapeutic development against delirium and AD targeting the key drug target biomolecules reported in this study.

Strength and limitations

The current study utilized AD-associated gene expression data collected from human brain samples, which could explain a greater genomic signature than blood and other tissue samples. This study collected a comprehensive delirium-associated gene encoded protein dataset which included an SLR and an independent CTD database that can be explored for further delirium research. The study outlined key drug-target biomolecules including hub-proteins, TFs, and miRNAs which are jointly functional in delirium and AD. These important biomarker genes will open a new dimension of research in diagnosis, prognosis, and therapeutic development. The proposed repurposable neurological drugs showed significant binding affinity against the therapeutic targets which augers well for therapeutic development for delirium and AD.

While the study identified common molecular signatures, it may not fully elucidate the intricate biological pathways linking delirium and AD. Further research is needed to gain a comprehensive understanding of the shared pathophysiological processes. There might be some inconsistencies about the common molecular functionality between delirium and AD, since AD is highly accountable for dementia whereas delirium is generally a short-term cognitive impairment. Therefore, the common pathophysiological functions between delirium and AD would be considered when they act conjugately. In this aspect, the identified key proteins and their functionalities may differ for independent delirium episodes and their subtypes. Predominantly, both neurological conditions are highly prevalent among older patients and have a great chance to be comorbid to each other when occur together. Although the present study reported several important key proteins, further research needs to be conducted to identify a single biomarker of delirium and AD. The study's suggestions for drug repurposing for delirium might be influenced by bias or limited data availability. Rigorous clinical trials are needed to validate the effectiveness and safety of repurposed drugs. Moreover, the delirium associated gene expression data should

be generated to elucidate the genetic engagement on disease pathophysiology.

Implementation

This study aimed to understand the pathophysiological relationship between delirium and AD along with identifying potential drug targets and repurposable drug candidates. The outcomes will significantly contribute to a better understanding of the common key genomic biomarkers and shared signaling pathways associated with delirium and AD. This will enrich the pathophysiological knowledge about delirium and AD, their cooccurrence, and also delirium superimposed on dementia. Healthcare policies should prioritize biomarker-based early detection of individuals at risk for both delirium and AD. The comorbidity analysis associated with delirium and AD reported significant symptoms which will contribute to healthcare practitioner knowledge for good practice of diagnosis, monitoring, and management of delirium and AD. Healthcare systems might adopt integrated care models that bring together specialists in geriatric medicine, neurology, psychiatry, and genetics to comprehensively address the overlapping risk factors and underlying genetic connections between delirium and AD. Finally, if the reported repurposable drugs are considered for in-depth clinical investigation for further validation, they will be a potential source for enhancing precision medicine and the process of therapeutic development against delirium and AD. This information could guide personalized risk assessment and early intervention strategies.

Conclusion

The literature supports that delirium individually is a common phenomenon among older patients and significantly increases the economic burden, mortality, and morbidity. When AD-affected patients develop delirium in a medical setting, the consequences are more severe. This study identified several significant biomarker proteins such as ALB, BDNF, GRIN2A, and GAD2 as potential candidates for diagnosis, prognosis, and therapeutic development against delirium and AD. The transmission across chemical synapses, neurodegeneration, signal transduction, neuroinflammation and glutamatergic signaling pathway, BDNF signaling pathway, fragile-X syndrome, oxidative stress, hypoxia, and cholinergic functional pathways were most significantly associated with delirium and AD-associated pathophysiology. Moreover, the MD analysis and simulation study (100 ns) among the common hub-proteins and neurological repurposable drugs provided the top-ranked drug candidates (tacrine and donepezil) and the prominent drug target proteins (ALB and GAD2), significant for therapeutic development against delirium and AD. The findings were consistent with and supported by the outcomes of previous studies as we discussed earlier. The findings of this study will strengthen the molecular research foundation for delirium and AD pathophysiological mechanisms. Furthermore, the reported drug targets and the drug molecules will enhance efficient therapeutic development for delirium and AD by further validation under in-depth pharmacological and clinical research.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05289-3.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.

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Authors' contributions
MPM conceptualized, collected data, analyzed, and wrote the first draft of the study. KA, JG, NHM, and RAM supervised the study as well as revised and edited the manuscript.

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Availability of data and materials
All the data used in this study is publicly available secondary data.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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