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A Systems Biology Approach to Understanding Delirium Pathophysiology and Identifying Natural Compounds for Potential Therapeutic Purposes

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Abstract

Delirium is an acute neurocognitive disorder marked by disruptions in attention, cognition, and awareness, particularly prevalent among older and critically ill patients. This study applies a systems biology framework to dissect the molecular underpinnings of delirium and evaluate natural compounds for potential therapeutic roles. Through bioinformatics analyses, key biomarkers related to delirium, including IL6, AKT1, JUN, APP, and PPARGC1A, were identified, implicating pathways tied to neuroinflammation, oxidative stress, and synaptic function. Traditional Chinese medicine (TCM) compounds were mapped to these biomarkers, revealing candidates that may modulate inflammatory and metabolic processes central to delirium. The study highlights the potential of compounds like melatonin, dehydroepiandrosterone (DHEA), resveratrol, progesterone, and paclitaxel to provide multi-targeted approaches for delirium management. Findings underscore the role of integrating natural compounds with conventional treatment to address delirium's complex pathophysiology. This research offers new insights into delirium's molecular landscape and introduces avenues for novel, natural compound-based therapeutic interventions.

Keywords
Delirium; systems biology; natural compounds; neuroinflammation; traditional Chinese medicine (TCM)

1. Introduction

Delirium is a complex neurocognitive disorder characterized by an acute disturbance in attention, awareness, and cognition, often resulting from underlying medical conditions. According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), delirium presents with a fluctuating course. It can manifest in various forms, including hyperactive, hypoactive, and mixed types [1, 2]. The prevalence of delirium is notably high among older adults, particularly in hospital settings, where it can affect up to 42% of inpatients and 70% of long-term care residents [3, 4].

The hyperactive subtype of delirium is marked by increased psychomotor activity, agitation, and heightened arousal. Patients may exhibit restlessness, hallucinations, and aggressive behavior, which can complicate their clinical management [5, 6]. In contrast, hypoactive delirium is characterized by reduced motor activity, lethargy, and decreased responsiveness. This subtype is often underdiagnosed due to its subtle presentation, leading to significant challenges in identification and treatment [7]. Studies indicate that hypoactive delirium is the most prevalent form, accounting for approximately 56.3% of cases in older populations [8]. The mixed subtype includes features of both hyperactive and hypoactive delirium, presenting a fluctuating clinical picture that can further complicate diagnosis and management [9].

The impact of delirium on patient outcomes is profound and multifaceted, varying significantly by subtype. Hyperactive delirium is associated with a higher risk of falls and other complications, while hypoactive delirium is linked to increased mortality rates and poorer overall outcomes [7, 10]. Beyond subtype-specific risks, delirium generally leads to increased morbidity and mortality, prolonged hospital stays, and higher healthcare costs [11, 12]. Patients often experience accelerated functional decline, particularly in the elderly population, which can lead to long-term cognitive impairment and diminished quality of life [13, 14].

Delirium is a significant concern in clinical settings, particularly among older adults and critically ill patients. Its prevalence varies widely depending on the patient population and the healthcare setting. For instance, studies indicate that delirium affects up to 80% of patients in intensive care units (ICUs), particularly those who are mechanically ventilated. In contrast, the prevalence in non-ICU hospitalized patients is considerably lower, estimated at less than 15% [11, 15]. In emergency departments, delirium is also prevalent, with rates reported as high as 14% among admitted patients [16]. The COVID-19 pandemic has further exacerbated the situation, with delirium being reported in less than 50% of non-ICU patients and up to 80% of ICU patients infected with the virus [17, 18]. It highlights the urgent need for effective screening and management strategies across various healthcare settings.

Identifying and managing delirium subtypes is crucial for improving patient care, as treatment strategies differ significantly based on the presentation. While antipsychotic medications may be employed in cases of hyperactive delirium, hypoactive delirium typically requires a more nuanced

approach focusing on environmental modifications and supportive care [19, 20]. Early intervention is critical, as studies have demonstrated that patients who resolve delirium during hospitalization have significantly better long-term outcomes than those who do not [14]. It is especially relevant in surgical contexts, where delirium has been linked to an increased risk of postoperative complications and poor functional recovery [21, 22].

Pharmacological treatments for delirium primarily involve the use of antipsychotics, such as haloperidol and atypical antipsychotics, to manage severe agitation and psychotic symptoms associated with hyperactive delirium [23, 24]. While these medications may provide symptomatic relief, their use is often controversial due to concerns about side effects, including sedation, extrapyramidal symptoms, and potential cardiovascular risks [25, 26]. Many pharmacological interventions for delirium treatment have not demonstrated significant improvement over placebo in terms of response rates. However, some specific interventions (like haloperidol plus lorazepam and haloperidol alone) have shown superiority, and other medications have been effective for delirium prevention. The efficacy of pharmacological interventions is therefore highly dependent on the specific agent and the context (treatment vs. prevention) [24].

Recent guidelines recommend using the lowest effective doses of antipsychotics and combining them with non-pharmacological strategies to enhance patient care [27, 28]. However, the reliance on pharmacological treatments can lead to a cycle of over-medication, particularly in populations such as older people, who may be more susceptible to adverse drug reactions [23, 29]. Additionally, there is a growing body of evidence suggesting that medications like dexmedetomidine may be more effective than traditional antipsychotics for managing delirium. However, further research is needed to establish standardized treatment protocols [25, 30].

Natural compounds have long been recognized for their therapeutic potential in medicine, serving as a source of inspiration for drug discovery and development. These compounds, derived from plants, fungi, and other natural sources, exhibit various biological activities that can be harnessed for multiple therapeutic applications. This overview discusses the role of natural compounds in therapeutic settings, highlighting their mechanisms of action, clinical applications, and the associated challenges.

Natural compounds possess diverse mechanisms of action, making them valuable in treating various diseases. For instance, bioactive compounds such as zerumbone, derived from the plant Zingiber zerumbet, have been shown to induce the expression of cytokines like interleukin-12, which plays a crucial role in immune response [31]. It highlights the potential of natural compounds in modulating immune functions and combating infections. Natural products have historically played a pivotal role in drug discovery. A review covering the period from 1981 to 2014 highlighted that a significant proportion of FDA-approved drugs are derived from natural sources or inspired by natural compounds [32]. For example, approximately 63% of anticancer drugs are natural products or semi-synthetic derivatives of natural compounds [33]. It underscores the continued relevance of natural products in the pharmaceutical industry, particularly in developing novel therapeutic agents.

Moreover, traditional medicine systems, such as Traditional Chinese Medicine (TCM), have utilized natural compounds for centuries, emphasizing their efficacy in treating various ailments, including cancer [34]. The active ingredients in these natural products often exhibit multitargeting capabilities, which can enhance their therapeutic effects while minimizing side effects [35]. This pleiotropic nature of natural compounds makes them attractive candidates for drug development. Despite their therapeutic potential, the clinical application of natural compounds faces several

challenges. One significant obstacle is their low bioavailability, particularly for lipophilic compounds, which complicates drug administration and efficacy [36]. Researchers are exploring modifications to enhance the druggability of natural products to address this issue, such as developing novel drug delivery systems [36]. Traditional Chinese medicine (TCM) has demonstrated the efficacy of various herbal compounds in treating conditions such as functional constipation and cancer. Clinical trials have shown that TCM compounds can provide significant therapeutic benefits, emphasizing the importance of integrating traditional knowledge with modern medical practices [37, 38].

Furthermore, the complexity of natural products, often consisting of multiple bioactive components, poses challenges in standardization and quality control. Rigorous characterization of these compounds is essential to ensure consistency in therapeutic effects [39].

Delirium management encompasses a range of treatment strategies, primarily categorized into pharmacological and non-pharmacological approaches. Both methods aim to address the underlying causes of delirium, alleviate symptoms, and improve patient outcomes. However, each approach has limitations, necessitating a comprehensive understanding of their efficacy and challenges.

Insights gained from studying complex biological systems can inform the design of more effective therapeutic strategies. For instance, understanding the intricate signaling networks involved in diseases such as cancer can lead to the development of targeted therapies that disrupt specific pathways, potentially improving treatment outcomes. Moreover, personalized medicine, which may be accompanied mainly by systems biology approaches, allows tailored treatments based on an individual's unique biological makeup [40].

This study integrates systems biology approaches to decipher delirium's complex pathophysiology and identify potential therapeutic natural compounds. By identifying significant biomarkers, mapping key molecular pathways, and systematically screening natural compounds, we aim to advance our understanding of delirium mechanisms while discovering promising therapeutic interventions. The research emphasizes ultimately working toward evidence-based natural treatment strategies for delirium prevention and management.

2. Materials and Methods

This study employed a comprehensive bioinformatics approach to identify differentially expressed genes (DEGs) and elucidate their potential interactions and implications in the context of delirium. The methodology was structured into several key phases: data acquisition, DEG identification, protein-protein interaction (PPI) network construction, significant gene identification, natural compound extraction, and relationship analysis using DisGeNET.

2.1 Data Acquisition and Identification of Differentially Expressed Genes (DEGs)

The primary data source utilized in this study is the Gene Expression Omnibus (GEO) dataset GSE163943. In this study, we used publicly available transcriptomic data from the Gene Expression Omnibus (GEO) database (Accession ID: GSE163943) to investigate the molecular mechanisms associated with postoperative delirium (POD). The dataset includes expression profiles from peripheral blood samples of 8 patients, divided into two groups: four individuals diagnosed with POD and four control volunteers without delirium. It focuses on long non-coding RNAs (lncRNAs) and messenger RNAs (mRNAs), offering a comprehensive view of the transcriptomic changes in POD.

This dataset was selected based on its clinical relevance, comprehensive transcriptomic data, and the inclusion of validated differentially expressed genes, all of which ensure the reliability of our analysis. GSE163943 thus provides a strong foundation for our systems biology approach to understanding the molecular mechanisms underlying postoperative delirium better. The dataset contains gene expression profiles crucial for identifying DEGs associated with specific conditions. The GEO2R tool was employed to perform differential expression analysis, allowing for comparing gene expression levels between different experimental conditions. GEO2R facilitates the identification of DEGs by applying statistical methods to the expression data, thus enabling researchers to pinpoint genes that exhibit significant changes in expression levels [41]. Using GEO2R, the GSE163943 dataset was analyzed to identify DEGs. This tool employs the limma package, which is widely recognized for its effectiveness in analyzing microarray data. The analysis was conducted with a significance threshold set at an adjusted p-value of <0.05, ensuring that only the most statistically significant DEGs were considered for further analysis [41]. The identified DEGs are a foundation for subsequent analyses, including PPI network construction and natural compound extraction.

2.2 Protein-Protein Interaction (PPI) Network Construction

To explore the interactions among the identified DEGs, we utilized the STRING plugin within Cytoscape 3.10.3. STRING is a robust database that provides information on known and predicted protein-protein interactions, integrating data from various sources, including experimental and computational predictions [42]. The PPI network was constructed by inputting the DEGs into the STRING database, which generated a network visualizing the interactions among these proteins. This network highlights potential biological pathways and interactions that may be relevant to the pathophysiology of delirium.

2.3 Identification of Significant Genes

To identify the top 10 significant genes from the PPI network, we employed the CytoHubba plugin of Cytoscape 3.10.3. This plugin offers multiple algorithms for ranking nodes based on their connectivity and importance within the network. Twelve different algorithms, including MCC, DMNC, MNC, Degree, EPC, BottleNeck, EcCentricity, Closeness, Radiality, Betweenness, Stress, and ClusteringCoefficient, were applied to ensure a comprehensive evaluation of the significance of each gene within the network [43]. The top 10 genes identified through this process were selected for further investigation regarding their potential roles in delirium.

2.4 Gene Ontology, Pathway, and Functional Enrichment Analyses of DEGs

In this study, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses on differentially expressed genes (DEGs) using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) web-based tool were performed (https://david.ncifcrf.gov/) [44, 45]. DAVID provides a comprehensive suite of functional annotation tools that facilitate the interpretation of large gene lists by identifying enriched biological functions and pathways associated with the DEGs.

The GO enrichment analysis categorizes genes into three main domains: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). This classification allows for a systematic understanding of the biological roles of the DEGs. For instance, in our analysis, we utilized a false discovery rate (FDR) threshold of <0.05 and a minimum gene count of >2 to ensure the reliability of the enriched terms. The KEGG pathway analysis complements the GO analysis by mapping the DEGs to known biological pathways, thereby elucidating the molecular interactions and regulatory networks in which these genes are involved. The DEGs were first uploaded to the DAVID platform for enrichment analyses, where the tool automatically annotates the genes based on the latest genomic databases. The results of the GO and KEGG analyses were then visualized using appropriate bioinformatics software, which aids in the interpretation of the data.

2.5 Relationship Analysis Using DisGeNET

Finally, to explore the relationships between the identified genes and delirium, we utilized the DisGeNET database. DisGeNET is a comprehensive platform that integrates information on gene-disease associations, making it an invaluable resource for understanding the genetic basis of diseases [46]. By querying the database with the identified DEGs, we uncovered relevant associations between these genes and delirium, thus providing a clearer picture of the molecular underpinnings of this condition.

2.6 Natural Compound Extraction

After identifying significant DEGs, we utilized the BATMAN-TCM (Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine) to extract natural compounds associated with these genes. BATMAN-TCM is specifically designed to analyze the molecular mechanisms of Traditional Chinese Medicine (TCM) and provides a platform for linking compounds to their biological targets [47]. By inputting the identified DEGs, we retrieved potential natural compounds that may interact with these genes, offering insights into delirium's therapeutic options.

3. Results

3.1 Data Acquisition and Identification of Differentially Expressed Genes (DEGs)

Differential expression analysis was performed using GEO2R with default parameters to identify significant genes between the experimental conditions. A total of 6536 DEGs were identified using a statistical threshold of $p < 0.05$. This substantial number of DEGs suggests widespread transcriptional changes in response to the experimental conditions, reflecting the complex molecular mechanisms involved in the biological process under investigation. These significant genes provide a comprehensive foundation for subsequent functional enrichment analysis and pathway mapping to understand the underlying biological mechanisms better.

3.2 Protein-Protein Interaction (PPI) Network Construction

The identified DEGs were subjected to PPI network analysis using Cytoscape version 3.10.3 with the STRING plugin. The generated PPI network comprised 2677 nodes and 16244 edges, representing the molecular interactions between the differentially expressed genes. This network

analysis provides a visual and systematic framework for understanding the complex relationships and functional connections among the genes, enabling the identification of key molecular players and potential regulatory hubs within the biological system under study.

3.3 Identification of Significant Genes

To identify the most critical hub genes within the PPI network, we employed the CytoHubba plugin in Cytoscape 3.10.3. A comprehensive analysis was performed by 12 different topological algorithms, including MCC, DMNC, MNC, Degree, EPC, BottleNeck, EcCentricity, Closeness, Radiality, Betweenness, Stress, and ClusteringCoefficient, to ensure robust identification of key network nodes (shown in Figure 1). Through this rigorous multi-algorithmic approach, 12 genes were consistently identified as hub genes across all algorithms: ERBB2, IL6, DLG4, AKT1, HIST1H4I, CALML4, JUN, APP, PPARGC1A, CALML5, HRAS, and IL4. These shared hub genes likely represent crucial molecular regulators in the biological process under investigation, as their significance was confirmed through multiple independent network centrality measures.

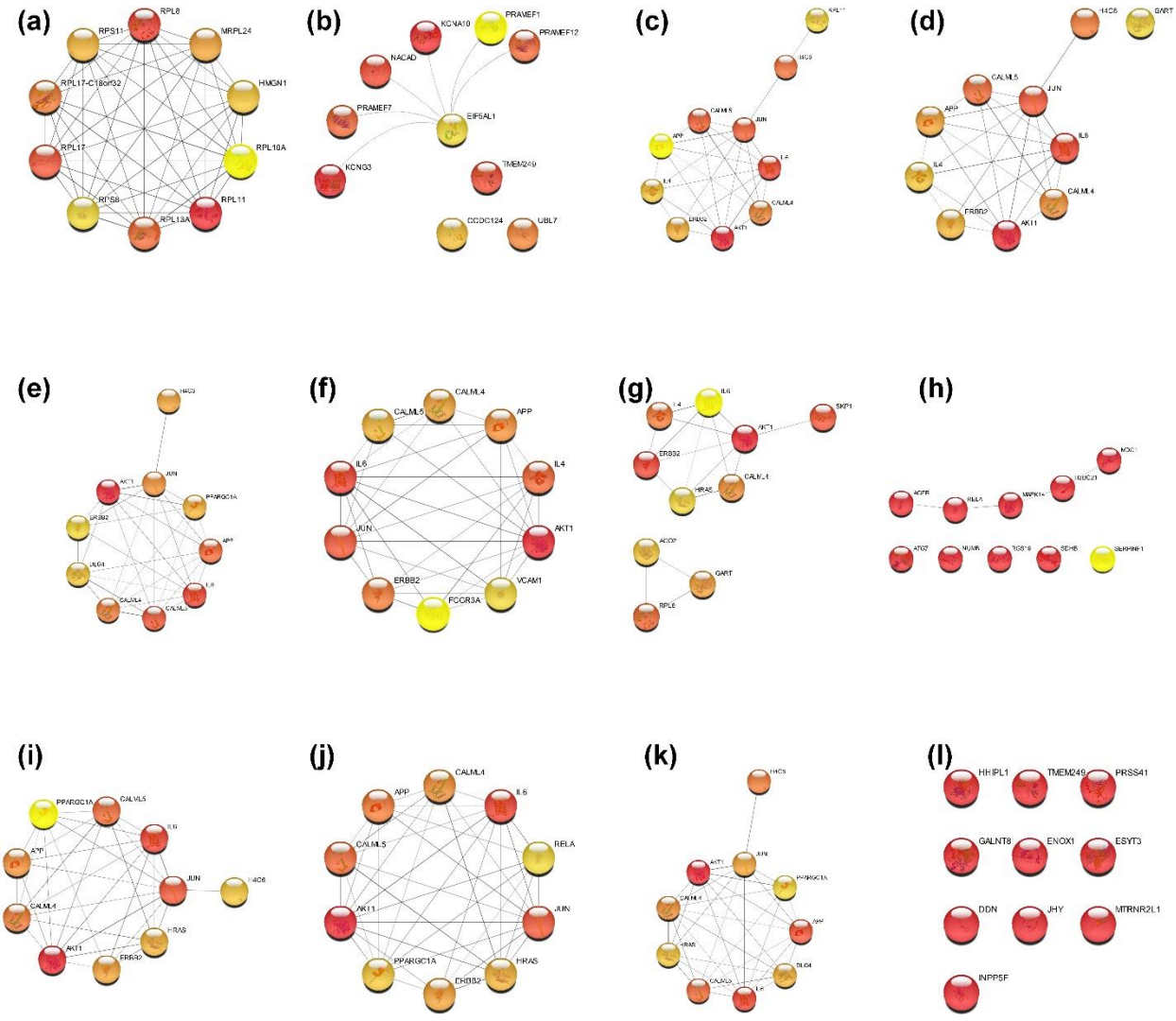

Figure 1 Outputs of twelve different algorithms of CytoHubba, including (a) MCC, (b) DMNC, (c) MNC, (d) Degree, (e) EPC, (f) BottleNeck, (g) EcCentricity, (h) Closeness, (i) Radiality, (j) Betweenness, (k) Stress, and (l) ClusteringCoefficient.

3.4 Gene Ontology, Pathway, and Functional Enrichment Analyses of DEGs

To relate the biological processes (BP), cellular components (CC), molecular functions (MF), and KEGG pathways listed to delirium syndrome, we need to explore how each may contribute to the underlying pathophysiology of delirium. Delirium is often linked to systemic inflammation, oxidative stress, neurotransmitter imbalances, and disrupted cellular signaling. Biological Processes (BP) GO: 0045944~Positive Regulation of Transcription by RNA polymerase, GO:0010628~Positive Regulation of Gene Expression, GO: 0033138~Positive Regulation of Peptidyl-Serine Phosphorylation, Cellular Components (CC): GO: 0031982~Vesicle, GO: 0005911~Cell-Cell Junction, Molecular Functions (MF): GO: 0019899~Enzyme Binding, GO: 0008134~Transcription Factor Binding, KEGG Pathways hsa04933: AGE-RAGE Signaling Pathway in Diabetic Complications, hsa05142: Chagas Disease, hsa04625: C-type Lectin Receptor Signaling Pathway. Further details are demonstrated in Figure 2.

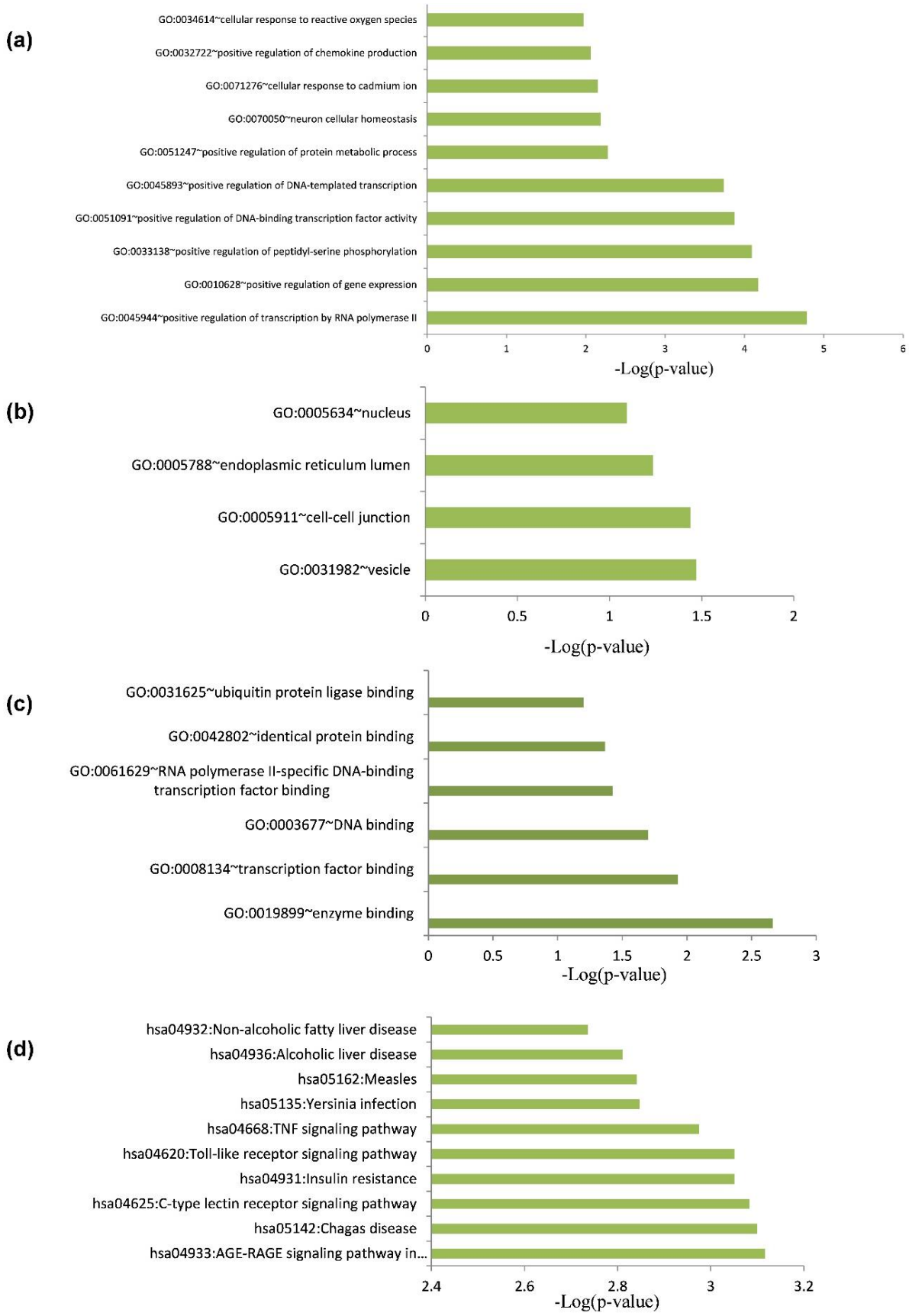

Figure 2 The (a) biological processes (BP), (b) cellular components (CC), and (c) molecular functions (MF) for GO analysis, as well as the (d) KEGG pathway assessment considering significant biomarkers identified for delirium.

3.5 Relationship Analysis Using DisGeNET

The five common biomarkers identified as related to delirium syndrome on the DisGeNET website, IL6, AKT1, JUN, APP, and PPARGC1A, are known to play key roles in various biological pathways associated with neuroinflammation, oxidative stress, and neuronal function, all of which are important in the development and progression of delirium. The interplay between these biomarkers highlights several key pathways central to delirium. Neuroinflammation is driven by IL6 and influenced by JUN, a critical component of delirium, and contributes to altered neurotransmission and neuronal damage. PPARGC1A and AKT1 are involved in maintaining cellular and mitochondrial health. Their dysregulation contributes to oxidative stress, particularly damaging to the aging brain, and can accelerate delirium onset. APP and its associated processing pathways influence synaptic function and neurotoxicity, particularly in inflammation and oxidative stress. Altered APP processing can exacerbate cognitive decline and delirium symptoms, especially in neurodegenerative contexts.

3.6 Natural Compound Extraction

Given these biomarkers' roles in delirium, traditional Chinese medicine (TCM) ingredients that target key molecular pathways - particularly IL6, AKT1, JUN, and PPARGC1A - may hold potential for therapeutic interventions. IL6, as a central inflammatory mediator in delirium pathogenesis, is especially relevant since elevated IL6 levels have been consistently associated with delirium development and severity. Compounds that can modulate inflammatory pathways through IL6 and JUN inhibition, enhance mitochondrial function (PPARGC1A), and protect synaptic health (APP) may provide multifaceted benefits in managing delirium symptoms and preventing exacerbation of cognitive decline. The detailed results on matched identified genes, enriched TCM ingredients, and enriched herbs, along with literature PubMed references, are listed in Table S1, Table 1, and Table 2, respectively.

Table 1 Enriched ingredients in BATMAN-TCM.

PubChem_ID	TCM ingredients	Enrichment_ratio	Associated_Genes
896	Melatonin	17.12	AKT1(known target)|JUN(0.72*)|PPARGC1A(0.72)|APP(0.72)
5881	Dehydroepiandrosterone	16.1	IL6(known target)|AKT1(known target)|JUN(0.72)|PPARGC1A(0.72)
445154	resveratrol	13.08	IL6(known target)|JUN(known target)|PPARGC1A(known target)|AKT1(known target)|
5994	progesterone	8.93	IL6(known target)|JUN(known target)|AKT1(known target)|PPARGC1A(0.72)
5352019	Paclitaxel [USAN:INN:BAN]	22.77	JUN(0.96)|PPARGC1A(0.72)|APP(0.72)|AKT1(0.72)
11869537	9beta-Estrone	17.04	JUN(0.72)|PPARGC1A(0.72)|AKT1(0.72)
5870	estrone	15.85	JUN(0.72)|PPARGC1A(0.72)|AKT1(0.72)
6013	testosterone	13.43	IL6(known target)|AKT1(known target)|JUN(0.72)|PPARGC1A(0.72)
444795	Retinoic acid	13.41	IL6(known target)|AKT1(known target)|JUN(0.94)|PPARGC1A(0.72)
9860744	(3S,10R,13S)-3-hydroxy-10,13-dimethyl-1,2,3,4,7,8,9,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-one	13.01	JUN(0.72)|PPARGC1A(0.72)|AKT1(0.72)
5754	hydrocortisone	12.88	IL6(known target)|APP(0.76)|JUN(0.72)|PPARGC1A(0.72)|AKT1(0.72)
16401562	MEGxm0_000472	8.84	JUN(0.72)|PPARGC1A(0.72)|AKT1(0.72)
44584733	Punicalagin	218.57	PPARGC1A(known target)|IL6(known target)|AKT1(known target)
25201694	25201694	117.38	APP(known target)|IL6(known target)|JUN(known target)
942	942	85.66	APP(known target)|AKT1(known target)|JUN(known target)
107985	triptolide	48.76	AKT1(known target)|IL6(known target)|JUN(known target)
5281767	(1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one	38.42	APP(known target)|AKT1(known target)|IL6(known target)|JUN(known target)
53477783	beta-estradiol 3-sulfate	22.16	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
6291	mestranol	20.65	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
31307	triamcinolone	19.69	APP(0.76)|PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)

16757678	HMS3369D13	19.69	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
5756	estriol	19.15	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
5998	Estra-1,3,5(10)-triene-3,17-diol, (17-alpha)-	18.98	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
11870431	Dihydrofolliculin,(S)	18.98	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
68570	17alpha-Estradiol	18.81	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
1548955	Zuclomiphene	15.97	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
2949	MLS003115428	14.44	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
5035	raloxifene	14.02	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
51340201	SCHEMBL9888462	13.21	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
5701998	(10R,13S,17S)-17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one	13.07	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
10343085	CHEMBL21987	11.57	APP(0.68)|JUN(0.66)
100171446	(2R)-4-(2,4-difluorobenzoyl)-N-(2-phenylethyl)-2,3-dihydro-1,4-benzoxazine-2-carboxamide	11.52	APP(0.66)|JUN(0.66)
644019	cannabidiol	10.8	PPARGC1A(known target)|IL6(known target)|AKT1(known target)
5755	prednisolone	10.08	APP(0.76)|PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
5995	testosterone propionate	9.87	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
8956	145-14-2	9.39	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
2244	aspirin	3.04	AKT1(0.78)|APP(0.72)|JUN(0.72)
5208	shikonin	105.64	AKT1(known target)|IL6(known target)
164676	Tanshinone IIA	105.64	IL6(known target)|AKT1(known target)|JUN(known target)
180751	NCI60_004184	103.35	AKT1(known target)
4091	4091	47.54	AKT1(known target)|JUN(known target)
6251	D-mannitol	27.48	APP(0.86)|PPARGC1A(0.66)|AKT1(0.66)
247704	(S)-adrenaline	25.42	AKT1(known target)|IL6(known target)|JUN(0.8)

6112	1200-22-2	22.75	PPARGC1A(known target)|IL6(known target)|APP(0.76)
6714002	PREDNICARBATE	21.51	PPARGC1A(0.72)|AKT1(0.72)|JUN(0.72)
453	Hexitol	17.48	APP(0.86)|PPARGC1A(0.66)|AKT1(0.66)
5281116	ERUCIC ACID	13.43	AKT1(known target)|PPARGC1A(0.66)
8747	MERCURIBENZOIC ACID	9.76	APP(0.7)|PPARGC1A(0.66)
5816	epinephrine	8.77	PPARGC1A(known target)|JUN(0.8)
6325610	Melanin	7.79	IL6(known target)|APP(0.88)

*The numbers in parentheses appear to be confidence scores from the BATMAN-TCM algorithm, which indicate the likelihood/strength of the association between the TCM ingredient and that particular gene ranging from 0 to 1, with higher scores indicating stronger predicted associations representing a relatively high confidence prediction.

Table 2 Enriched herbs in BATMAN-TCM.

Herb (Latin)	Herb (Pinrin)	TCM ingredients	Target Proteins	Enrichment ratio
Polygonum cuspidatum	HU ZHANG	4	9	8.66
Leonurus heterophyllus [syn. Leonurus artemisia]	YI MU CAO	5	8	9.4
Aloe marlothii	MA SHI LU HUI	1	7	35.78
Caulis clematidis armandii	CHUAN MU TONG	4	7	17.31
Agastache rugosus	HUO XIANG	4	7	10.32
Penis cervi	LU BIAN	5	7	10.17
None	CHU SHI ZI	19	7	10.09
Bufo bufo gargarizans, bufo melanostictus	CHAN SU	6	7	8.51
Smilax glabra	TU FU LING	7	7	8.48
Flos puerariae lobatae	GE HUA	11	7	7.78
Homo sapiens	ZI HE CHE	10	7	7.46
Laminaria japonica	KUN BU	8	7	7.23
Salvia miltiorrhiza	DAN SHEN	8	7	7.1
Moschus moschiferus, moschus berezovskii, moschus sifanicus	SHE XIANG	7	7	6.87
Fructus leonuri	CHONG WEI ZI	5	7	6.8
Ilex cornuta	GOU GU YE	4	7	5.82
Rheum officinale	DA HUANG	10	7	5.71
Panax ginseng [syn. panax schinseng]	REN SHEN	12	7	5.66
Perilla frutescens var. arguta	ZI SU	18	7	5.41
Oviductus ranae	HA MA YOU	12	7	4.44
Fructus hippophae	SHA JI	10	7	4.35
Manis pentadactyla	CHUAN SHAN JIA	3	6	22.06
Squama manitis praeparata	PAO SHAN JIA	3	6	22.06
Squama manitis praeparata	ZHI CHUAN SHAN JIA	3	6	22.06
Syngnathus	HAI LONG	5	6	18.61
Gentiana macrophylla	QIN JIAO	7	6	17.41
Bombyx mori	BAI JIANG CAN	3	6	15.36
Conioselinum vaginatum	XIN JIANG GAO BEN	4	6	14.81
Senecio oryzetorum	DA BAI DING CAO	2	6	14.56
Folium viticis negundo	MU JING YE	2	6	12.22
Herba glechomae	LIAN QIAN CAO	4	6	11.87
Plastrum testudinis	GUI BAN	7	6	11.58
Asarum heterotropoides var. mandshuricum	LIAO XI XIN	4	6	11.29
Homo sapiens	REN NIAO	5	6	11.15
Foeniculum vulgare	HUI XIANG	6	6	10.83
Polygonum multiflorum	HE SHOU WU	1	6	10.73
Polygonum cuspidatum	HU ZHANG YE	1	6	10.73

Rhinoceros unicornis, rhinoceros sondaicus, rhinoceros sumatrensis	XI JIAO	2	6	9.82
Aristolochia debilis [syn. aristolochia longa]	MA DOU LING	7	6	9.62
Euphorbia lathyris	QIAN JIN ZI	4	6	9.49
Bupleurum sibiricum	XING AN CHAI HU	5	6	9.41
Eclipta prostrata [syn. eclipta alba]	MO HAN LIAN	3	6	9.06
Flos sophorae	HUAI HUA	12	6	8.91
Rheum tanguticum	TANG GU TE DA HUANG	4	6	8.57
Cyathula officinalis	CHUAN NIU XI	3	6	8.54
Morus alba	SANG ZHI	4	6	8.18
Juncus effusus	DENG XIN CAO	7	6	8.05
Tripterygium wilfordii	LEI GONG TENG	6	6	7.62
Asarum sieboldii	XI XIN	13	6	7.3
Bos taurus domesticus, bubalus bubalis	NIU SHEN	4	6	7.3

Table 2 presents a list of herbs identified as significantly enriched within the BATMAN-TCM database. This table provides a valuable resource for understanding the herbal composition and potential therapeutic targets associated with Traditional Chinese Medicine (TCM) formulas. This analysis offers insights into the commonly used and potentially most impactful herbal components within TCM applications by identifying enriched herbs. Further analysis of these herbs, their known pharmacological activities, and their target genes could reveal key mechanisms of action and potential applications for the identified TCM formulas.

4. Discussion

Delirium is a complex neuropsychiatric syndrome characterized by acute disturbances in attention, awareness, and cognition, affecting elderly patients and resulting in significant morbidity and mortality. Despite its high prevalence and severe clinical impact, the underlying pathophysiological mechanisms remain incompletely understood. Current evidence suggests that delirium involves multiple interacting pathways, including neuroinflammation, oxidative stress, neurotransmitter imbalances, and disruption of neural networks. This complexity poses significant challenges to understanding the condition and developing effective therapeutic interventions. The present study employed a systems biology approach to provide a more comprehensive understanding of delirium's molecular mechanisms, mainly focusing on the intricate interplay between various biological pathways and potential therapeutic targets among natural compounds.

The interleukin-6 (IL-6) gene has been increasingly recognized as a significant factor in the pathophysiology of delirium. Elevated levels of IL-6 are associated with neuroinflammation, which is a critical component in the development of delirium, particularly in vulnerable populations such as older people and those undergoing surgical procedures.

IL-6 is a pro-inflammatory cytokine that plays a pivotal role in the immune response and has been implicated in the neuroinflammatory processes associated with delirium. Studies have shown that elevated serum levels of IL-6 correlate with the incidence of delirium, particularly in postoperative settings. For instance, researchers found that higher IL-6 levels were present in patients who developed postoperative delirium, suggesting that IL-6 (primary inducer of CRP gene expression)

may be a biomarker for predicting delirium in surgical patients [48]. Similarly, Girard et al. reported associations between markers of inflammation, including IL-6, and delirium during critical illness, further supporting the role of IL-6 in neuroinflammation and cognitive dysfunction [49].

The relationship between IL-6 and postoperative delirium has been extensively studied. Yamanashi et al. observed that inflammatory cytokines, including IL-6, increase after neurosurgery, which may contribute to the development of delirium [50]. Furthermore, studies have indicated elevated IL-6 levels are associated with a higher incidence of delirium in elderly patients undergoing major surgeries, as Jia et al. noted a positive correlation between serum IL-6 levels and postoperative delirium [51]. It suggests that IL-6 may play a crucial role in the inflammatory response triggered by surgical stress, leading to delirium.

In critical care settings, IL-6 has been identified as a significant predictor of acute brain dysfunction, including delirium. Alexander et al. highlighted the role of IL-6 in predicting outcomes in critically ill patients, noting that elevated IL-6 levels were associated with cognitive disorders and increased mortality [52]. Additionally, Munster et al. found that higher levels of IL-6 in cerebrospinal fluid were associated with delirium in elderly patients, reinforcing that IL-6 is involved in the neuroinflammatory processes contributing to delirium [53].

Research using animal models has provided further insights into the mechanisms by which IL-6 may mediate delirium-like phenotypes. For example, Rashid et al. demonstrated that IL-6 levels were significantly elevated in a murine model of urinary tract infection, which induced delirium-like behaviors [54]. It suggests that IL-6 may directly influence neuroinflammatory pathways that lead to cognitive disturbances.

While the inflammatory hypothesis of delirium is gaining traction, studies exploring genetic variations in the IL-6 gene have yielded mixed results. Munster et al. investigated functional genetic variations in the IL-6 gene and its receptor. Still, they found no direct association with delirium, indicating that while IL-6 is involved in the inflammatory response related to delirium, genetic predispositions may not significantly influence its role [55].

The AKT1 gene encodes a serine/threonine kinase involved in various cellular processes and has been implicated in the pathophysiology of delirium. This connection is primarily based on the role of AKT1 in neuroinflammation, cellular signaling, and its association with psychiatric symptoms.

AKT1 is a critical component of the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway, which plays a significant role in cellular responses to growth factors and stress. Dysregulation of this pathway has been associated with various psychiatric disorders, including delirium. Tsimberidou et al. highlighted that changes in AKT expression and activity can lead to psychiatric symptomatology, suggesting that alterations in AKT1 signaling may contribute to cognitive disturbances observed in delirium [56]. The activation of AKT1 is known to influence inflammatory responses in the brain, and its inhibition can exacerbate neuroinflammatory processes, potentially leading to delirium-like symptoms [57, 58].

Recent studies have identified AKT1 as a hub protein associated with delirium. Mosharaf's research indicated that AKT1 is one of the key proteins involved in the regulatory networks associated with delirium, particularly in inflammation and oxidative stress [59]. The study emphasized that AKT1 interacts with various cytokines and signaling pathways closely connected to the development of delirium, reinforcing that AKT1 plays a significant role in the neurobiological mechanisms underlying this condition [59].

The relationship between AKT1 and psychiatric symptoms further supports its relevance to delirium. Tsimberidou et al. noted that AKT1 mutations and altered signaling can lead to psychiatric manifestations, which may overlap with the cognitive dysfunction seen in delirium [56]. The study's findings suggest that AKT1's role in neuronal signaling and its impact on mood and cognitive functions could be critical in understanding the mechanisms of delirium, especially in patients with pre-existing psychiatric conditions.

The involvement of AKT1 in the pathophysiology of delirium may represent a potential therapeutic target. Modulating AKT1 activity could influence neuroinflammatory responses and improve cognitive outcomes in at-risk populations. Identifying AKT1 as a hub protein in delirium-related pathways suggests that pharmacological interventions targeting this pathway might mitigate the risk or severity of delirium [59].

The JUN gene, which encodes the c-Jun protein, is a critical component of the AP-1 transcription factor complex and has been implicated in various cellular processes, including inflammation, cell proliferation, and apoptosis. Recent studies have begun to explore the potential links between the JUN gene and delirium, particularly in neuroinflammation and cognitive dysfunction.

The c-Jun protein regulates the expression of various genes involved in inflammatory responses. In neuroinflammation, c-Jun plays a role in activating glial cells and releasing pro-inflammatory cytokines, which can contribute to cognitive disturbances. Research has shown that c-Jun is activated in response to inflammatory stimuli, leading to gene expression mediating inflammatory responses in the brain [60]. It suggests that c-Jun may be involved in inflammatory processes that underlie delirium.

C-Jun is also implicated in neuronal injury and repair mechanisms. In models of axonal injury, c-Jun is upregulated and plays a role in the transcriptional response to injury, which may influence neuronal survival and regeneration [60]. This response is critical in the context of delirium, as acute brain injuries, such as those resulting from surgery or severe illness, can trigger delirium. Activating c-Jun in response to such injuries may contribute to developing delirium by modulating the inflammatory response and neuronal repair processes.

The role of c-Jun in regulating genes associated with apoptosis and cell survival further underscores its relevance to cognitive dysfunction. Studies have indicated that c-Jun can promote the expression of pro-apoptotic factors, which may lead to neuronal cell death and contribute to cognitive decline [61]. It is particularly pertinent in delirium, where acute changes in mental function are observed. The balance between pro-survival and pro-apoptotic signals regulated by c-Jun may influence the severity and duration of delirium episodes.

Given its involvement in neuroinflammatory responses and neuronal survival, c-Jun may serve as a potential biomarker for delirium. Elevated levels of c-Jun or its downstream targets could indicate heightened neuroinflammation and increased risk of cognitive disturbances in the injury context [62]. Identifying c-Jun as a biomarker could aid in the early detection and management of delirium.

Targeting the c-Jun/AP-1 signaling pathway may offer therapeutic opportunities for preventing or treating delirium. Inhibitors of c-Jun or modulators of its activity could potentially mitigate the neuroinflammatory responses associated with delirium and promote neuronal survival. Further research is needed to explore the therapeutic potential of targeting c-Jun in delirium management [63].

The amyloid precursor protein (APP) gene has been increasingly recognized in the context of neurodegenerative diseases, particularly Alzheimer's disease (AD), and its potential links to delirium.

Delirium is often observed in patients with cognitive impairments, and the interplay between APP processing, amyloid-beta (Aβ) accumulation, and neuroinflammation may provide insights into the mechanisms underlying delirium. Below is a synthesis of the evidence linking the APP gene to delirium, supported by relevant references.

The APP gene is crucial for the production of amyloid-beta peptides, which are central to the pathogenesis of Alzheimer's disease. Mutations in the APP gene can lead to abnormal processing of APP, resulting in increased production of Aβ, which forms plaques in the brains of individuals with AD [64]. This accumulation of Aβ is associated with neuroinflammation, synaptic dysfunction, and cognitive decline, all of which are relevant to the development of delirium [65]. The relationship between APP processing and cognitive impairment suggests that alterations in APP may contribute to the risk of delirium, particularly in older adults or those with pre-existing cognitive deficits.

Neuroinflammation is a key factor in both delirium and neurodegenerative diseases. The processing of APP can influence inflammatory responses in the brain. For instance, elevated levels of Aβ can activate microglia, leading to the release of pro-inflammatory cytokines that may exacerbate cognitive dysfunction [66]. This neuroinflammatory response is thought to play a significant role in the onset of delirium, particularly in hospitalized patients who may experience acute stressors that trigger inflammatory pathways [67]. The connection between APP, Aβ, and neuroinflammation underscores the potential for APP to influence the development of delirium.

Research has shown that cognitive decline associated with delirium may be linked to the same pathological processes that underlie Alzheimer's disease. For example, studies have indicated that patients with delirium often exhibit elevated levels of Aβ and tau proteins, which are markers of neurodegeneration [68]. These biomarkers suggest that the underlying mechanisms of delirium may overlap with those of AD, particularly in APP processing and the resulting neuroinflammatory responses [69]. This relationship highlights the importance of APP in understanding the cognitive disturbances seen in delirium.

Genetic variations in the APP gene and related pathways may also influence the risk of developing delirium. For instance, specific polymorphisms in the APP gene have been associated with increased susceptibility to cognitive decline and neurodegenerative diseases [70]. These genetic factors may predispose individuals to delirium, particularly in the context of acute medical events or surgeries that can trigger cognitive disturbances [71]. Understanding the genetic underpinnings of APP processing could provide valuable insights into identifying individuals at higher risk for delirium.

Given the links between APP processing, neuroinflammation, and cognitive dysfunction, targeting the APP pathway may offer potential therapeutic strategies for preventing or managing delirium. Interventions aimed at modulating Aβ levels or reducing neuroinflammation could be beneficial in at-risk populations, such as elderly patients undergoing surgery or those with pre-existing cognitive impairments [14]. Further research is needed to explore the therapeutic potential of targeting APP processing in delirium.

The potential links between the PGC-1α gene (PPARGC1A) and delirium are an emerging area of research, particularly in neuroinflammation, mitochondrial function, and metabolic regulation. PGC-1α is a key regulator of mitochondrial biogenesis and energy metabolism, and its dysregulation has been implicated in various neurodegenerative diseases and cognitive impairments, which are relevant to the development of delirium.

PGC-1α plays a critical role in regulating mitochondrial biogenesis and function. It coactivates several transcription factors, including nuclear respiratory factor 1 (NRF1) and estrogen-related receptor alpha (ERRα), which are essential for the expression of genes involved in oxidative phosphorylation and mitochondrial function [72]. Mitochondrial dysfunction is increasingly recognized as a contributing factor to cognitive decline and delirium, particularly in elderly patients or those with pre-existing conditions [73-75]. Studies have shown that reduced expression of PGC-1α is associated with impaired mitochondrial function, leading to increased oxidative stress and inflammation in the brain, both known to exacerbate delirium [76].

The relationship between PGC-1α and inflammation is particularly relevant in delirium. PGC-1α has been shown to exert anti-inflammatory effects in Parkinson's disease by regulating the expression of inflammatory cytokines and modulating the activity of immune cells [77]. In conditions where PGC-1α expression is reduced, such as in metabolic disorders or neurodegenerative diseases, pro-inflammatory cytokines often increase, which may contribute to the neuroinflammatory processes associated with delirium [78]. For instance, activating inflammatory pathways can lead to the release of cytokines like IL-6, which have been implicated in the pathogenesis of delirium [79, 80].

Metabolic dysregulation is another critical aspect linking PGC-1α to delirium. PGC-1α regulates glucose metabolism and fatty acid oxidation, and its deficiency can lead to metabolic disturbances that may predispose individuals to delirium [81-83]. For example, studies have shown that PGC-1α deficiency is associated with insulin resistance and obesity, both risk factors for cognitive impairment and delirium [84, 85]. The interplay between metabolic dysfunction and neuroinflammation suggests that targeting PGC-1α could be a potential therapeutic strategy for preventing or mitigating delirium in at-risk populations.

Research has also indicated that PGC-1α may be protective in neurodegenerative diseases often associated with delirium. For instance, in models of Parkinson's disease, PGC-1α has been shown to regulate mitochondrial function and protect against neuronal loss [86-88]. The downregulation of PGC-1α in neurodegenerative conditions may lead to increased vulnerability to acute stressors, such as infections or metabolic disturbances, which can trigger episodes of delirium [89, 90].

The biological processes associated with "GO:0045944~positive regulation of transcription by RNA polymerase II," "GO:0010628~positive regulation of gene expression," and "GO:0033138~positive regulation of peptidyl-serine phosphorylation" are intricately linked to various mechanisms of gene regulation and transcriptional control. These processes are critical for maintaining cellular functions and responding to environmental stimuli, and they have been extensively studied in various biological contexts.

Positive regulation of transcription by RNA polymerase II is a fundamental aspect of gene expression. Transcription factors and coactivators play pivotal roles in this regulation. For instance, Hnisz et al. discuss the concept of super-enhancers, clusters of enhancers that drive high transcription levels of key regulatory genes, highlighting the importance of transcription factors and the Mediator complex in this process [91]. Similarly, Zhao et al. emphasize the role of feedback mechanisms in regulating gene expression, where small activating RNAs can enhance their transcription, showcasing a sophisticated layer of transcriptional control [92]. Additionally, the work of Li et al. illustrates how specific transcription complexes, such as those involving Ldb1 and Gata1, are crucial for the activation of erythroid genes, further underscoring the complexity of transcriptional regulation [93].

In the context of positive regulation of gene expression, various studies have identified mechanisms that enhance transcriptional activity. For example, Yuan et al. highlight the critical role of promoter elements in initiating transcription, which is a key step in gene expression regulation [94]. Furthermore, the interaction between long non-coding RNAs (lncRNAs) and transcription factors has been shown to modulate gene expression by altering chromatin architecture, as described by Szafrański et al. [95]. This interplay between lncRNAs and transcription factors exemplifies the multifaceted nature of gene regulation.

Moreover, the regulation of peptidyl-serine phosphorylation is another critical aspect of cellular signaling and gene expression. This post-translational modification can influence the activity of transcription factors and other proteins involved in gene regulation. For instance, Budimir et al. discuss how redox-active cysteines in transcription factors can affect gene expression in response to environmental signals, indicating a link between phosphorylation and transcriptional regulation [96]. Additionally, the role of specific transcription factors in mediating responses to signaling molecules, such as salicylic acid in plants, further illustrates the connection between phosphorylation and gene expression [97].

Johnson et al. provide evidence that changes in heat shock protein expression in the brains of individuals with cocaine-related fatalities may reflect underlying neurobiological processes related to delirium [98]. It suggests that the regulatory mechanisms governing gene expression are vital for normal cellular function and play a significant role in pathological conditions such as delirium.

The molecular functions "GO:0019899~enzyme binding" and "GO:0008134~transcription factor binding" are essential for understanding the biochemical and regulatory mechanisms underlying various physiological and pathological conditions, including delirium. Delirium, characterized by acute confusion and cognitive dysfunction, can be influenced by enzyme activity and transcriptional regulation alterations.

Enzyme binding is a critical molecular function that affects metabolic pathways and signaling cascades. For instance, Jin et al. discuss how functionalized graphene oxide can modulate enzyme activity and stability, indicating that the binding of enzymes to substrates or inhibitors can significantly influence their catalytic efficiency [99]. This modulation of enzyme activity is particularly relevant in delirium, where metabolic disturbances may lead to altered neurotransmitter levels and cognitive function. Furthermore, Pattammattel et al. highlight the importance of enzyme binding in enzyme immobilization, which can affect enzyme kinetics and stability, potentially impacting metabolic processes crucial for maintaining cognitive health [100].

Transcription factor binding, on the other hand, plays a vital role in gene expression regulation. Transcription factors are proteins that bind to specific DNA sequences to regulate the transcription of genes, and various factors, including post-translational modifications and interactions with other proteins, can influence their activity. Moreover, the interplay between enzyme and transcription factor binding can create a complex regulatory network. For example, binding transcription factors to their target genes can influence the expression of enzymes involved in neurotransmitter synthesis and degradation. This relationship is critical in understanding how metabolic and transcriptional dysregulation can contribute to delirium. The study by Mörtl et al. provides insights into enzymes' structural and functional aspects, suggesting that understanding these interactions can inform therapeutic strategies for conditions like delirium [101].

The KEGG signaling pathways "hsa04933:AGE-RAGE signaling pathway in diabetic complications," "hsa05142:Chagas disease," and "hsa04625:C-type lectin receptor signaling

pathway" provide critical insights into the molecular mechanisms that may contribute to the development of delirium, particularly in the context of metabolic and inflammatory conditions.

The AGE-RAGE signaling pathway is particularly relevant in the context of diabetic complications and its potential link to delirium. Advanced glycation end products (AGEs) accumulate in individuals with diabetes and interact with their receptor, RAGE, activating various intracellular signaling pathways, including NF-κB and MAPK [102, 103]. This activation promotes oxidative stress and inflammation, which affect neuronal function and can contribute to cognitive disturbances observed in delirium. For instance, studies have shown that the engagement of AGEs with RAGE can exacerbate vascular damage and promote neuroinflammation, which may be implicated in the pathogenesis of delirium [104].

In addition to the AGE-RAGE pathway, the C-type lectin receptor signaling pathway has been implicated in immune responses and inflammation, which are crucial in delirium. C-type lectin receptors (CLRs) play a significant role in recognizing pathogens and modulating immune responses. Gorjestani et al. discuss how CLRs, through their interaction with various signaling molecules, can influence inflammatory pathways relevant to infections and systemic inflammation, both known triggers for delirium [105]. The activation of CLRs can lead to the production of pro-inflammatory cytokines, which can further exacerbate neuroinflammation and contribute to the cognitive decline seen in delirium.

Chagas disease, while primarily a tropical disease caused by the parasite Trypanosoma cruzi, can also lead to neurological complications, including delirium. The inflammatory response associated with Chagas disease can result in neuroinflammation and neuronal damage, which may manifest as cognitive dysfunction. The interplay between the immune response elicited by the infection and the resulting inflammatory mediators can create a milieu that predisposes individuals to delirium [106].

The potential role of various Traditional Chinese Medicine (TCM) ingredients, particularly melatonin, dehydroepiandrosterone (DHEA), resveratrol, progesterone, and paclitaxel, in the treatment of delirium, has been explored in several studies. These compounds are known for their neuroprotective, anti-inflammatory, and regulatory effects on circadian rhythms, which are critical in managing delirium, especially in vulnerable populations such as the elderly or those undergoing surgery.

Melatonin has been extensively studied for its effects on sleep regulation and circadian rhythm disturbances, which are closely linked to delirium. Jonghe et al. conducted a systematic review that highlighted the effectiveness of melatonin in treating circadian rhythm disturbances in dementia, suggesting implications for delirium management [107]. Furthermore, a randomized clinical trial by Javaherforooshzadeh demonstrated that melatonin significantly reduced the incidence of delirium in patients undergoing coronary artery bypass graft surgery compared to a placebo group [108]. This finding aligns with other studies indicating that melatonin administration can lower delirium rates in postoperative settings [109]. Additionally, Baumgartner et al. noted that melatonin could effectively prevent delirium in critically ill patients, emphasizing the need for further multicenter studies to validate these findings [110].

Dehydroepiandrosterone (DHEA) has also been implicated in cognitive function and mood regulation. Ouanes et al. found that DHEA sulfate levels were associated with neuropsychiatric symptoms in patients with Alzheimer's disease, suggesting that DHEA may have a role in mitigating cognitive decline and potentially delirium [111]. The anti-glucocorticoid effects of DHEA might

counteract the negative impacts of elevated cortisol levels, which are often linked to cognitive dysfunction and delirium [112].

Resveratrol, a polyphenolic compound found in red wine, has been recognized for its neuroprotective properties. While specific studies directly linking resveratrol to delirium treatment are limited, its anti-inflammatory and antioxidant effects could theoretically contribute to reducing neuroinflammation associated with delirium. The modulation of signaling pathways related to inflammation and oxidative stress may provide a protective effect against cognitive decline [113].

Progesterone has been studied for its neuroprotective effects, particularly in the context of traumatic brain injury and neurodegenerative diseases. Trzepacz et al. discussed how hormonal changes, including those involving progesterone, could influence cognitive function and the risk of delirium, especially in aging populations [114]. The potential neuroprotective effects of progesterone may help mitigate the cognitive impairments associated with delirium.

Paclitaxel, primarily known as a chemotherapeutic agent, has been associated with cognitive side effects, including delirium, particularly in cancer patients. While its direct therapeutic effects on delirium are not well established, understanding its impact on cognitive function is crucial, as managing these side effects is essential for improving the quality of life in patients undergoing cancer treatment [115].

Delirium is a complex, multifactorial syndrome that disrupts cognition, attention, and perception, stemming from various underlying pathophysiological mechanisms. In this study, we applied a systems biology approach to identify key differentially expressed genes (DEGs) and potential therapeutic natural compounds. Our findings highlight IL6, AKT1, JUN, APP, and PPARGC1A as central to delirium pathophysiology, aligning with mechanisms like neuroinflammation, oxidative stress, and cognitive dysfunction. Furthermore, our exploration of natural compounds, particularly those used in Traditional Chinese Medicine (TCM), suggests promising adjunctive strategies for delirium management.

The study offers a multi-dimensional view of delirium, revealing how the identified genes and pathways contribute to its diverse symptoms. IL6, AKT1, and JUN play key roles in neuroinflammation, regulating the NF-κB and MAPK signaling pathways, which are critical in delirium-related inflammation. Elevated IL6 levels, commonly seen in delirium patients, further support its potential as a biomarker. PPARGC1A, a regulator of mitochondrial function, is linked to oxidative stress and neuronal damage, while APP contributes to oxidative stress-related injury, exacerbating cognitive impairments. Both AKT1 and JUN are involved in synaptic plasticity and cognitive function, with disruptions in the PI3K/AKT pathway being associated with cognitive decline in delirium and neurodegenerative diseases. The involvement of APP suggests shared mechanisms between delirium and long-term mental disorders.

These findings align with existing literature that ties IL6 and AKT1 to inflammatory responses in postoperative and ICU-related delirium, PPARGC1A to mitochondrial dysfunction in delirium, and JUN and APP to neurodegenerative mechanisms.

We also investigated the potential of natural compounds to modulate delirium-related pathways. Compounds such as melatonin, dehydroepiandrosterone (DHEA), resveratrol, progesterone, and paclitaxel have shown anti-inflammatory, neuroprotective, and neurodegenerative properties. These compounds can modulate cytokine activity (e.g., IL6, TNF-α), enhance mitochondrial function (via PPARGC1A), and improve cognitive function by modulating the PI3K/AKT pathway. Their multi-

target effects make them promising candidates for addressing delirium's complex pathology and complementing conventional treatment strategies.

Overall, our study provides a validated, literature-supported computational framework for understanding delirium at a molecular level. By integrating transcriptomic data with systems biology and network pharmacology approaches, we identify key genes and herbal compounds with strong potential for further investigation. These findings align with existing evidence, reinforcing their biological relevance and therapeutic promise.

While our study does not delve into compound combinations, dosages, or pharmacokinetics, it is an initial framework for identifying natural compounds that may modulate delirium-related pathways. Future research should prioritize preclinical trials and clinical studies to assess the optimal combinations, dosages, bioavailability, safety, and therapeutic efficacy of the identified compounds in delirium models. It aligns with the growing body of work demonstrating the success of computational predictions in drug discovery, where in silico results have been validated through subsequent experimental and clinical studies. Our study contributes to this trend as an essential first step in exploring potential therapeutic avenues for delirium.

4.1 Limitations and Future Directions

Our study primarily focuses on computational analysis and hypothesis generation rather than pharmacokinetic or dosage-based research. While experimental validation is ideal for confirming gene-compound interactions, it is currently challenging due to the lack of established in vitro or in vivo models specifically for delirium. Given this limitation, our study is an essential hypothesis-generating framework, providing a foundation for future research. In silico approaches have been widely recognized as valuable tools in drug discovery, often preceding and guiding experimental investigations. The network-based methodology ensures that our predictions are biologically meaningful and prioritizes genes and compounds with the highest potential for therapeutic relevance. Although direct experimental validation is not currently feasible, our study is a foundational resource for future research into delirium.

5. Conclusions

This study offers insights into the molecular and biochemical processes underlying delirium, identifying key genes and pathways associated with neuroinflammation, oxidative stress, and cognitive impairment. Employing a systems biology approach shows that highlighted biomarkers, including IL6, AKT1, JUN, APP, and PPARGC1A, are central to delirium pathophysiology. The integration of natural compounds, particularly those found in Traditional Chinese Medicine, demonstrated potential for modulating these critical pathways, presenting a promising adjunctive strategy for managing delirium. The findings suggest that compounds with anti-inflammatory and neuroprotective properties, such as melatonin, dehydroepiandrosterone, resveratrol, progesterone, and paclitaxel, may reduce delirium symptoms or mitigate its onset by addressing the complex, multifactorial nature of the disorder. These compounds may enhance conventional therapeutic approaches by simultaneously targeting multiple aspects of the disease, from modulating cytokine activity to improving mitochondrial function. Further research, including clinical trials, is needed to validate the therapeutic benefits of these compounds in delirium, assess safety profiles, and establish standardized treatment protocols. In conclusion, this study underscores the potential of

combining systems biology with natural compound therapies to address delirium's multifaceted pathology, paving the way for more effective, personalized, and less invasive treatment options for vulnerable populations.

Author Contributions

BS - Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; original draft; review & editing. The author read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Identified matched genes in BATMAN-TCM.

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