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RESEARCH ARTICLE

Gene Expression Omnibus database analysis reveals comorbidity mechanisms of type 2 diabetes mellitus and vascular dementia and predicts potential herbal therapeutics

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Abstract

Objective: This study aimed to investigate the comorbid mechanisms linking type 2 diabetes mellitus (T2DM) and vascular dementia (VaD), focusing on the roles of astrocytes and neurons, and to identify potential therapeutic traditional Chinese medicines (TCMs) and compounds.

Methods: T2DM (GSE161355) and VaD (GSE122063) transcriptomic datasets were retrieved from the Gene Expression Omnibus database. Differential expression analysis, functional enrichment, and druggability assessment were conducted to identify potential core targets. Corresponding TCMs and compounds were predicted by using the TCMSP and HERB databases, followed by analyses of their pharmacokinetics, toxicity, and binding affinity.

Results: In astrocytes, eight core genes (e.g., HSP90AA1, HIF1A, PTEN) were identified and primarily enriched in autophagy and inflammatory pathways. Eight TCMs, including *Corydalis yanhusuo* and *Phellodendron chinense*, were predicted to be relevant. Indigo exhibited a relatively strong binding affinity to HSP90AA1 (−10.0 kcal/mol). In neurons, eight core genes (e.g., NFKB1, CYCS, PTGS2) were enriched in apoptosis and neuroinflammation pathways. Potential TCMs, such as *Tripterygium wilfordii*, were identified. Palmatine showed a relatively strong binding affinity to PTGS2 (−8.1 kcal/mol). Most predicted TCMs were characterized as bitter and cold in property, associated with the liver meridian, and attributed with heat-clearing effects.

Conclusion: Our findings suggest that the comorbidity of T2DM and VaD may involve dysregulated inflammatory and apoptotic pathways in astrocytes and neurons. The predicted TCMs and compounds represent multitarget intervention candidates, consistent with TCM theories of "Yin deficiency with internal heat" and "phlegm-stasis transforming into heat." These findings provide a theoretical basis for future experimental validation and the development of TCM-based therapies.

KEYWORDS

astrocytes, neurons, traditional Chinese medicines, type 2 diabetes mellitus, vascular dementia

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INTRODUCTION

Vascular dementia (VaD) is a syndrome characterized by cognitive impairment resulting from cerebrovascular lesions [1]. Type 2 diabetes mellitus (T2DM) is defined by peripheral insulin resistance and chronic hyperglycemia [2]. With advancing age, persistent hyperglycemia in T2DM leads to systemic complications, including neuropathy and vascular damage, which may substantially increase the risk of developing VaD [3]. Epidemiological studies indicate that the risk of neuropathy and VaD in T2DM patients is approximately 2.3–2.9 times higher than that in the general population [4]. Chronic hyperglycemia in T2DM is thought to accelerate cerebrovascular injury by inducing oxidative stress, insulin resistance, and neuroinflammation, which potentially contribute to VaD pathogenesis [5]. However, the molecular mechanisms underlying the progression from diabetic encephalopathy to VaD remain incompletely understood.

Astrocytes and neurons play important roles in T2DM-associated cognitive decline. Astrocytes, the most abundant glial cells in the central nervous system, interact extensively with neurons, blood vessels, and other glial cells to maintain brain metabolic homeostasis and regulate cerebral blood flow [6]. T2DM may disrupt astrocyte function through reactive gliosis [7], increased blood–brain barrier (BBB) permeability [8], neuroinflammation [9], and altered metabolic regulation [10], which can collectively contribute to neuronal damage [11] and cognitive impairment. Neurons, the fundamental units of the brain, are essential for learning, memory, perception, and motor control. In T2DM, hyperglycemic toxicity and impaired insulin signaling are associated with BBB dysfunction, neuronal injury, and apoptosis,

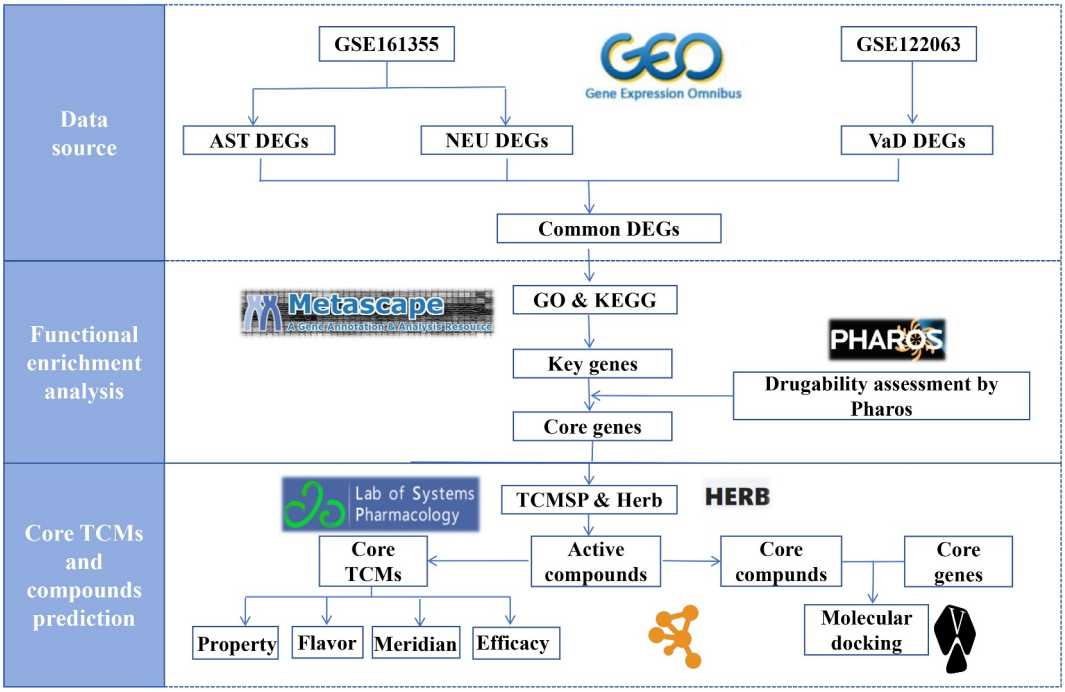

FIGURE 1 Integrative bioinformatics and network pharmacology workflow for elucidating type 2 diabetes mellitus-vascular dementia comorbidity.

TABLE 1 Basic information of the analyzed GEO datasets in the study.

	GSE161355		GSE122063	
GSE series	**Control**	**T2DM**	**Control**	**VaD**
Type	mRNA	mRNA	mRNA	mRNA
Platform	GPL570	GPL570	GPL16699	GPL16699
Sample source	Temporal lobe cortex	Temporal lobe cortex	Temporal lobe cortex	Temporal lobe cortex
Sample size	15	18	22	18
Age (range)	77.4 ± 5.7 (73–87)	79.8 ± 7.5 (73–91)	78.6 ± 8.5 (60–91)	81.4 ± 10.1 (62–96)
Male (%)	6 (40.0%)	12 (66.7%)	11 (50%)	10 (55.5%)

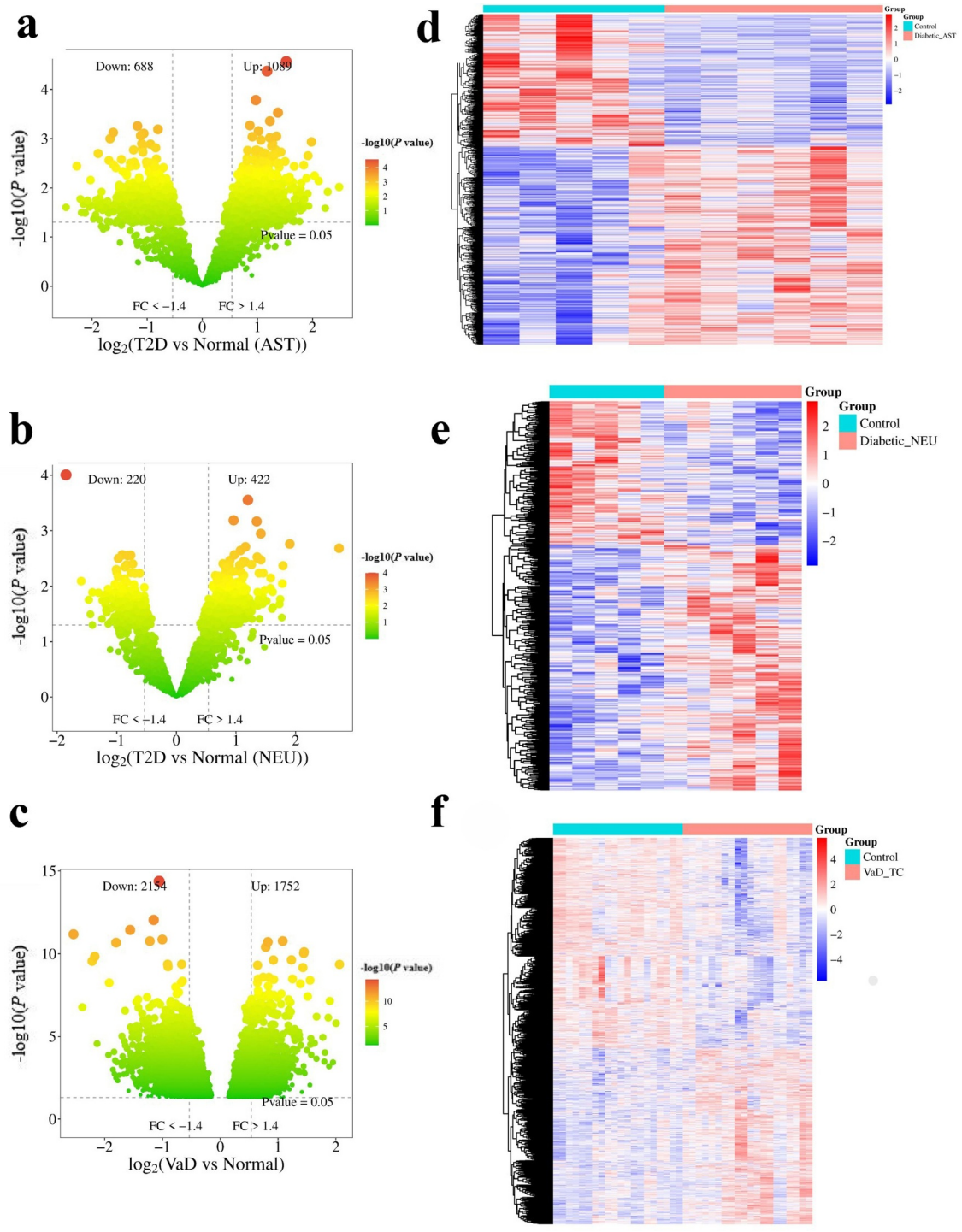

FIGURE 2 DEG analysis between controls and T2DM and/or VaD patients. (a–c) Volcano plots of DEGs (a) in astrocytes and (b) in neurons between controls and T2DM patients, and (c) between controls and VaD patients. (d–f) Heatmaps of DEGs (d) in astrocytes (ASTs) and (e) in neurons (NEUs) between controls and T2DM patients, and (f) between controls and VaD patients, respectively. DEG, differentially expressed gene; T2DM, type 2 diabetes mellitus; VaD, vascular dementia.

potentially leading to cognitive decline [12]. Although astrocytes and neurons serve distinct yet interconnected roles in diabetic cognitive impairment, current studies largely focus on individual targets rather than their interactions. Investigating their distinct and synergistic mechanisms may provide insights into the pathological continuum from T2DM to VaD and facilitate the development of therapies targeting both cellular systems.

In traditional Chinese medicine (TCM), the comorbidity of T2DM and VaD is generally classified under “wasting

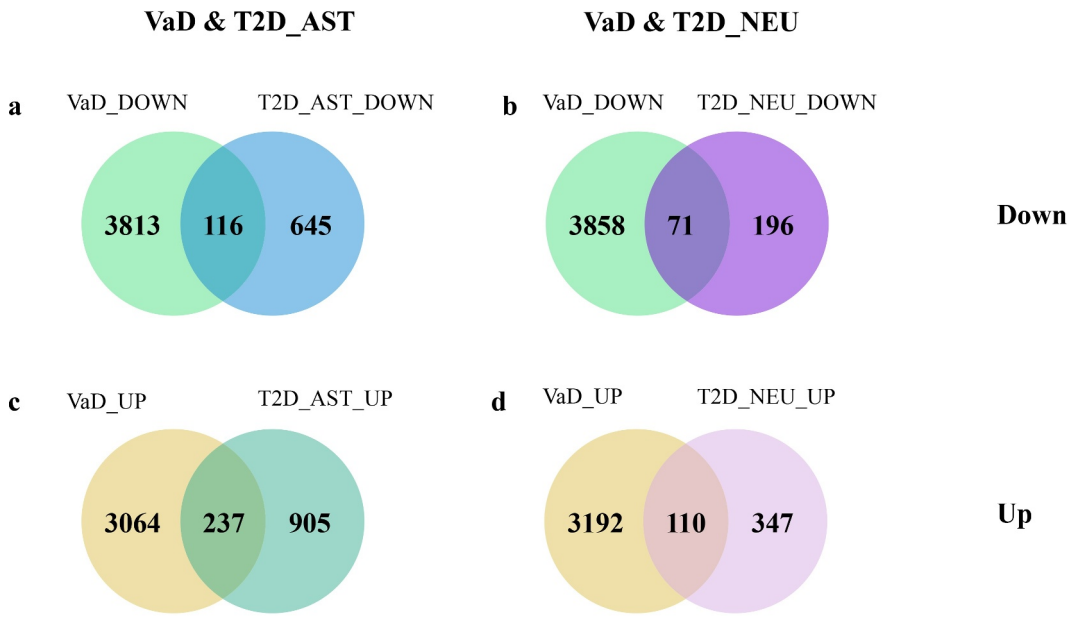

FIGURE 3 Shared DEGs in type 2 diabetes mellitus and vascular dementia. Venn diagrams depict the coexpressed DEGs within (a, c) astrocytes and (b, d) neurons. DEG, differentially expressed gene.

thirst" and "dementia," with clinical manifestations such as forgetfulness and cognitive decline. TCM theory attributes this comorbidity primarily to deficiencies of the kidney and spleen [13]. According to TCM principles, the kidney stores essence and generates marrow, thereby nourishing the brain. The deficiency of kidney essence is thought to result in insufficient brain nourishment [14]. Meanwhile, spleen deficiency—often attributed to dietary excess and inactivity—may lead to dampness and phlegm accumulation that could obstruct the orifices and impair cognitive function [15]. Correspondingly, TCM treatment strategies often focus on tonifying the kidney, replenishing essence, nourishing the brain, resolving phlegm, and promoting blood circulation depending on the syndrome pattern. Modern research confirms that some TCM interventions may improve T2DM-VaD comorbidity by increasing astrocyte numbers [16], inhibiting neuronal apoptosis, enhancing hippocampal synaptic plasticity, and regulating neurotrophic factors [17]. Nevertheless, due to the complex composition of TCMs, their precise pharmacological mechanisms remain to be fully elucidated.

To address this gap, this study employed bioinformatics approaches to analyze gene expression data from T2DM and VaD patients, along with matched healthy controls, aiming to identify shared differentially expressed genes (DEGs) in astrocytes and neurons. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted to explore associated biological pathways, followed by druggability assessment using the Pharos database. Active compounds and related TCMs were predicted using the TCMSP and HERB databases. Network pharmacology was applied to identify core herbs and compounds. Molecular docking was conducted to validate binding interactions. This integrated approach seeks to elucidate potential comorbid mechanisms of T2DM and VaD, which may provide a foundation for developing novel therapeutic and/or preventive strategies. The research workflow is illustrated in Figure 1.

MATERIALS AND METHODS

Data acquisition

Gene expression datasets of T2DM (GSE161355) and VaD (GSE122063) were obtained from the Gene Expression Omnibus (GEO) database. Detailed information on the microarray platforms, sample sources, group sizes, age, and sex distribution is presented in Table 1. The temporal lobe cortex was selected for analysis due to its recognized involvement in cognitive processes and its reported vulnerability to metabolic and vascular pathologies.

Data processing and DEG screening

Raw transcriptomic data were processed using the "affy" package in R for background correction, normalization, and $\log_2$ transformation. DEGs were identified using the "limma" package with $p < 0.05$ as the significance threshold. Volcano plots and heatmaps were generated using the "ggplot2" package and the microbioinformatics platform to visualize significant DEGs.

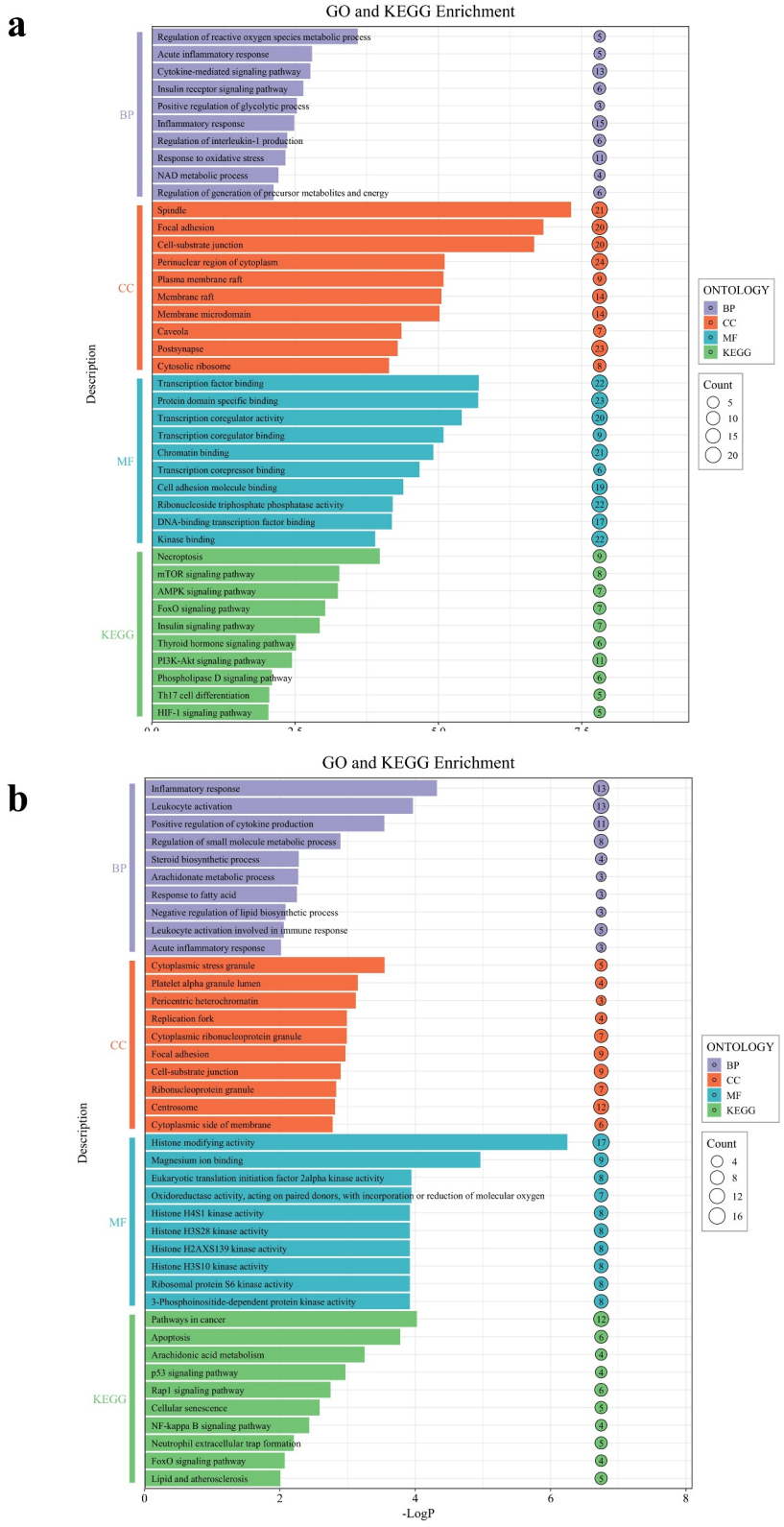

FIGURE 4 Functional enrichment analysis of shared differentially expressed genes in type 2 diabetes mellitus and vascular dementia. Bar plots display the top 10 significantly enriched Gene Ontology terms and Kyoto Encyclopedia of Genes and Genomes pathways in (a) astrocytes and (b) neurons.

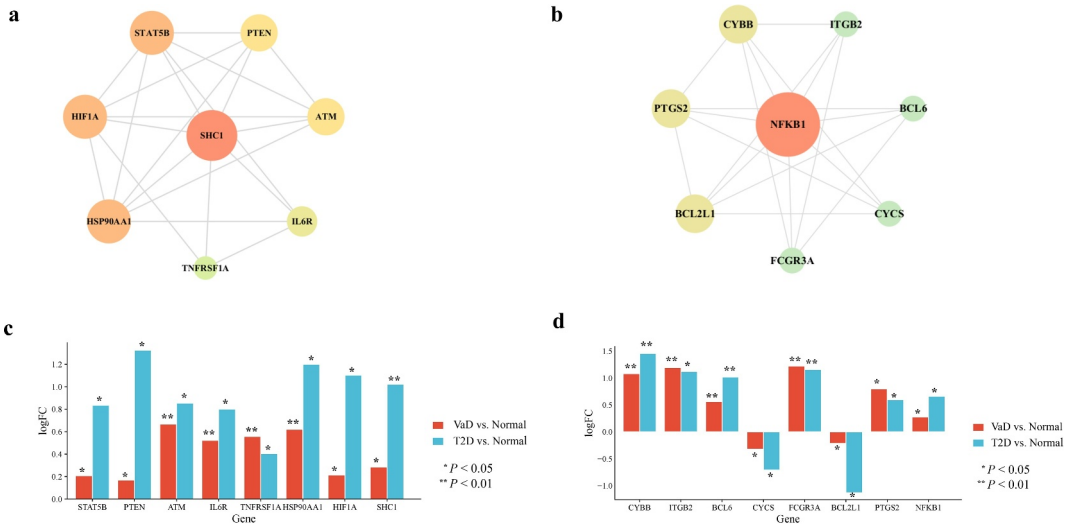

FIGURE 5 Protein–protein interaction network and expression profiles of core DEGs in astrocytes and neurons between T2D and VaD. PPI network of core genes identified in (a) ASTs and (b) NEUs. Node size corresponds to degree value, with orange indicating higher connectivity and green indicating lower connectivity. Expression levels (log_2FC) of core DEGs in (c) AST and (d) NEU under VaD or type 2 diabetes conditions, compared with normal control, respectively. Statistical significance was determined as $^*P < 0.05$ and $^{**}P < 0.01$. ASTs, astrocytes; DEGs, differentially expressed genes; NEUs, neurons; VaD, vascular dementia.

Acquisition and functional enrichment analysis of important coexpressed DEGs

Common DEGs between T2DM and VaD datasets were identified and visualized using the jvenn web tool. GO and KEGG enrichment analyses of these shared DEGs were performed using the "enrichplot" package in R. Enrichment results were visualized using the "ggplot2" package in R. The druggability of encoded proteins was assessed using the Pharos database, focusing on targets with known associations to approved drugs or active ligands. Protein–protein interaction (PPI) networks were constructed using the STRING database and visualized in Cytoscape 3.10.3, with nodes ranked by degree centrality.

Active compound prediction

Potential bioactive compounds were screened from TCMSP [18] using screening criteria of oral bioavailability (OB) $\geq$ 30% and drug-likeness (DL) $\geq$ 0.18, supplemented with data from HERB [19]. Pharmacokinetic properties were further evaluated using SwissADME, retaining compounds with high GI absorption, positive BBB permeability, and compliance with $\geq$3 drug-likeness rules. Toxicity risk was assessed via ADMETlab 3.0 [20] using thresholds of $LC50^{DM} \geq 5.0$, hERG $\leq$ 0.5, and Ames $\leq$ 0.5.

Core compound and TCM screening and analysis of properties, flavors, meridians, and efficacy

TCMs containing the screened compounds were identified through reverse lookup in the TCMSP and HERB databases. Gene-compound-TCM networks were constructed and analyzed in Cytoscape 3.10.3. Nodes with higher degree values were considered as core TCMs and compounds. The China Medical Information Platform was used to analyze properties, flavors, meridian associations, and efficacies of TCMs, which were visualized via radar charts in Microsoft Excel.

Molecular docking validation

Two-dimensional structures of core compounds were retrieved from PubChem and optimized using Chem3D 20.0 to obtain the lowest-energy 3D conformations. Target protein structures were downloaded from the Protein Data Bank. Water molecules and original ligands were removed using PyMOL 2.5.2, and hydrogenation was performed with AutoDockTools 1.5.7. Docking simulations were executed in AutoDock Vina with 20 runs per compound. The conformation exhibiting the lowest binding energy and optimal hydrogen bonding interactions was selected and visualized in PyMOL 2.5.2.

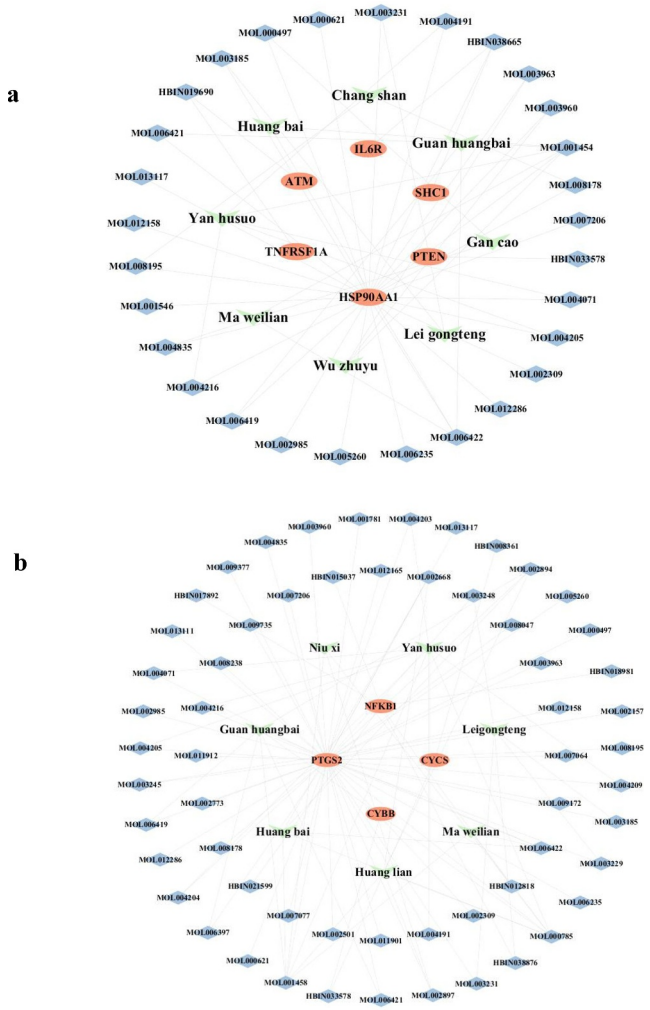

FIGURE 6 Network pharmacology insights into potential therapeutical herbs. Gene–herb–compound interaction network for (a) astrocyte-related and (b) neuron-related targets. Orange nodes represent core genes, green nodes denote herbs, and blue nodes indicate active compounds. Chang shan: *Dichroa febrifuga*, Gan cao: *Glycyrrhiza uralensis*, Guan huang bai: *Phellodendron chinense*, Huang bai: *Phellodendron amurense*, Huang lian: *Coptis chinensis*, Lei gong teng: *Tripterygium wilfordii*, Ma wei lian: *Thalictrum foliolosum*, Niu xi: *Achyranthes bidentata*, Wu zhu yu: *Evodia rutaecarpa*, Yan hu suo: *Corydalis yanhusuo*.

RESULTS

Identification of DEGs

Compared with control, a total of 1903 astrocyte-related DEGs were identified in T2DM (Figure 2), including 761 downregulated and 1142 upregulated genes. Similarly, 724 neuron-related DEGs were detected, with 267 downregulated and 457 upregulated genes. Compared with the control, 7232 DEGs were identified in VaD, including 3930 downregulated and 3302 upregulated genes.

Identification of coexpressed DEGs between T2DM and VaD

Overlapping DEGs between T2DM and VaD datasets were identified and visualized using the jvenn tool (Figure 3). A total of 353 coexpressed DEGs were shared between astrocyte-related T2DM and VaD datasets, consisting of 116 downregulated and 237 upregulated genes. Similarly, 181 coexpressed DEGs were shared between neuron-related T2DM and VaD datasets, including 71 downregulated and 110 upregulated genes.

Functional enrichment analysis of coexpressed DEGs

Gene enrichment analyses revealed that astrocyte-related coexpressed DEGs were primarily enriched in biological processes such as reactive oxygen species (ROS) metabolism, acute inflammatory response, and cytokine-mediated signaling. Enriched cellular component items included spindle, focal adhesion, and cell–substrate junctions, whereas enriched molecular function items were related to transcription factor binding and protein domain-specific binding. KEGG pathway items were enriched in necroptosis, mechanistic target of rapamycin (mTOR), and adenosine monophosphate-activated protein kinase (AMPK) signaling pathways.

For neuron-related coexpressed DEGs, enriched biological process items were observed in inflammatory response, leukocyte activation, and cytokine regulation. Cellular component items were enriched in cytoplasmic stress granules and platelet alpha granule lumen, whereas molecular function items included histone modification and magnesium ion binding. Pathway analysis showed significant enrichment in cancer-related pathways, apoptosis, and arachidonic acid metabolism (Figure 4).

Identification of core DEGs and related protein interaction networks

Eight core coexpressed genes were identified for astrocyte-related datasets: HSP90AA1, HIF1A, PTEN, ATM, STAT5B, TNFRSF1A, SHC1, and IL6R. Similarly, eight core genes were identified in neurons: NFKB1, CYCS, PTGS2, ITGB2, BCL2L1, BCL6, CYBB, and FCGR3A. The PPI network revealed SHC1 and NFKB1 as central nodes in astrocyte and neuron networks, respectively (Figure 5a,b). Expression profiling showed that most astrocytic genes were significantly upregulated in T2DM and moderately increased in VaD, suggesting enhanced stress and inflammatory responses

TABLE 2 Core bioactive compounds identified from network pharmacology analysis.

Cell type	Target	Compound name	PubChem CID	Compound ID	Classification
AST	TNFRSF1A	Capsaicin	1548943	HBIN019690	Phenyls
	HSP90AA1	Berberine	2353	MOL001454	Alkaloids
	HSP90AA1	Thalifendine	3084288	MOL006422	Alkaloids
	SHC1, IL6R, HSP90AA1	Palmatine	19009	HBIN038665	Alkaloids
	HSP90AA1	Indirubin	10177	MOL002309	Alkaloids
	HSP90AA1	Armepavine	442169	MOL007206	Alkaloids
	HSP90AA1	Dasycarpamin	6325017	MOL006235	Alkaloids
	HSP90AA1	Hyndarin	5417	MOL004071	Alkaloids
	HSP90AA1	Licochalcone A	5318998	MOL000497	Flavonoids
NEU	PTGS2	Palmatine	19009	MOL000785	Alkaloids
	PTGS2	Coptisine	72322	MOL001458	Alkaloids
	PTGS2	Berberrubine	145994872	MOL002894	Alkaloids
	PTGS2	Indigo	10215	MOL001781	Alkaloids
	PTGS2	Thalifendine	3084288	MOL006422	Alkaloids
	NFKB1	Alantolactone	72724	HBIN015037	Terpenoids
	NFKB1	Costunolide	5281437	HBIN021599	Terpenoids
	NFKB1	6-Shogaol	5281794	HBIN012818	Phenyls
	NFKB1	Parthenolide	7251185	HBIN038876	Terpenoids

Abbreviations: AST, astrocyte; NEU, neuron.

(Figure 5c). In neurons, several NFKB1-related genes (FCGR3A, CYBB, ITGB2) were markedly elevated, whereas CYCS and BCL2L1 showed inverse expression patterns (Figure 5d). These findings indicate shared molecular disturbances between T2DM and VaD, with cell type-specific pathway contributions in astrocytes and neurons.

Core compounds and TCM screening

From the TCMSP and HERB databases, 29 compounds targeting core DEGs were identified in astrocyte-related datasets (Figure 6a). Eight core TCMs and nine core compounds (capsaicin, berberine, thalifendine, palmatine, indirubin, armepavine, dasycarpamin, hyndarin, and licochalcone A) were identified based on degree values (Table 2). TCMs included *Corydalis yanhusuo* (Yan husuo), *Phellodendron chinense* (Guan huangbai), *Evodia rutaecarpa* (Wu zhuyu), *Dichroa febrifuga* (Chang shan), *Phellodendron amurense* (Huang bai), *Thalictrum foliolosum* (Ma weilian), *Glycyrrhiza uralensis* (Gan cao), and *Tripterygium wilfordii* (Lei gongteng).

For neuron-related datasets, 59 compounds were identified (Figure 6b), leading to the recognition of seven core TCMs and nine key compounds (palmatine, coptisine, berberrubine, indigo, thalifendine, alantolactone, costunolide, 6-shogaol, and parthenolide) (Table 2). TCMs included *Corydalis yanhusuo* (Yan husuo), *Phellodendron chinense* (Guan huangbai), *Tripterygium wilfordii* (Lei gongteng), *Phellodendron amurense* (Huang bai), *Coptis chinensis* (Huang lian), *Thalictrum foliolosum* (Ma weilian), and *Achyranthes bidentata* (Niu xi). Detailed information for all identified compounds targeting core DEGs is provided in Table S1.

Characterization of core TCMs' properties

According to the China Medical Information Platform, the physicochemical characteristics of core TCMs are presented in Table 3 and Figure 7. Core TCMs targeting astrocytes were predominantly cold in property, bitter in flavor, and mainly associated with the liver, kidney, and heart meridians, functioning primarily as heat-clearing agents. Neuron-targeting TCMs shared similar cold and bitter characteristics, with tropism for liver, heart, and kidney meridians.

Molecular docking validation

Molecular docking results demonstrated strong binding affinities between core compounds and target proteins (Table 4). Among astrocyte-related interactions, indirubin showed the strongest affinity for HSP90AA1

TABLE 3 Systematic profiling of core traditional Chinese medicines.

Cell type	Herb name	Property	Flavor	Meridian	Efficacy
AST	*Corydalis yanhusuo*	Warm	Pungent, bitter	Heart, liver, spleen	Blood-circulating and pain-resolving medicines
	Phellodendron chinense	Cold	Bitter	Kidney, bladder	Interior heat-clearing medicines
	Evodia rutaecarpa	Heat	Pungent, bitter	Liver, spleen, stomach, kidney	Interior warming medicines
	Dichroa febrifuga	Cold	Pungent, bitter	Lung, liver, heart	Emetic medicines
	Phellodendron amurense	Cold	Bitter	Kidney, bladder	Interior heat-clearing medicines
	Thalictrum foliolosum	Cold	Bitter	Heart, lung, liver, gallbladder, colon	Interior heat-clearing medicines
	Glycyrrhiza uralensis	Neutral	Sweet	Heart, lung, spleen, stomach	Qi-tonifying medicines
	Tripterygium wilfordii	Cold	Pungent, bitter	Liver, kidney	Interior heat-clearing medicines, wind-eliminating and dampness-resolving medicines
NEU	*C. yanhusuo*	Warm	Pungent, bitter	Heart, liver, spleen	Blood-circulating and pain-resolving medicines
	P. chinense	Cold	Bitter	Kidney, bladder	Interior heat-clearing medicines
	T. wilfordii	Cold	Pungent, bitter	Liver, kidney	Interior heat-clearing medicines, wind-eliminating and dampness-resolving medicines
	P. amurense	Cold	Bitter	Kidney, bladder	Interior heat-clearing medicines
	Coptis chinensis	Cold	Bitter	Heart, spleen, gallbladder, stomach, colon	Interior heat-clearing medicines
	T. foliolosum	Cold	Bitter	Heart, lung, liver, gallbladder, colon	Interior heat-clearing medicines
	Achyranthes bidentata	Neutral	Bitter, sweet, sour	Liver, kidney	Blood-circulating and blood stasis-resolving medicines

Abbreviations: AST, astrocyte; NEU, neuron.

(−10.0 kcal/mol). For neuron-related targets, palmatine exhibited the highest binding affinity for PTGS2 (−8.1 kcal/mol). These interactions suggest potential roles for indirubin and palmatine in modulating neuroinflammation and apoptosis in T2DM-VaD comorbidity (Figures 8 and 9).

HSP90AA1, a molecular chaperone involved in misfolded protein repair, demonstrates altered expression during T2DM-VaD progression. Previous studies indicate that reduced HSP90AA1 expression under diabetic conditions may promote abnormal tau protein phosphorylation and neurofibrillary tangle (NFT) formation [21]. Vascular injury and BBB disruption potentially exacerbate this process through enhanced neuroinflammation, thereby accelerating cognitive decline. Indirubin, a bioactive alkaloid from *Indigo naturalis* (Qing Dai), has been reported to downregulate HSP90AA1 expression and suppress chronic myeloid leukemia progression [22]. Beyond its antitumor effects, indirubin exhibits neuroprotective properties through inhibition of NF-κB, MAPK, and JAK/STAT pathways, and modulation of CDK and GSK-3β activity [23]. Recently, HSP90 has shown its therapeutic potential in neuroinflammatory disorders through interacting with receptor-interacting protein kinase—a regulator of innate immunity and cell death, which triggers proinflammatory cytokine production through NF-κB [24]. These multimodal actions suggest indirubin is a promising therapeutic candidate for T2DM-VaD comorbidity via targeting HSP90AA1.

PTGS2 (cyclooxygenase-2, COX-2) is a key inflammatory enzyme implicated in disease progression. Palmatine, a protoberberine alkaloid from the Berberidaceae and Papaveraceae families, exhibits diverse pharmacological activities, including inhibition of β-amyloid deposition, tau aggregation, and acetylcholinesterase/butyrylcholinesterase activity. Previous research

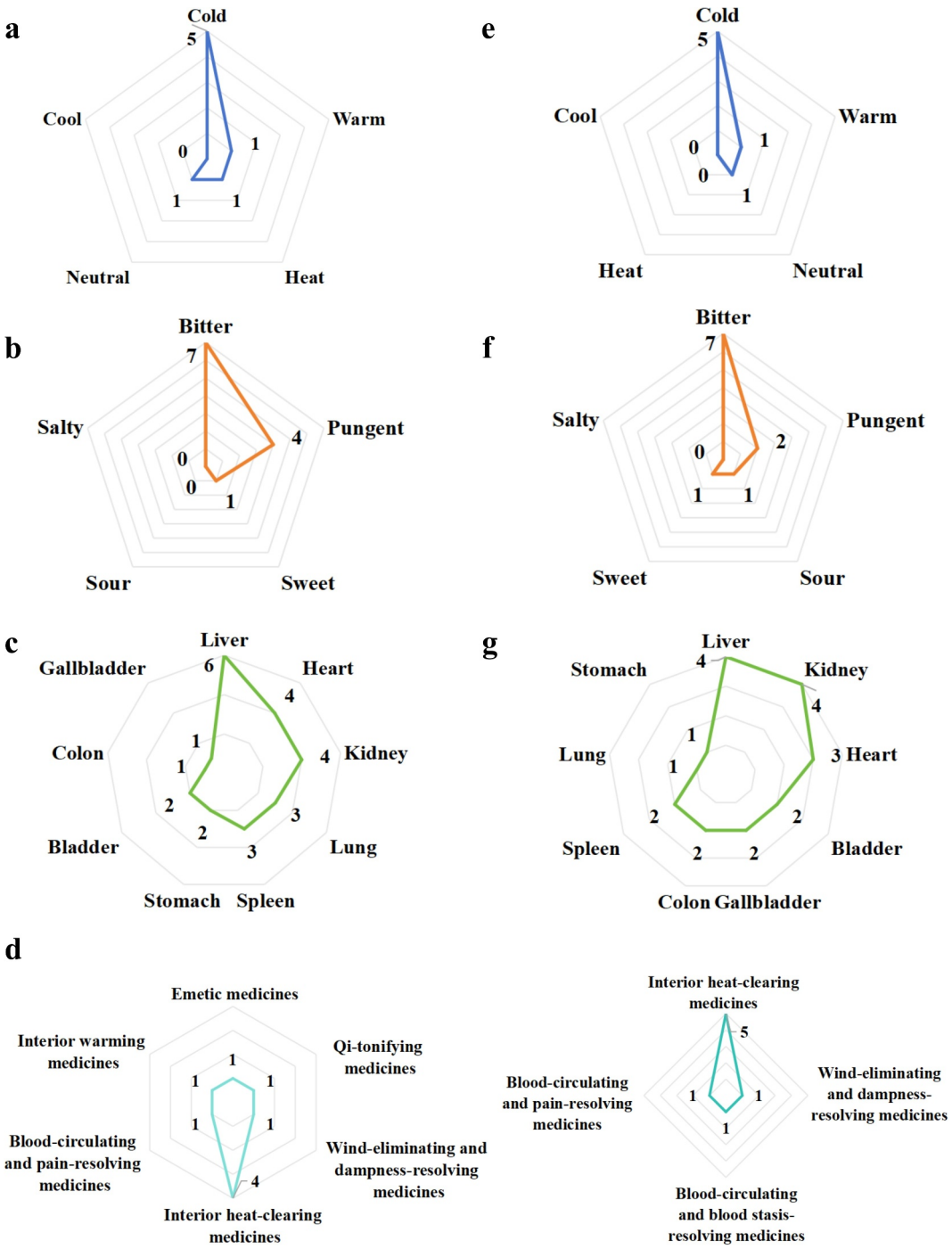

FIGURE 7 Radar chart of property-flavor-meridian-efficacy profiles for herbs targeting core differentially expressed genes in (a–d) astrocytes and (e–h) neurons.

indicates its antidepressant effects by reducing plasma nitrite and corticosterone levels, and its anti-inflammatory effects by inhibiting PTGS2, NF-κB, and NO production. It also exerts antidiabetic effects by inhibiting α-glucosidase, enhancing GLUT-4 expression, and promoting insulin secretion [25]. This multi-target modulation suggests palmatine's potential therapeutic relevance for T2DM-related VaD.

DISCUSSION

This study employed an integrated bioinformatic approach to delineate the shared molecular landscape between T2DM and VaD, with a specific focus on astrocytes and neurons. Our analysis not only identifies potential therapeutic targets but also predicts a set of candidate TCMs and related compounds. To our

TABLE 4 Molecular docking results of core bioactive compounds and target proteins.

Cell type	Target	Compound	Affinity (kcal/mol)
AST	TNFRSF1A	Capsaicin	−5.4
	HSP90AA1	Berberine	−7.9
	HSP90AA1	Thalifendine	−8.7
	HSP90AA1	Palmatine	−7.6
	HSP90AA1	Indirubin	−10.0
	HSP90AA1	Armepavine	−7.3
	HSP90AA1	Dasycarpamin	−6.7
	HSP90AA1	Hyndarin	−6.7
	HSP90AA1	Licochalcone A	−9.2
	SHC1	Palmatine	−7.0
	IL6R	Palmatine	−5.3
NEU	PTGS2	Palmatine	−8.1
	PTGS2	Coptisine	−6.4
	PTGS2	Berberrubine	−6.4
	PTGS2	Indigo	−7.0
	PTGS2	Thalifendine	−7.1
	NFKB1	Alantolactone	−5.8
	NFKB1	Costunolide	−5.9
	NFKB1	6-Shogaol	−5.4
	NFKB1	Parthenolide	−6.5

Abbreviations: AST, astrocyte; NEU, neuron.

knowledge, this systematically stratified comorbid mechanisms, coupled with proposing a multitarget therapeutic strategy based on TCM theory for the first time.

Neuroimaging and neuropathological studies have consistently demonstrated gray matter loss, cortical thinning, and perfusion deficits in temporal and frontal lobes of T2DM patients [26, 27]. The medial temporal lobe, including the hippocampus and adjacent cortices, is particularly sensitive to chronic hyperglycemia, insulin resistance, and microvascular dysfunction, which may collectively contribute to neuronal loss and synaptic impairment [4, 5]. In VaD, ischemic injury and hypoperfusion frequently affect the temporal and parietal cortices, potentially disrupting hippocampal-cortical networks and contributing to cognitive decline. Compared with Alzheimer's disease, temporal lobe atrophy in VaD tends to be milder and more heterogeneous in MRI examinations, which possibly reflects localized ischemic or hypoperfusion-induced damage rather than diffuse neurodegeneration [28]. Given its dual vulnerability to metabolic and vascular insults, the temporal cortex may serve as a relevant region for investigating shared transcriptomic alterations between T2DM and VaD.

T2DM may contribute to VaD pathogenesis through astrocyte dysfunction. Persistent hyperglycemia triggers the release of proinflammatory cytokines [29], potentially activating the NFκB1–TYMP–VEGFA axis in astrocytes. This pathway downregulates tight-junction proteins of claudin-5 and occludin, resulting in BBB disruption [30]. NF-κB activation has been further implicated in white matter injury and cognitive decline [31]. Additionally, reduced expression of astrocytic glutamate transporter-1 (GLT-1) might promote glutamate accumulation, oxidative stress, and neuronal apoptosis [32]. Impaired calcium signaling also impairs neurovascular coupling (NVC) and worsens cerebral hypoperfusion [33]. These alterations may collectively drive neuronal injury and hippocampal dysfunction in VaD. Besides, brain insulin resistance and metabolic dysfunction are central to cognitive impairment in T2DM. Impaired insulin signaling may disrupt protein homeostasis, damage neuronal structures, and hamper amyloid-β (Aβ) clearance, thereby aggravating its neurotoxicity [34]. Concurrent endothelial dysfunction could impair cerebral perfusion while promoting ROS generation, potentially leading to disrupted neurovascular coupling and neuronal hypoxia [35], vascular integrity, and BBB structure [36]. Chronic oxidative stress could cause lipid peroxidation and mitochondrial dysfunction, exacerbate neuronal energy failure, and degeneration [37]. Moreover, O-glycosylation and overactivation of CaMKII might contribute to excitotoxicity and ion-channel dysfunction [38]. These interconnected processes could collectively promote neuronal apoptosis and neurodegeneration in VaD. Several molecular pathways drive these pathological changes in astrocytes and neurons. Proinflammatory signaling may be sustained by TNFRSF1A-mediated NF-κB activation [39] and IL6R-driven JAK–STAT5B signaling [40] and inhibit insulin signaling [41]. HSP90AA1 and ATM could potentially reinforce the inflammatory network by facilitating IKK, JAK, and TAK1 activation through IKKγ/NEMO- and ELKS-dependent mechanisms [42, 43]. The stress adapter protein p66Shc (encoded by SHC1) might mediate oxidative injury independently of NF-κB [44]. Additionally, hyperglycemia may also suppress PTEN and activate Akt/mTOR signaling, potentially exacerbating glutamate-induced excitotoxicity and neuronal apoptosis [45, 46]. Under hypoxic conditions, HIF1A upregulation could increase VEGFA expression and BBB permeability [47]. PTGS2-encoded COX-2 might promote prostaglandin synthesis and disrupt BBB integrity [48], whereas ITGB2 could facilitate leukocyte infiltration. FCGR3A might mediate microglial phagocytosis, potentially causing lysosomal dysfunction and inflammasome activation [49, 50]. Activated microglia may release IL-1β, TNF-α, and ROS, contributing to neuronal damage. BCL6 dysregulation could maintain a proinflammatory microglial phenotype [51], whereas CYBB overactivation might serve as a major ROS source, inducing lipid peroxidation

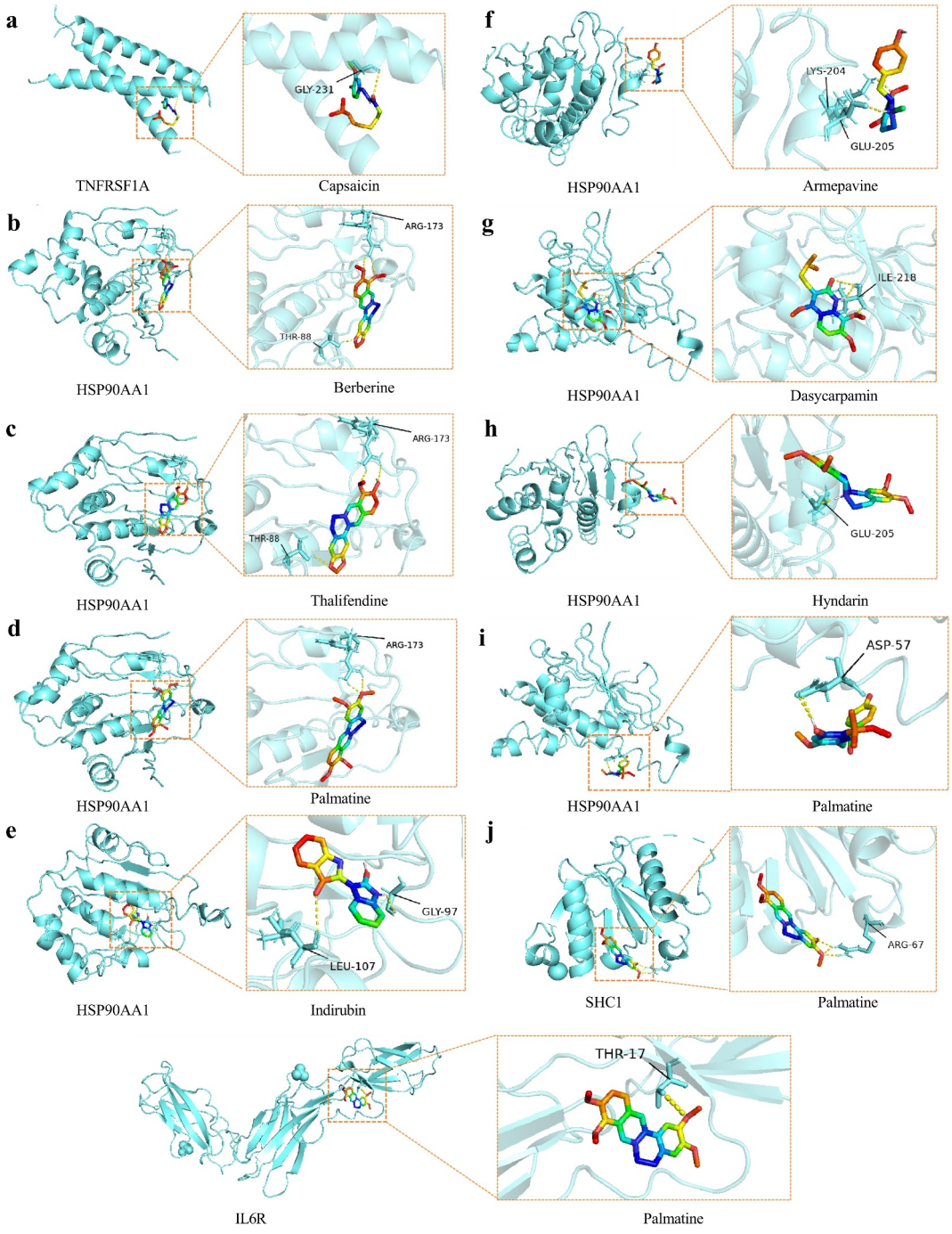

FIGURE 8 Structural visualizations of the binding modes between astrocyte-related targets and core bioactive compounds.

and mitochondrial injury [52]. Additionally, CYCS dysregulation could reduce ATP synthesis and trigger apoptosis, potentially enhanced by suppression of the antiapoptotic regulator BCL2L1 [53]. These represent potential targets for interventions aimed at preserving neurovascular function in T2DM-VaD progression.

In TCM theory, "wasting thirst" syndrome (T2DM) is often attributed to Yin deficiency and internal heat. Spleen dysfunction may disturb metabolism, whereas emotional stress—conceptualized as liver Qi stagnation and heart fire—could further deplete Yin reserves [54]. VaD aligns with mental dullness (*dai bing*) and forgetfulness (*jian wang*), potentially caused by liver Qi stagnation and blood stasis that obstruct cerebral nourishment [55]. The ancient medical book *Sheng Ji Zong Lu* noted that "prolonged wasting-thirst leads to forgetfulness," whereas *Lan Shi Mi Cang* and *Lin Zheng Zhi Nan Yi An* attributed cognitive decline to "internal fire" from emotional constraint and liver Qi stagnation [56–58]. These concepts are supported by

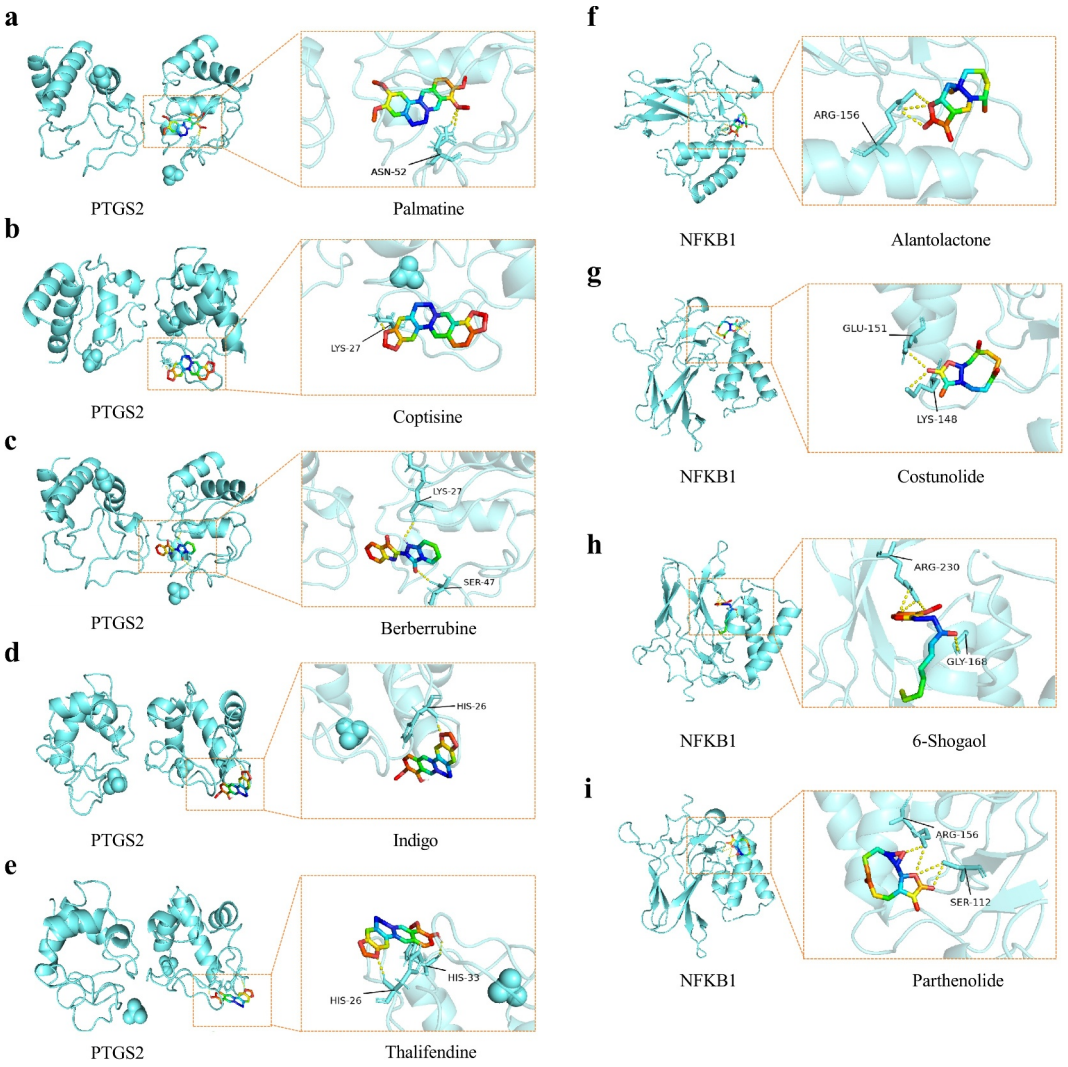

FIGURE 9 Structural visualizations of the binding modes between neuron-related targets and core bioactive compounds.

pharmacological research. T2DM patients with liver stagnation syndrome show increased HOMA-IR and CRP levels, suggesting metabolic inflammation and vascular pathology [58]. Hyperglycemia and vasculopathy worsen cognition by causing ischemia and neuroinflammation through IL-1β and TNF-α signaling [59].

Predicted herbs were mainly linked to the liver meridian, followed by the kidney and heart meridians, which was consistent with TCM theories of liver stagnation, kidney deficiency, and heart vessel obstruction. Heat-clearing herbs dominated functional profiling for both astrocyte and neuron targets, potentially aligning with TCM approaches to dispel internal heat, resolve phlegm, and protect cerebral collaterals. Two top docking compounds were anti-inflammatory alkaloids, suggesting neuroinflammation may represent an important mechanism in T2DM–VaD comorbidity, though structural optimization may be needed to reduce toxicity. Consistent with network pharmacology results, several identified herbs have been experimentally validated for neuroprotective effects. Alkaloids represented the predominant class of active constituents identified, consistent with their bitter-cold nature and traditional heat-clearing properties. Previous studies have reported that total alkaloids from *Coptis chinensis* may enhance cognition via cholinergic activation [60]. Berberine, abundant in *Coptis chinensis*, *Thalictrum foliolosum*, *Phellodendron chinense*, and *Phellodendron amurense*, exhibits potent antidiabetic and neuroprotective properties [61]. It enhances insulin sensitivity through AMPK and PI3K/Akt activation [62], mitigates oxidative stress and neuroinflammation via Nrf2/HO-1 and NF-κB/AGEs-RAGE pathways, and preserves BBB integrity and cholinergic function [63], thereby improving cognitive outcomes. Other compounds demonstrate complementary actions: Glycyrrhizin from *Glycyrrhiza uralensis* may inhibit HMGB1-TLR4/RAGE-NF-κB signaling [64]; tetrahydropalmatine from *Corydalis yanhusuo* and evodiamine from *Evodia rutaecarpa* might suppress oxidative stress and glial

activation [65, 66]; components of *Achyranthes bidentata* could enhance glucose metabolism and vascular function [67, 68]; and *Dichroa febrifuga* extract potentially enhances cholinergic transmission [69]. These findings provide preliminary support for the predicted herb–compound–target interactions, highlighting the multitarget therapeutic potential of TCM in addressing T2DM-VaD comorbidity.

This study has several limitations that should be considered when interpreting the results. First, the limited sample size may reduce statistical power and increase the risk of false-negative results. Therefore, larger independent cohorts are required for future validation. Second, despite age-matched controls, the cohort's advanced age may confound the interpretation of temporal cortex transcriptomic changes. Normal aging alters synaptic transmission, mitochondrial function, and neuroinflammation [70, 71], particularly in vulnerable regions such as the temporal lobe [72, 73]. Thus, we prioritized genes and pathways consistently altered across datasets and mechanistically linked to T2DM and VaD rather than aging. Future analyses incorporating age as a covariate or using age-stratified comparisons could better disentangle these effects [73]. Finally, the computational predictions of compound–target interactions and regulatory mechanisms require experimental validation. In vitro and in vivo models of T2DM-related VaD will be pursued to define the functional roles of core targets and compounds.

CONCLUSION

In summary, this study applied an integrated transcriptomic and network pharmacology approach to elucidate potential molecular mechanisms linking T2DM to VaD progression. Our results revealed astrocyte-related mechanisms involved genes of HSP90AA1, HIF1A, PTEN, ATM, STAT5B, TNFRSF1A, SHC1, and IL6R. Neuron-related mechanisms involved genes of NFKB1, CYCS, PTGS2, ITGB2, BCL2L1, BCL6, CYBB, and FCGR3A. Ten core TCMs—primarily characterized by bitter flavor, cold property, and liver meridian tropism—were identified as candidate therapeutic agents. Representative compounds such as indirubin and palmatine may exhibit relatively strong binding affinities with key targets. These findings provide insights into the shared pathology of T2DM and VaD and offer a theoretical basis for developing multitarget, TCM-inspired interventions. Further experimental validation remains essential to confirm these predictions.

AUTHOR CONTRIBUTIONS

Meiyue Li: Data curation; formal analysis; investigation; methodology; validation; visualization. **Xue Li**: Data curation; investigation; validation; visualization. **Lijia Xu**: Conceptualization; project administration; resources; supervision. **Peigen Xiao**: Conceptualization; project administration; resources; supervision. **Pei Ma**: Conceptualization; funding acquisition; methodology; visualization; writing—review and editing. **Lifeng Yue**: Conceptualization; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENTS

The data underpinning this network pharmacology analysis are derived from previously reported studies and databases, all of which have been duly cited. Upon reasonable request, the data that support the findings of this study can be acquired from the corresponding author.

ETHICS STATEMENT

Because the data employed for bioinformatics analysis were obtained from publicly accessible databases, and our research did not involve the use of human or animal samples nor any experiments related to biosafety, no ethical approval was required. Moreover, all the data sourced from these public databases have been previously published and can be openly cited.

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SUPPORTING INFORMATION

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