

Traditional Chinese Medicine Natural Products Targeting Shared Mechanisms of T2DM and AD: Potential Therapeutic Insights

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Abstract: As highly prevalent chronic diseases globally, AD (Alzheimer's disease) and T2DM (type 2 diabetes mellitus) not only severely affect the quality of life of patients but also impose a significant burden on their families. Numerous studies have gradually revealed that T2DM and AD are bidirectional risk factors, each capable of exacerbating the other. There is a notable correlation in their pathological mechanisms, primarily manifested in insulin resistance, OS (oxidative stress), and inflammatory responses. Currently, available drugs can only delay the progression of AD, such as Donepezil, Galantamine, and Carbamylcholine, making complete cures challenging to achieve. TCM (Traditional Chinese medicine) natural products exhibit characteristics such as multi-targeting, multi-pathway interactions, diverse biological activities, and relatively mild side effects, enabling synergistic intervention in both diseases. In recent years, TCM natural products have garnered increasing attention in research concentrated on the prevention and management of AD and T2DM. This article aims to comprehensively elucidate the collective pathogenic mechanism of AD and T2DM, and explore the progress of TCM natural products based on these mechanisms in the prevention and treatment of both diseases, thereby providing a theoretical foundation for the advancement of innovative treatment tactics.

Keywords: natural products, traditional Chinese medicine, type 2 diabetes mellitus, T2DM, Alzheimer's disease, AD

Introduction

AD (Alzheimer's disease) is a progressive, persistent, and degenerative disorder of the CNS (central nervous system).¹ Its main features include a gradual decline in memory, cognitive deficits, alterations in personality, language issues, and various other neuropsychiatric symptoms. In 2018, the Alzheimer's Disease International Organization approximated that around 50 million people worldwide were affected by dementia, with forecasts suggesting that this number could triple by the year 2050.² According to its etiopathology, AD is typically classified into fAD (familial AD) and sAD (sporadic AD), with sAD comprising the largest proportion. This form is often associated with complications such as stroke, obesity, cardiovascular diseases, and T2DM (type 2 diabetes mellitus), which can exacerbate the progression of sAD.³ Among these complications, diabetes is one of the most common diseases affecting human beings. In 2019, the worldwide occurrence of diabetes was estimated to be 9.3%, affecting 463 million people. This figure is anticipated to increase to 10.2% (578 million individuals) by 2030 and reach 10.9% (700 million individuals) by 2045.⁴ Diabetes is a metabolic disorder characterized by elevated blood sugar levels, with T2DM accounting for approximately 90% of all diabetes cases. Many studies have shown a intense association between AD and T2DM, with the risk of AD being nearly twice as high in diabetic patients compared to those without diabetes.^{5,6} Notably, T2DM is closely linked to an increased

risk of developing AD,^{7,8} and the incidence of AD rises with age.^{9,10} AD can be considered a central metabolic disorder characterized by impaired glucose metabolism, which is associated with compromised insulin and IGF (insulin-like growth factor) signaling pathways in the brain.¹¹ Additionally, both AD and T2DM are characterized by neuronal and β -cell loss.¹² Consequently, AD is often referred to as type 3 diabetes.¹³ Current research identifies extracellular amyloid protein deposition and intracellular tau protein phosphorylation as the two primary pathological markers of AD.¹⁴ Furthermore, IR (insulin resistance) in the brain is recognized as a potential etiological factor in AD¹⁵ and serves as a crucial link between AD and T2DM.¹⁶ Similarly, significant genetic risk elements for AD, including the ApoE (apolipoprotein E) gene, could intensify the impact of diabetes on cognitive abilities.¹⁷

T2DM and AD exhibit overlapping molecular pathways, which encompass IR, OS (oxidative stress), A β (amyloid β -protein) deposition, inflammatory, tauhyperphosphorylation, mitochondrial dysfunction, the presence of the ApoE4 allele, and AGEs (advanced glycation end products).¹¹ Peripheral IR can disrupt insulin signaling pathways in the CNS, while IR of CNS may lead to increased A β levels, tau hyperphosphorylation, OS, and neuroinflammation.⁹ Research has found that individuals with diabetes had a 65% higher risk of developing AD than those without diabetes.^{18,19} Richard et al²⁰ discovered that participants diagnosed with diabetes encountered a more rapid deterioration in cognitive function over the following decade. In studies involving diabetic monkeys, peripheral IR was found to exacerbate AD-related pathology, suggesting that T2DM has the potential to serve as a risk factor for AD.²¹ An autopsy case revealed the presence of aggregated A β and p-tau (phosphorylated tau) protein in the pancreatic islet cells of T2DM patients.²² Juliette et al²³ reported that the likelihood of T2DM and impaired fasting blood glucose levels increased among AD patients, with autopsy findings indicating a higher frequency of pancreatic islet amyloidosis in this population. A prospective cohort study indicated that T2DM contributes to A β protein deposition.²⁴ In the frontal cortex of T2DM patients undergoing autopsy, an increase in tau phosphorylation was observed, further suggesting that T2DM may elevate the risk of AD.²⁵ Harold et al²⁶ found that abnormal insulin levels in the brain may lead to reduced cognitive function suggests a potential link between IR and AD. Neuroimaging studies have indicated that elderly individuals with IR and T2DM are more likely to exhibit structural and functional brain changes, such as brain atrophy.²⁷ Recent research has indicated that damage to gray matter is closely associated with cognitive impairment,^{28,29} and cortical atrophy may serve as an independent predictor of cognitive decline,^{30,31} underscoring the strong relationship between T2DM and AD.

Despite the unremitting efforts of medical researchers, current drugs provide only limited relief of symptoms and do not prevent or reverse T2DM and AD. Metformin has been shown to reduce the prevalence of AD,³² but it may also lead to the overphosphorylation of p-tau and affect A β protein aggregation.^{33,34} The insulin sensitizer rosiglitazone can improve IR in T2DM and protect synapses;³⁵ however, it is not utilized in cases of T2DM combined with AD due to its inability to cross the BBB (blood-brain barrier) and its serious side effects.³⁶ Tacrine has demonstrated efficacy in resisting AD and enhancing cognitive function in db/db mice,³⁷ but it poses significant risks to cardiac and hepatic health.³⁸ Rivastigmine can inhibit neuroinflammation and enhance memory capabilities in T2DM-AD mice, yet it does not modify the insulin abnormalities or amyloid pathology observed in these models.³⁹ Hai et al, investigated the potential of identifying anti-AD medicines within hypoglycemic traditional Chinese medicinal formulas, presenting an alternative approach for screening AD medications. They found that Huangqi-Gegen is a promising treatment for AD, with its mechanism possibly involving the suppression of protein production of acetylcholinesterase (AChE) and cyclooxygenase-2 (PTGS2), reduction of serotonin (5-HT) intake, and subsequent decrease in A β deposition.⁴⁰ Huang-Lian-Jie-Du decoction (HLJDD) is a traditional Chinese formula known for its efficacy in treating diabetes mellitus, Alzheimer's disease, and diabetic encephalopathy. Tian et al, demonstrated that HLJDD ameliorates cognitive dysfunction in rats with T2DM. The neuroprotective effects are mediated through the modulation of glucose and lipid metabolism, the upregulation of autophagy, and the inhibition of the NLRP3 inflammasome signaling pathway.⁴¹ The findings indicate that research on TCM concerning AD and T2DM is still in its nascent stages and requires urgent exploration. Consequently, scholars both domestically and internationally are continuously investigating innovative therapeutic approaches. Over the past few years, TCM (traditional Chinese medicine) has garnered more popularity and acclaim among the general populace. It is regarded as economical, safe, and associated with minimal side effects, while also possessing multi-target functions, which has attracted the attention of a growing number of researchers. Notably, natural products derived from TCM and their active components have shown considerable potential in inhibiting

A β deposition, reducing p-tau, and improving IR, thus demonstrating significant therapeutic effects on both AD and T2DM. Research has demonstrated that Berberine and Geniposide significantly mitigates hippocampal neuronal injury, reduces A β plaque deposition, alleviates abnormal tau protein phosphorylation, and suppresses neuronal apoptosis in diabetic rat model.^{42,43}

This article compiles recent studies on the use of natural products from TCM in the treatment of AD complicated by T2DM, aiming to provide a theoretical and experimental basis for both diseases.

Search Strategy and Selection Criteria

We conducted a comprehensive literature search utilizing Google Scholar, PubMed, the Chinese National Knowledge Infrastructure database, the full-text database of the Chinese Medical Journal (yiggle.com), and the Excerpta Medica (EMBASE) database. The search was guided by the following keywords: “Alzheimer’s disease”, “AD”, “T2DM”, “Type 2 Diabetes Mellitus”, “Cognitive Dysfunction”, “Cognitive Impairment”, “Natural Products”, and “Traditional Chinese Medicine”. This search specifically targeted articles published between 2015 and 2025 and was executed by the author LF.

Shared Pathogenesis of T2DM and AD

Compared to healthy individuals, diabetic patients exhibit a reduction in gray matter volume in the bilateral frontal cortex, parahippocampal gyrus, cerebellar cortex, vermis, brainstem, and bilateral cerebellar tonsil regions.⁴⁴ Analyses from the cross-sectional study suggested that the decrease in gray matter volume may play a mediating role in the connection between diabetes and cognitive capabilities.⁴⁵ Currently, the primary pathogenesis of diabetes complicated by cognitive dysfunction includes IR, inflammation, OS, microbiota-gut-brain axis disorder, and cerebral microvascular dysfunction. Among these, IR is a vital feature of T2DM, encompassing both peripheral and central IR. In diabetic patients, IR diminishes the expression of AChE (acetylcholinesterase), reduces ACh (acetylcholine) synthesis, and consequently affects learning and memory functions.

The main pathological features of AD include A β and tau protein hyperphosphorylation.⁴⁶ A β is produced through the hydrolysis of APP (amyloid precursor protein) by β and γ -secretases.⁴⁷ IR has the capacity to affect signaling pathways involving the IRS (insulin receptor substrate) and Akt (protein kinase B), stimulate GSK (glycogen synthase kinase)-3, and facilitate both extracellular deposition of A β and hyperphosphorylation of intracellular tau protein,^{48,49} ultimately leading to NFTs (neurofibrillary tangles).⁵⁰ The inflammation occurring in the CNS is regarded as one of the underlying pathological mechanisms found in individuals with AD. Research has shown that this inflammatory response is similarly evident in patients with diabetes, characterized by the activation of microglia and astrocytes alongside the infiltration of neuroimmune cells. When astrocytes are activated, they produce a range of pro-inflammatory substances, such as cytokines, chemokines, complement proteins, and ROS (reactive oxygen species), all of which are essential features of CNS inflammation.

Additionally, brain tissue possesses physiological characteristics such as a high oxygen consumption rate, a rich lipid content, and relatively fewer antioxidant enzymes, making it susceptible to oxidative damage. Research findings demonstrate that hyperglycemia can elevate the production of ROS by decreasing the activities of SOD (superoxide dismutase) and GPx (glutathione peroxidase), leading to neuronal apoptosis and necrosis.⁵⁰ Furthermore, OS is involved in inflammatory responses, by activating microglia and astrocytes and releasing pro-inflammatory cytokines, it contributes to neuroinflammation and neurodegenerative changes. The intestinal microbiota primarily exerts effects on the host through the bacteria themselves and their metabolites. GLP-1 (Glucagon-like peptide-1) and other substances are significantly influenced by the intestinal microbiota and its metabolites, playing roles in the CNS and cognitive function. Another study found that patients suffering from DCD (diabetic cognitive dysfunction) exhibit thickening of the vascular basement membrane, dysfunction in the vascular endothelium, and heightened permeability of the BBB within their brain microvascular system.⁵¹ Vascular endothelial dysfunction primarily relates to the accumulation of AGEs, toxic lipids, and protein clumps within small blood vessels. Such deposition can enhance the production of ROS, increase vascular permeability, and damage brain neurons.⁵²

Common molecular pathologies between T2DM and AD

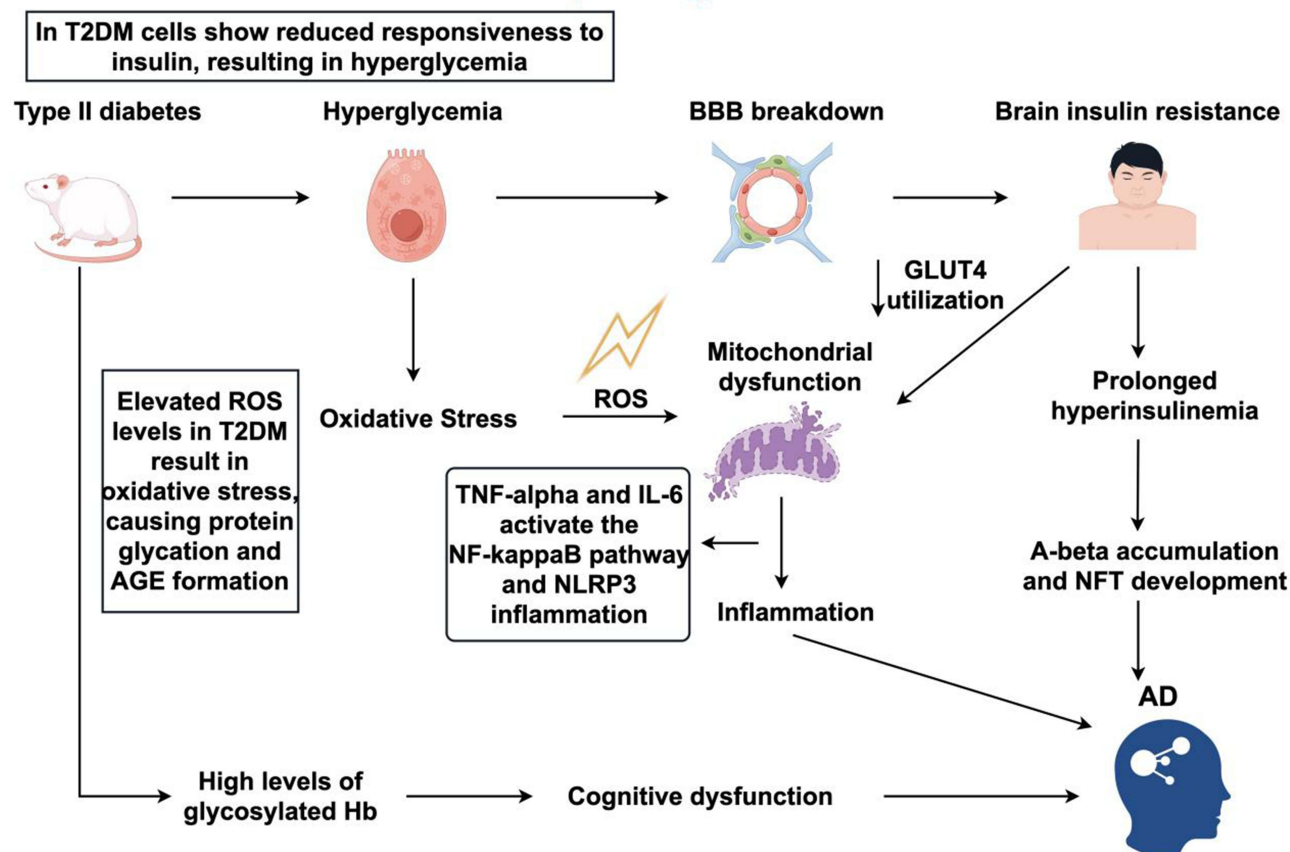


Figure 1 The pathogenesis of Type 2 Diabetes Mellitus and Alzheimer's disease. In T2DM, the sensitivity of cells to insulin decreases, leading to hyperglycemia. The hyperglycemic state results in elevated levels of reactive oxygen species (ROS), which produce oxidative stress (OS), subsequently causing protein glycation and the formation of advanced glycation end products (AGEs). Additionally, hyperglycemia increases the level of glycated hemoglobin (Hb), which can lead to cognitive dysfunction. OS Cascade: The ROS generated by OS can cause mitochondrial dysfunction. Mitochondrial dysfunction further promotes inflammation, during which cytokines such as TNF- α and IL-6 activate the NF- κ B signaling pathway and the NLRP3 inflammasome. Blood-Brain Barrier (BBB) and Brain Insulin Resistance: Hyperglycemia can also lead to the disruption of the BBB, resulting in insulin resistance in the brain. Brain insulin resistance impedes the utilization of glucose transporter 4 (GLUT4), leading to a prolonged state of hyperinsulinemia.

Substantial epidemiological findings indicate a correlation between AD and T2DM. To investigate whether A β and p-tau are present in T2DM, pancreatic tissues from 21 autopsy cases (including 10 with T2DM and 11 control subjects) were examined. The analysis reveals that the deposition of A β , the hyperphosphorylation of tau, along with immunoreactivities for ubiquitin and ApoE, are distinctive traits associated with T2DM.²² Similar to AD, the deposition of amyloid peptides in the pancreas is a characteristic of T2DM. A β and IAPP (islet amyloid polypeptide, also known as amylin) exhibit similar folding patterns and conformations, with approximately 90% overlap in their structural characteristics.²³ IAPP is a peptide secreted by islet β cells and induces toxicity in these cells in a manner analogous to A β 's effect on neurons.⁵³ Comprising 37 amino acids, IAPP has been shown to exist in the brain either as independent plaques or co-precipitating with A β to form composite plaques.⁵⁴ Under pathological conditions, A β and its oligomers exhibit neurotoxicity towards neurons, leading to OS and inflammatory damage, which in turn results in further A β deposition and IR (Figure 1).⁵⁵ Notably, A β binds to the insulin receptor, and following specific knockout of this receptor, the activity of GSK-3 β increases, leading to neuroinflammation, excessive tau phosphorylation, and the induction of A β generation.^{56–58}

TCM Natural Products Target Mechanisms of T2DM and AD

Insulin Resistance

The insulin signaling pathway predominantly comprises the PI3K (phosphatidylinositol 3-kinase)/Akt signaling pathway and the MAPK (mitogen-activated protein kinase) signaling pathway.⁵⁹ Abnormalities in this pathway can result in IR, which refers to a diminished sensitivity of the body's tissues and organs to insulin.⁶⁰ Given that insulin can traverse the BBB, IR may manifest in both central and peripheral systems,⁶¹ contributing to the development of diabetes and leading to the deposition of A β and p-tau.⁵⁵ Under normal conditions, insulin and IGF receptors are abundantly present in the brain, with their degradation primarily mediated by IDE (insulin-degrading enzyme). Both types of receptors are classified as RTKs (receptor tyrosine kinases). Upon binding with their respective ligands, these receptors undergo self-phosphorylation, which subsequently promotes the phosphorylation of various intracellular receptor substrates, including IRS molecules, Shc (SH2-containing proteins), and PI3K, thereby activating distinct pathways and fulfilling physiological functions. In T2DM, impaired insulin signaling can lead to excessive tau phosphorylation, resulting in the formation of NFTs and ultimately causing hippocampal atrophy.⁶²

Research has shown that under normal conditions, the activation of the PI3K/AKT signaling pathway by insulin or IGF primarily influences the synthesis of A β 40 and A β 42 by inhibiting the activity of GSK-3 α and regulating γ -secretase. A deficiency of insulin or IGF can disrupt A β formation and hinder its extracellular transport. Concurrently, elevated levels of A β can enhance the clearance of insulin receptors from the cell surface, leading to IR, thereby creating a vicious cycle.⁶³ The promoter region of the human BACE1 (beta-site amyloid precursor protein cleaving enzyme 1) features two active binding sites for NF- κ B (nuclear factor- κ B). Both in vitro and in vivo studies have indicated that the activation of GSK-3 β plays a role in the nuclear translocation of NF- κ B/p65 and its interaction with the BACE1 promoter regions, leading to enhanced levels of BACE1 protein and the processing of APP mediated by BACE1, consequently resulting in the production of A β .⁶⁴ The cholinergic system effectively regulates inflammation and immunity by releasing ACh, which acts on the nAChRs (α 7-nicotinic acetylcholine receptor) and the M-AchRM1 (muscarinic acetylcholine receptor M1).⁶⁵ There is an interaction between the signaling pathways downstream of the insulin receptor and the transduction of signals from inflammatory factors. Inflammatory factors produced during non-specific inflammation disrupt the IRS/PI3K signaling pathway, which is the primary molecular mechanism that leads to IR.⁶²

IDE is a protease that degrades A β , insulin, IGF-1, and IAPP.^{61,66} A deficiency in IDE leads to IR. IDE is a neutral thiol endopeptidase with a relative molecular weight of 110,000. Research have indicated that knocking out the IDE gene in mice significantly increases the levels of A β ₄₀ and A β ₄₂ in the mouse brain.⁶⁷ Leissring et al⁶⁸ transfected neurons to overexpress IDE, resulting in a significant reduction in the level of A β in the brain. This overexpression could also slow down and block the formation of amyloid plaques and related cellular pathological changes. Jia et al⁶⁹ found in their research that the PS-1 V97L mutation may inhibit the expression of IDE by upregulating the transcription factor GATA-3, thereby affecting the content of A β ₄₂ and participating in the formation of AD. Research indicates that IDE can not only degrade extracellular monomeric A β and disrupt the functional domain of APP but also regulate the degradation and clearance of A β in the brain, thereby reducing the toxic effects of A β .⁷⁰ Insulin signaling plays a direct role in regulating IDE. The suppression of insulin signaling through PI3K leads to a decrease in IDE protein levels. Strategies aimed at enhancing insulin signaling may represent a novel treatment option for AD. IDE serves as a key regulator of A β levels in both microglial and neuronal cells. It was observed that a reduction in PI3K activity resulted in increased A β deposition, causing a gradual accumulation of A β plaques due to the reduced function of IDE linked to PI3K inhibition and a corresponding decline in insulin signaling. IDE is pivotal in the metabolism of A β and its buildup in the brain.⁷¹ The increased levels of IDE lead to the down-regulation of IGF-1, which subsequently enhances the activity of IL (interleukin)-1 β . An excess of interleukins generates OS within the brain. Various research efforts suggest that IL-1 β interacts with A2M (alpha-2-microglobulin), influencing ApoE function, which is involved in the production of APP and, consequently, affects the pathology related to AD.⁷²

Kim et al⁷³ investigated the beneficial impacts of ginsenoside Re on IR induced by a HFD (high-fat diet) in C57BL/6 mice to evaluate its physiological role. Their findings suggest that ginsenoside may improve HFD-induced IR by alleviating hyperglycemia through the protection of cholinergic and antioxidant systems in the brains of the mice.

Kang et al⁷⁴ investigated the EFAA (effects of *Artemisia argyi*) and 4,5-diCQA (4,5-dicaffeoylquinic acid) on cognitive dysfunction induced by a HFD. Both EFAA and 4,5-diCQA demonstrated efficacy in enhancing cognitive function in the context of HFD-induced cognitive impairment. In conclusion, it is suggested that EFAA may contribute to the amelioration of cognitive deficits associated with HFD, an effect that appears to be closely linked to the physiological activity of 4,5-diCQA. Liu et al⁷⁵ revealed that injection with STZ (streptozotocin) can effectively inhibit IDE expression and diminish the degradation of A β peptides, leading to increased levels of A β peptides and the promotion of various pathological features associated with AD. Furthermore, they proposed that treatment with geniposide ameliorated this phenomenon in STZ-induced rats. Zhang et al⁴² found that administering geniposide for a period of four weeks led to a notable reduction in the phosphorylated levels of tau, as well as a decrease in the acceleration of GSK-3 β phosphorylation, in the brains of APP/PS1 (APPswe/PSEN1dE9) transgenic mice affected by insulin deficiency. These results establish a mechanistic and possibly fundamental relationship between diabetes and AD, supporting the idea that geniposide might be crucial in promoting tau protein phosphorylation through the enhancement of insulin signaling, potentially conveying therapeutic benefits in AD. Yan et al⁷⁶ explored the treatment of AD from two perspectives. On one hand, they demonstrated that a HFD can exacerbate the progression of AD. On the other hand, they found that Okra polysaccharides can ameliorate cognitive disorders in AD model mice. Furthermore, their study confirmed that Okra polysaccharides can reverse cognitive impairment and metabolic disorders induced by HFD through the insulin signaling pathway. Schisandrin A, a lignan derived from the dried fruit of *Schisandra chinensis*, exhibits a variety of pharmacological effects, including the modulation of immune system control, suppression of apoptosis, and properties of antioxidant and anti-inflammation. Guo et al⁷⁷ demonstrated that Schisandrin A can improve the deficiencies in spatial learning and memory associated with diabetes, presumably by reducing inflammatory responses and regulating the insulin signaling pathway. BBR (Berberine), derived from TCM, has been utilized for the treatment of diabetes and diabetic cognitive impairment, although its underlying mechanisms remain largely unexplored. In the study conducted by Zhang et al,⁷⁷ a STZ-induced diabetic rat model fed a HFD was employed to evaluate the effects of BBR in comparison to metformin. The results indicated a decrease in hippocampal neuronal damage, A β deposition, tau protein abnormal phosphorylation, and neuronal apoptosis, which are considered to be related mechanisms of action. Another study⁷⁸ demonstrated that BBR has the potential to enhance memory function, reorganize misaligned nerve cells, and lessen neuronal injury. Additionally, it increased the count of TUNEL-positive cells and lowered high levels of fasting blood glucose, triglycerides, total cholesterol, and glycosylated serum protein in diabetic rats suffering from AD. Furthermore, The treatment with BBR reduced both the transcription levels of mRNAs and the protein expression related to ER (endoplasmic reticulum) stress. Chen et al⁷⁹ also demonstrated that BBR inhibited the activation of inflammatory pathways and IR in the mPFC (medial prefrontal cortex) of diabetic rats. Furthermore, it improved cognitive impairment in these diabetic rats. Finally, it alleviated cognitive impairment Wu et al⁷⁹ demonstrated that monomeric BBR treatment improved IR, potentially through the modulation of proteins associated with the dysfunctional insulin signaling pathway. Furthermore, BBR was found to inhibit the production of A β 42 and mitigate axonal damage in neurons. Ultimately, these findings suggest that BBR may alleviate cognitive impairments induced by diabetes mellitus. Gypenoside LXXV, a novel natural Peroxisome PPAR- γ (proliferator-activated receptor- γ) agonist isolated from *Gynostemma pentaphyllum*, has been shown to ameliorate cognitive deficits in db/db mice. In the study conducted by Meng et al⁸⁰ it was demonstrated that Gypenoside LXXV enhanced the cognitive function of APP/PS1 and APP/PS1/db/db mice. This improvement was achieved by promoting glucose uptake, triggered by the activation of the PPAR γ /Akt/Glucose transporter (GLUT) 4 signaling pathways. Parida et al⁸¹ demonstrated that 1-Deoxynojirimycin seemed to reduce the rise in p-tau and A β 1-42 levels driven by IR by facilitating the insulin-induced phosphorylation of GSK-3 β (a principal tau kinase) and boosting the mRNA expression of the IDE, which is crucial for the clearance of insulin and A β . Wang et al⁸² discovered that Calycosin improved cognitive deficits caused by diabetes in rats by decreasing OS through the PI3K/Akt/GSK-3 β signaling pathway.

IR, as a “common soil” for T2DM and AD, is transitioning its research focus from single organ pathology to a systemic metabolic network. Future efforts may involve the design and development of dual-site modulators (such as peripheral IR inhibition combined with brain IR activation), providing a new paradigm for addressing the global health challenge posed by diabetes coexisting with AD.

Neuroinflammation

Glial cells in the CNS primarily consist of microglia, astrocytes, and oligodendrocytes.⁸³ Research has demonstrated that activated microglia aggregate near A β . Initially, they clear extracellular A β by engulfing, degrading, or releasing lysosomes; however, if the concentration of A β secreted by neurons increases to a critical level, disrupting the balance between A β clearance and accumulation, long-term chronic inflammation may ensue.^{84,85} Soluble A β oligomers and A β fibrils can bind to various receptors on the surface of microglia (such as CD14, CD36, CD47, and TLRs (Toll-like receptors)), thereby triggering the release of inflammatory cytokines and chemokines (including IL-1, IL-6, IL-12, IL-23, TNF (tumor necrosis factor)- α , and other inflammatory markers). This cascade leads to chronic inflammation, mediating neuroinflammation and neurotoxicity, and contributes to the accumulation of A β and p-tau.^{86–90} Astrocytes, the most common and largest type of glial cells, support and separate nerve cells while participating in the formation of the BBB.⁹¹ Microglia inhibit the destructive phenotype of astrocytes induced by NF- κ B, chemokines, and vascular endothelial growth factor by releasing IL-17, sphingolipids, neurotrophin receptors, and cytokine signaling pathways. This inhibitory effect leads to the loss of astrocyte's ability to promote neuronal survival, growth, synaptogenesis, and phagocytosis, ultimately resulting in the death of neurons and oligodendrocytes.⁹² In the brain, inflammation caused by IR intensifies neuroinflammatory processes.⁹³ IR leads to persistently high blood sugar levels and an unhealthy imbalance of lipids in the bloodstream, factors that can harm and increase the permeability of the BBB.⁹⁴ When the BBB is compromised, free fatty acids and elevated blood glucose levels activate microglia, prompting them to adopt a pro-inflammatory phenotype. This activation can result in the release of cytokines, triggering neuroinflammatory cascades and reactive astrogliosis.^{94,95} Consequently, neuroinflammation exacerbates further damage to the BBB, resulting in even greater permeability.⁹⁶ This increased permeability raises the already high levels of glucose in the brain, contributing to a detrimental cycle of neuroinflammation driven by hyperglycemia.^{97,98}

Liu et al⁹⁹ demonstrated that Cucurbitacin B treatment resulted in an increased density of viable neurons in the cortex and hippocampus of rats subjected to STZ- ICV (intracerebroventricular) neurotoxicity. This treatment was associated with enhanced antioxidant activity, a reduction in inflammatory markers, decreased cell death biomarkers, and lower levels of AChE and glutamate. The majority of the *Elettaria cardamomum* compounds identified were terpenoids. Administration of the *Elettaria cardamomum* extract over a period of 8 weeks mitigated AD-like alterations through the activation of the damaged insulin signaling pathway in the brain.¹⁰⁰ This intervention also reduced associated OS and neuroinflammation, evidenced by a decrease in hippocampal TNF- α and IL-1 β levels, while IL-6 levels remained unchanged. Additionally, there was a reduction in GSK-3 β levels in the brains of T2DM rats.¹⁰⁰ Resveratrol, a type of polyphenol mainly located in grapes and red wine, demonstrates properties that protect against OS, reduce inflammation, and neuroprotective properties. Tian et al¹⁰¹ reported that cognitive performance in the diabetic group was significantly impaired, which was accompanied by notable alterations in OS and inflammatory parameters, as well as reduced expression of SYN (synapse) and GAP-43 (growth-associated protein-43) in the hippocampus. In contrast, chronic administration of resveratrol improved cognitive function and reduced neuronal damage in diabetic rats by alleviating OS and inflammation, while also preventing synaptic degeneration. Another study demonstrated that Resveratrol notably enhanced the expression of sirtuin1 and effectively suppressed memory impairment and mitigated the elevated levels of AChE, MDA (malondialdehyde), IL-1 β , and IL-6, while also restoring the decreased levels of ChAT (choline acetyltransferase), SOD, and GSH (glutathione) in this rat model of diabetes and concomitant AD.¹⁰² Hyperoside, a flavanone glycoside, is recognized for its wide-ranging pharmacological advantages, such as antioxidant and anti-inflammatory characteristics. Chen et al¹⁰³ reported that hyperoside mitigated neuroinflammation, cognitive impairment, and OS by suppressing the TNF- α /NF- κ B/caspase-3 signaling pathway in rats with T2DM. The findings of Park et al¹⁰⁴ demonstrated that *Agrimonia pilosa* Ledeb, *Lonicera japonica* Thunb, and *Cinnamomum cassia* Blume are effective in preventing cognitive dysfunction as well as the disturbance in energy and glucose homeostasis resulting from A β accumulation. This effect was mediated through the reduction of neuroinflammation and the enhancement of insulin signaling, which occurred via the activation of the AKT/GSK-3 β signaling pathway, alongside an increase in iNOS (inducible nitric oxide synthase) and TNF- α levels. Dioscin exhibits a range of pharmacological activities against various diseases; however, its underlying mechanisms related to DCD remain unclear. The P2X7R (P2X7 receptor), consisting of 595 amino acids, serves as a crucial plasma membrane receptor.¹⁰⁵ It promotes the release of pro-inflammatory cytokines,

including IL-6, IL-10, and TGF- β (transforming growth factor- β), in microglial cells, fibroblasts, and mast cells.^{106–108} Additionally, P2X7R is a potent activator of NLRP3 (NOD-like receptor protein 3) inflammasome signaling and facilitates the cleavage of Caspase-1, leading to the release of IL-1 β .^{109,110} Lu et al¹¹¹ performed a series of pharmacological assessments involving the P2X7R in conjunction with dioscin. Their findings revealed that both P2X7R and NLRP3 inflammasome pathways were initiated in DCD through both in vivo and in vitro analyses. Furthermore, it was established that dioscin's anti-DCD effects were associated with the suppression of the P2X7R/NLRP3 pathway.¹¹¹ TMP (Tetramethylpyrazine) is recognized for its anti-diabetic and neuroprotective properties. In the research carried out by Dhaliwal et al¹¹² it was observed that the treatment of diabetic rats with TMP resulted in improved insulin sensitivity, as well as a reduction in hyperglycemia and dyslipidemia. Additionally, the treatment led to increased levels of BDNF (brain-derived neurotrophic factor), p-Akt, and p-CREB (phosphorylated cAMP response element-binding protein), normalization of cholinergic dysfunction, and suppression of OS, inflammation, and apoptotic markers in the hippocampus. Lu et al¹¹³ reported that a 2-week administration of TMP reduced impairments in both short-term and long-term memory caused by the ICV injection of STZ in an established rat model of AD. Furthermore, TMP was found to inhibit GSK-3 β activity, an essential kinase involved in hippocampal synaptic dysfunction and memory impairments linked to DM. Ultimately, the researchers discovered that treatment with TMP led to the restoration of cholinergic neuron functionality.¹¹³ In recent years, extensive research has demonstrated that *Rhodiola* exhibits a broad spectrum of pharmacological effects on cardiovascular diseases, primarily through its ability to eliminate superoxide anions and hydroxyl radicals in various chemical reactions. The findings of one study indicated that salidroside effectively mitigated cognitive impairment, lowered serum glucose levels, and promoted body weight gain.¹¹⁴ Additionally, salidroside decreased the levels of fasting blood glucose and lipids while inhibiting OS, inflammation, and neuronal apoptosis in a diabetic rat model.¹¹⁴ These findings indicate that salidroside protects against diabetes-induced cognitive impairment by modulating the Rho/ROCK (Rho-associated coiled-coil kinase) / SIRT1 (sirtuin 1)/NF- κ B signaling pathway.¹¹⁴

Future research can focus on the penetration of anti-inflammatory components of TCM across the BBB. This can be achieved by utilizing AI-assisted design of brain-targeting carriers, combined with organoid models to predict the distribution and anti-inflammatory activity of effective components from natural products and formulas of TCM within the brain.

Mitochondrial Homeostasis and Oxidative Stress

Mitochondria serve as the primary energy factories of eukaryotic cells, and the adult human brain stands out as one of the body's most dynamically metabolizing organs, consuming 20% of the total energy supply. In neurons, mitochondria synthesize ATP (adenosine triphosphate) via the ETC (electron transport chain) to support physiological activities, including neurotransmitter transmission and calcium homeostasis.¹¹⁵ Mitochondrial homeostasis is closely linked to mitochondrial biogenesis, dynamics (including fission and fusion), and the regulatory processes of mitophagy. An imbalance in mitochondrial homeostasis, characterized by a reduction in mitochondria, impaired fusion and fission, and defective mitophagy, is associated with the onset and progression of AD and T2DM.^{116,117} OS is defined as the imbalance between the processes of oxidation and antioxidation that occur within the body, which can diminish peripheral insulin sensitivity by causing dysfunction in pancreatic β -cells and mitochondria, promoting inflammatory responses, downregulating GLUT 4, and impairing normal insulin signaling pathways. This cascade ultimately leads to IR and the onset of diabetes.¹¹⁸ Concurrently, OS is a critical factor in neuronal damage and serves as a significant trigger for the core pathological changes related to the occurrence and advancement of AD.^{119–123} The brain exhibits a high oxygen consumption rate, and its cell membranes are abundant in polyunsaturated fatty acids, rendering it vulnerable to OS, which can result in neuronal damage and synaptic loss.¹²⁴ In animal models of IR, an imbalance in redox reactions—characterized by excessive mitochondrial fusion and diminished ATP production—has been observed, demonstrating a correlation between IR and OS. Xu et al also reported the generation of OS in T2DM rats induced by a HFD.¹²⁵ Research has indicated that OS can induce the serine phosphorylation of IRS-1, which impairs insulin signal transduction and concurrently boosts the expression of phosphorylated GSK-3 β , and upregulating the expression of the BACE1 gene, which further exacerbates the production of A β and induces neuronal apoptosis.^{125–127} A substantial accumulation of ROS gives rise to the generation of AGEs and stimulates the expression of the pro-inflammatory transcription factor NF-

κB.^{128,129} It can be inferred that IR, OS, and related factors are closely associated with T2DM and AD, contributing to damage in pancreatic β cells and neurons, which ultimately exacerbates both T2DM and AD.^{130,131}

Ermiş et al¹³² found that diabetic rats exhibited elevated levels of Aβ, tau protein, and TOC (total oxidant capacity), while TAC (total antioxidant capacity) levels were reduced. Furthermore, in rats with active diabetes that received curcumin treatment, the levels of Aβ protein were decreased both in the serum and the brain. Additionally, serum TAC levels were higher in curcumin-treated rats. These results suggest that curcumin may ameliorate the complications of diabetes by enhancing antioxidant activity and mitigating OS associated with the condition. *Centella asiatica* has been reported to exhibit CNS activity, including the enhancement of cognitive functions such as intelligence. Another study demonstrated that due to its neuroprotective properties, *Centella asiatica* effectively reduced cognitive decline and alleviated OS caused by disrupted brain glucose metabolism in rats treated with ICV-STZ.¹³³ Crocin improved spatial learning ability and mitigated memory impairments in diabetic rats by lessening oxidative damage in the cerebral cortex.¹³⁴ This effect might be credited to its antidiabetic and antioxidant properties, suggesting potential clinical applications for treating cognitive dysfunction in diabetic patients.¹³⁴ Xia et al¹³⁵ demonstrated that an appropriate dose of quercetin could attenuate OS through the PI3K/AKT/ Nrf 2 (nuclear factor erythroid-2-related factor 2) signaling pathway, thereby enhancing hippocampus-dependent cognition in mice with T2DM. Quercetin exerts beneficial impacts by decreasing protein glycation, OS, and inflammation. It achieves this through upregulating Glo-1 (Glyoxalase 1), a mechanism that has the potential to alleviate diabetic encephalopathy. Glo-1 is a widely distributed cellular enzyme involved in the detoxification process of MG (methylglyoxal), a harmful byproduct of glycolysis that causes protein modification, specifically AGEs, OS, and inflammation. These findings provide a novel strategy for the treatment of AD in conjunction with T2DM.¹³⁶ Parvin et al¹³⁷ demonstrated that both simultaneous and separate administration of artemisinin significantly ameliorated the adverse effects associated with AD by significantly decreasing the formation of Aβ plaques in the hippocampus. Additionally, artemisinin reduced levels of glucose, MDA, ROS, and TNF-α, while increasing TAC levels.¹³⁷ These research results indicate that artemisinin possesses the capacity to ameliorate the pathological manifestations of AD in a rat model that simulates both AD and diabetes. Consequently, artemisinin has the potential to act as an auxiliary therapeutic option and a safeguard for individuals suffering from AD.¹³⁷ Khan et al¹³⁸ conducted a study aiming to evaluate the effectiveness and dose-response relationship of nuciferine and the crude extract derived from *Nelumbo nucifera* in treating T2DM and AD. The study concluded that both nuciferine and the crude extract of *Nelumbo nucifera* remarkably enhance memory and can potentially be regarded as an effective phytomedicine for T2DM, AD, and OS.¹³⁸ Diosgenin, a steroidal saponin, is noted for its anti-diabetic effects and multiple protective properties. Mahmoudi et al¹³⁹ demonstrated that diosgenin can improve cognitive deficits in animals with STZ-induced diabetes. This enhancement is partly due to its ability to reduce OS, inflammation, and astrogliosis, while also potentially improving cholinergic function and exhibiting neuroprotective properties. Paeoniflorin, a natural glycoside derived from the *Paeonia lactiflora* Pall, is recognized for its properties that include anti-diabetic, antioxidant, anti-inflammatory, and neuroprotective effects.¹⁴⁰ Wang et al¹⁴⁰ demonstrated the protective effects of Paeoniflorin on neurobehavior, OS, brain insulin signaling, and synaptic alterations in mice with cognitive impairment induced by ICV-STZ. Overall, the findings of their research indicate that Paeoniflorin may possess therapeutic potential for alleviating the cognitive impairments induced by ICV-STZ. Furthermore, another study demonstrated that Paeoniflorin has beneficial effects in alleviating cognitive deficits associated with diabetes by modulating the SOCS2 (suppressor of cytokine signaling 2)/IRS-1 pathway.¹⁴¹ This suggests that Paeoniflorin may offer a viable therapeutic approach for managing cognitive dysfunction related to diabetes.¹⁴¹ Matrine, an active component derived from the root extracts of *Sophora flavescens* Ait, exhibits a wide range of pharmacological activities. Zhang et al¹⁴² demonstrated that Matrine ameliorates fasting blood glucose levels and attenuates the spatial learning and memory dysfunctions caused by diabetes. The PK2/PKR (prokineticin 2/prokineticin receptors) signaling pathway plays a role in the neuroprotective actions of Matrine. Furthermore, Matrine alleviated the expression of ER stress-related proteins in diabetic mice. Oxymatrine serves as the major quinolizidine alkaloid that is extracted from the root of *Sophora flavescens* Ait. Huang et al¹⁴³ demonstrated that Oxymatrine alleviates the cognitive decline associated with diabetes, OS, and apoptosis through the inhibition of NOX 2 (nicotinamide adenine dinucleotide phosphate hydrogen oxidase) and NOX 4. However, the aforementioned research indicates that the

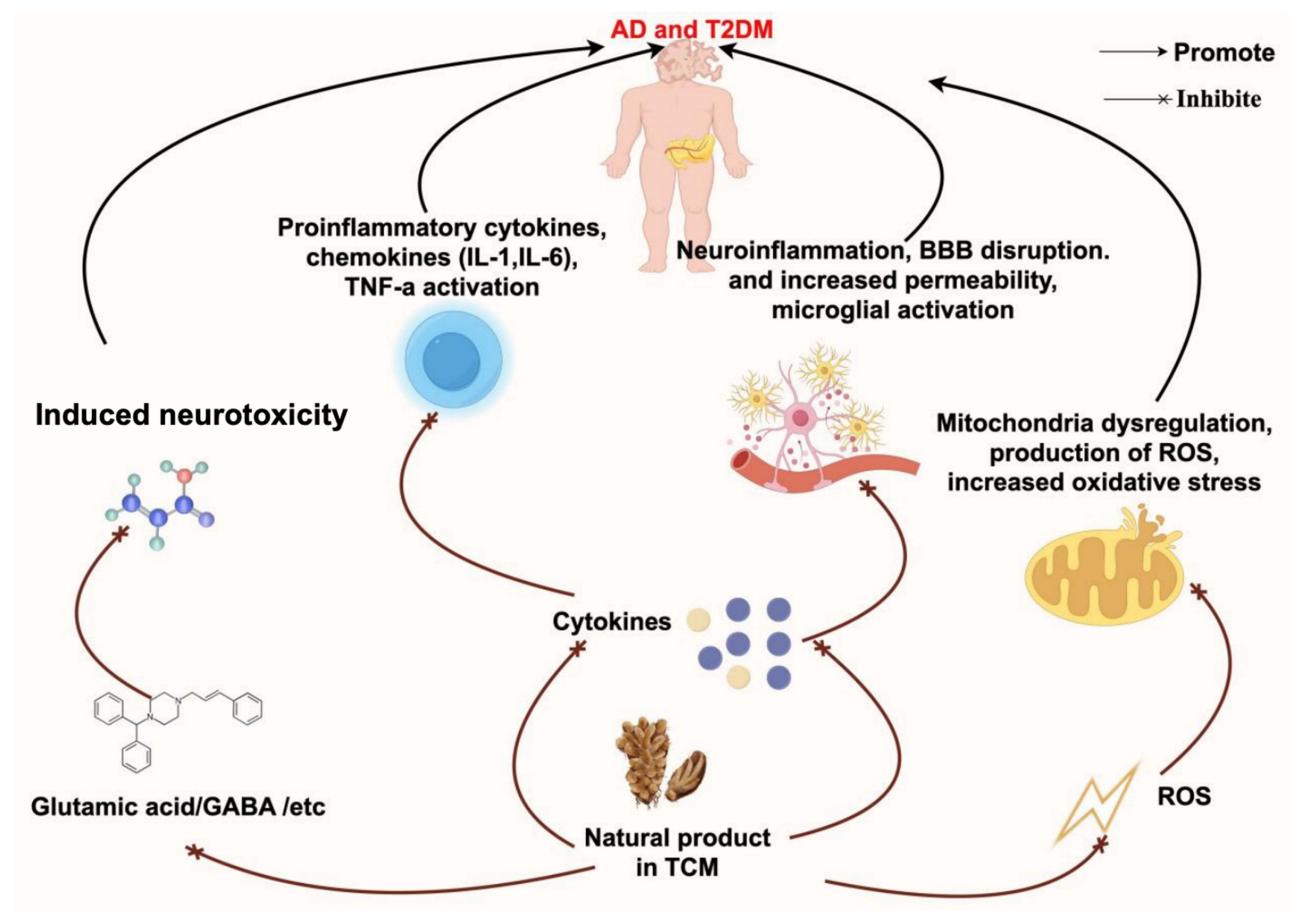


Figure 2 The potential mechanisms of action of Natural products in traditional Chinese medicine: on Type 2 Diabetes Mellitus and Alzheimer's disease. Natural products in Traditional Chinese Medicine (TCM) exhibit mechanisms of action as follows: Regulation of cytokines: Natural products in TCM act on cytokines, inhibiting the activation of pro-inflammatory cytokines and chemokines (such as IL-1, IL-6) and TNF- α , thereby reducing neuroinflammation, blood-brain barrier (BBB) disruption, increased permeability, and microglial activation, which in turn affects Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM). Inhibition of neurotoxicity: These products can inhibit neurotoxicity induced by glutamic acid and γ -aminobutyric acid (GABA), thereby mitigating their adverse effects on AD and T2DM. Improvement of mitochondrial function: By inhibiting mitochondrial dysregulation, they reduce the production of reactive oxygen species (ROS) and oxidative stress, thus playing a role in AD and T2DM.

investigation of TCM natural products in regulating mitochondrial homeostasis in the context of T2DM combined with AD remains in its early stages, presenting significant potential for further exploration (Figure 2).

Future research could further explore the dual-edged effects of OS regulation, such as designing responsive release of antioxidants that break through the limitations of traditional antioxidant therapies through 'smart responses', upgrading "passive antioxidant" strategies to "active precision interventions". Additionally, cryo-electron microscopy could be employed to elucidate the binding sites between TCM components and mitochondrial proteins, analyzing the interactions between components and targets.

AGEs

AGEs are irreversible end products formed through a series of reactions between the aldehyde or ketone groups of glucose or other reducing sugars in the body and the free amino groups of macromolecules, such as proteins, nucleic acids, and lipids. These products trigger a cascade of oxidative reactions within the organism, subsequently leading to tissue damage.^{144,145} The primary mechanism by which AGEs induce IR and diabetic complications involves their binding to the RAGE (receptor for advanced glycation end) products, which subsequently initiates a series of pathological effects.¹⁴⁶ The extracellular domain of AGEs binds to RAGE and activates its cytoplasmic domain, generating multiple signaling pathways, including MAPK, JNK (c-Jun N-terminal kinase)/ SAPK (stress-activated

protein kinase), ERK (extracellular signal-regulated kinases), and JAK-STAT (Janus kinase-signal transducer and activator of transcription). This activation results in the sustained activation of intracellular NF- κ B and STAT 3, ultimately upregulating various inflammatory cytokines and activating reduced nicotinamide adenine dinucleotide oxidase to generate ROS.¹⁴⁷ In recent years, AGEs have been recognized as significant risk factors for cognitive dysfunction. The serum of diabetic patients contains six distinct AGE structures, referred to as AGEs-1 through AGEs-6. Among these, AGE-2 demonstrates biological activity towards vascular wall cells and cortical neurons, playing a crucial role in the pathogenesis of diabetic complications and AD. Studies have indicated that the accumulation of AGEs occurs in the brains of diabetic rats, where they can promote the formation of NFT and A β , enhance the cytotoxicity of A β , and participate in the pathological processes associated with AD.¹⁴⁸ In transgenic AD mice, RAGE in microglia increases the release of pro-inflammatory cytokines such as IL-1 β and TNF- α , which impairs neuronal function and directly influences A β accumulation.¹⁴⁹ Furthermore, glycosylation of AGEs at the N-terminal of tau protein, the microtubule binding site, results in microtubule instability.¹⁵⁰ This instability promotes the entanglement of neurofilaments and the aggregation of amyloid oligomers within brain tissue.¹⁵¹ Moreover, animal models have confirmed that AGEs precursors can induce symptoms of AD, contributing to the onset and progression of cognitive dysfunction in diabetes.^{152,153} In vivo studies have shown that, compared to patients with AD alone, the postmortem brains of patients with both AD and diabetes exhibit increased levels of RAGE and elevated AGE levels in immunohistochemical markers. This suggests that the OS mechanism promoted by AGEs may underlie the development of AD pathology in diabetic patients.^{52,154} A cross-sectional study involving 167 patients with T2DM revealed that elevated serum AGE levels and reduced RAGE concentrations are significantly associated with an increased prevalence of mild cognitive impairment.¹⁵⁵ Schnaider Beerl et al¹⁵⁶ included 684 non-demented elderly individuals in a cohort study with an average follow-up of three years to explore the association between dietary AGEs and cognitive decline in the elderly. The study found that higher baseline dietary AGEs were linked to a faster decline in overall cognitive function, indicating a close relationship between AGEs and cognitive dysfunction in diabetes.

Lychee seed is a TCM known for its numerous beneficial effects, including the regulation of blood glucose and lipid levels, antioxidant effects, antiviral properties, and antitumor activities.¹⁵⁷ Research has shown that the possible mechanisms linked to lychee seed could be related to enhanced IR and a reduction in the production of tau protein, A β , and AGEs within the hippocampus of rats suffering from T2DM.¹⁵⁷ *Astragalus membranaceus*, commonly referred to as “Huangqi”, is a herb widely utilized in TCM and is also employed in the formulation of various health supplements. The herb’s antioxidant,¹⁵⁸ anti-diabetic,¹⁵⁹ and neuroprotective¹⁶⁰ properties have contributed to its extensive clinical applications. Calycosin, a bioactive flavonoid compound isolated from *Astragalus membranaceus* roots, exhibits diverse pharmacological properties, holds considerable importance in its therapeutic applications. Studies indicated that calycosin successfully suppresses GSK-3 β activity, leading to a significant reduction in p-tau.¹⁶⁰ Additionally, it inhibited the expression of RAGE and BACE-1 proteins, leading to attenuated A β generation. Furthermore, calycosin regulated the PGC-1 α /TFAM (peroxisome proliferator-activated receptor- γ coactivator-1 α /mitochondrial transcription factor A) signaling pathway to repair mitochondrial dysfunction.¹⁶¹ Therefore, it can be concluded that calycosin may have considerable therapeutic benefits that can be utilized in managing AD, particularly in cases related to diabetes mellitus.¹⁶¹ *Scutellaria baicalensis* Georgi is a renowned herbal remedy in TCM, incorporated into a range of clinical formulations. Modern pharmacological studies have demonstrated that the ethanol extract from *S. baicalensis* has the ability to improve memory in mice subjected to chronic injections of D-galactose and sodium nitrate.¹⁶² This restorative effect is attributed to its antioxidant, anti-inflammatory, and anti-apoptotic properties.¹⁶³ Zheng et al¹⁶⁴ demonstrated that baicalin could reinstate cognitive and spatial memory in diabetic GK (Goto-Kakizaki) rats. Moreover, it lessened the loss of neurons and degraded the expression levels of A β and p-tau within these rats.¹⁶⁴ At the cellular level, baicalin exhibited significant antioxidant and anti-inflammatory effects in response to high-glucose stimulation.¹⁶⁴ The primary molecular mechanism underlying baicalin neuroprotective action against diabetes-induced cognitive impairment is the upregulation of Nrf2 signaling. AGE is a recognized risk factor and emerging biomarker for the chronic complications of diabetes. Numerous studies have confirmed the correlation between AGE and these complications. However, therapeutic interventions targeting AGE are still in their infancy and require further clinical trials to assess therapeutic potential and safety. The current challenges primarily include the lack of standardized detection methods for AGEs. In the future,

multi-center clinical data calibration detection methods could be employed to reduce inter-laboratory variability. Additionally, targeted traditional Chinese medicine formulations for AGEs could be developed; targeted nanoenzymes for AGEs could also be created. Furthermore, network pharmacology combined with organoid models can be utilized to screen for effective components. With advancements in technology and the accumulation of clinical research experience, AGE is poised to become a significant predictor and intervention target for the chronic complications of diabetes. For more details about Natural Products on T2DM and AD, please refer to [Table 1](#).

Discussion

In 1950, Russell first proposed the concept of diabetic encephalopathy, describing the central neuropathy associated with diabetes and incorporating cognitive impairment as a complication of the disease. In 1965, pathological changes observed in the brains of 16 adolescents who died from diabetic vascular complications further substantiated the existence of diabetic encephalopathy.¹⁶⁶ Moheet et al¹⁶⁷ discovered that patients with T2DM experienced a notable decline in cognitive abilities in comparison to the control group. Previous cross-sectional studies have indicated that the prevalence of MCI (Mild Cognitive Impairment) among patients with T2DM ranges from approximately 20% to 30%, while the incidence of dementia is about 17.3%.¹⁶⁸ A domestic meta-analysis established that patients with T2DM exhibit significantly elevated risks of developing cognitive dysfunction, when contrasted with the general populace, revealing a risk for developing AD that is 1.46 times greater than that of non-diabetic individuals.¹⁶⁹ The cognitive dysfunction associated with diabetes has an insidious onset, primarily affecting middle-aged and elderly individuals. Following the onset of the disease, the decline in cognitive function among patients occurs approximately 50% faster than that observed in the naturally aging population.¹⁶⁸ Advances in medical technology and the extension of life expectancy have drawn increasing attention to chronic diseases in the elderly. Diabetes, as a prominent example of chronic metabolic diseases, leads to cognitive dysfunction that significantly impairs the quality of life among the aging population and reduces family happiness indices. Consequently, there is an urgent need for improved diagnostic and therapeutic methods for intervention. The treatment of T2DM in conjunction with AD using natural products from TCM has attracted growing interest from scholars due to its stable efficacy, fewer adverse reactions, and multi-target characteristics. These treatments can improve IR, inhibit OS, mitochondrial dysfunction, and neuroinflammation, thereby delaying the onset and progression of diabetic complications to some extent.

Research on the application of natural products derived from TCM in the treatment of AD in conjunction with T2DM presents unique advantages across multiple dimensions. In terms of mechanisms of action, natural TCM products typically exhibit multi-component and multi-target properties. They not only regulate the core pathological processes of T2DM but also intervene in the neurodegenerative changes associated with AD by inhibiting A β , improving excessive p-tau, and reducing neuroinflammation, thereby achieving a synergistic regulation of both diseases. Moreover, many natural TCM products have demonstrated a high level of safety in long-term clinical applications, which can minimize the risk of adverse reactions often associated with single-target medications. This characteristic makes them particularly suitable for patients with chronic and complex conditions requiring prolonged treatment. Additionally, TCM adheres to the principle of “holistic regulation”, which can simultaneously enhance the overall metabolic status and cognitive function of patients. This approach offers more comprehensive benefits in alleviating systemic symptoms related to comorbidities, thus providing a treatment strategy that better aligns with the overall health needs of individuals suffering from the complex interplay of AD and T2DM.

Despite the significant associations in clinical comorbidity and pathological features between T2DM and AD, the direct mechanisms of action between the two remain under exploration. Current research primarily relies on epidemiological correlations and indirect evidence, such as the markedly increased risk of cognitive dysfunction in diabetic patients and the manifestation of insulin resistance in both diseases. However, there is still a lack of direct elucidation regarding how diabetes drives the pathological processes of AD, or how AD-related lesions affect the molecular mechanisms of glucose metabolic homeostasis. Currently, existing studies mainly focus on the mechanisms of single herbs or herb pairs, or predict potential targets of formulas through network pharmacology and molecular docking techniques, yet often do not integrate multi-omics approaches. Additionally, the number of targets investigated remains limited, and the mechanisms explored are frequently overly simplistic. Future research should consider exploring more

Table 1 The Potential Mechanisms of Natural Products on Type 2 Diabetes Mellitus and Alzheimer's Disease

Natural Products/ Extracts	Natural Products/ Extract Source	Chemical Class	Molecular Formula	Molecular Weight	CAS No.	Models	Mechanism of Action/Effectiveness	References
Ginsenoside Re	<i>Panax notoginseng</i>	Triterpenoids	C ₄₈ H ₈₂ O ₁₈	947.2	52,286-59-6	HFD-induced IR in C57BL/6 mice	Ginsenoside Re regulated the ACh AChE, MDA, SOD and oxidized GSH/ total GSH by regulating the c-Jun N-terminal protein kinase pathway.	[73]
<i>Artemisia argyi</i>	<i>Artemisia argyi</i>	–	–	–	–	HFD-induced cognitive dysfunction in C57BL/6 mice	Inhibited the reduction of neurotransmitters as well as OS and mitochondrial dysfunction. Inhibited Aβ accumulation by increasing the expression of IDE.	[74]
4,5-dicaffeoylquinic acid	<i>Artemisia argyi</i>	Phenolic acids	C ₂₅ H ₂₄ O ₁₂	516.4	57,378-72-0	HFD-induced cognitive dysfunction in C57BL/6 mice	Inhibited the reduction of neurotransmitters, OS and mitochondrial dysfunction; Inhibited Aβ accumulation by increasing the expression of IDE.	[74]
Geniposide	<i>Gardenia jasminoides J. Ellis</i>	Iridoid glycosides	C ₁₇ H ₂₄ O ₁₀	388.4	24,512-63-8	STZ and HFD-induced male SD rats; SH-SY5Y cells	Improved of insulin and blood glucose; Decreased the Aβ ₁₋₄₂ level and improved the expression of IDE, which is the key degrading enzyme of Aβ peptide.	[75]
Geniposide	<i>Gardenia jasminoides J. Ellis</i>	Iridoid glycosides	C ₁₇ H ₂₄ O ₁₀	388.4	24,512-63-8	APP/PS1 transgenic mice	Decreased p-tau, and increased p-Akt in primary cultured cortical neurons; Enhanced the role of insulin on the p-Akt, GSK-3β and tau.	[42]
Okra polysaccharides	<i>Abelmoschus esculentus</i>	Polysaccharides	–	–	–	HFD-induced Aβ ₁₋₄₂ mice	Inhibited histopathological damage associated with both AD and T2DM. PI3K /AKT/GSK-3β signaling pathway, as well as on ERK 1/2 and p-ERK 1/2 were also investigated.	[76]
Schisandrin A	<i>Schisandra chinensis</i>	Lignans	C ₂₄ H ₃₂ O ₆	416.5	61,281-38-7	STZ and HFD-induced male SD diabetic rats	Upregulated phosphorylation levels of insulin signaling pathway connected proteins and by the decreased expression levels of inflammatory-related factors.	[77]

(Continued)

Table I (Continued).

Natural Products/Extracts	Natural Products/Extract Source	Chemical Class	Molecular Formula	Molecular Weight	CAS No.	Models	Mechanism of Action/Effectiveness	References
Berberine	<i>Coptis chinensis Franch</i>	Isoquinoline alkaloid	C ₂₀ H ₁₈ NO ₄ ⁺	336.4	2086-83-1	STZ and HFD-induced male SD diabetic rats	Decreased in serum and hippocampal Aβ peptide content; Reduced apoptosis in the hippocampi; A reduction in tau, p-tau, and insulin receptor protein expression.	[43]
Berberine	<i>Coptis chinensis Franch</i>	Isoquinoline alkaloid	C ₂₀ H ₁₈ NO ₄ ⁺	336.4	2086-83-1	Intraperitoneal injection of STZ in combination with injection of Aβ ₂₅₋₃₅	Improved TUNEL-positive cell counts and reduces elevated fasting blood glucose, triglyceride, total cholesterol, and glycosylated serum protein levels.	[78]
Berberine	<i>Coptis chinensis Franch</i>	Isoquinoline alkaloid	C ₂₀ H ₁₈ NO ₄ ⁺	336.4	2086-83-1	STZ and high sugar and high fat diet-induced male Wistar rats	The activation of the PI3K/Akt/ mechanistic target of rapamycin and MAPK signaling pathways, along with two novel isoforms, PKC η and PKC ε as well as the translocation of NF-κB in neurons.	[79]
Berberine	<i>Coptis chinensis Franch</i>	Isoquinoline alkaloid	C ₂₀ H ₁₈ NO ₄	336.4	2086-83-1	STZ and HFD-induced male Wistar rats	Downregulated expression of PI3K, GLUT 3, PKC ε, and APP; Upregulated expression of p-IRS Ser307.	[165]
Gypenoside LXXV	<i>Gynostemma pentaphyllum</i> (Thunb.) Makino	Triterpenoid Saponins	C ₄₂ H ₇₂ O ₁₃	785.0	110,261-98-8	db/db mice	Increased the p-Akt (Ser 473)/total Akt levels and the expression levels of PPAR-γ and GLUT4; Decreased the levels of p-IRS-I (Ser 616)/total IRS-I.	[80]
l-Deoxynojirimycin	<i>Morus alba</i> L.	Piperidine alkaloid	C ₆ H ₁₃ NO ₄	163.17	19,130-96-2	SK-N-SH cells with insulin in fetal bovine serum/Minimum Essential Medium-α media for 24h.	Increased the expression of key molecules implicated in IR and the expression of GLUT3 and GLUT4.	[81]
Calycosin	<i>Fabaceae</i>	Isoflavone	C ₁₆ H ₁₂ O ₅	284.26	20,575-57-9	STZ-induced male SD diabetic rats	Stimulated p-Akt and decreased GSK-3β and p-tau, and changes could be restored by the PI3K/Akt inhibitor LY294002.	[82]

Cucurbitacin B	Melon stalk	Tetracyclic triterpenoid	C ₃₂ H ₄₆ O ₈	558.7	6199-67-3	Wistar rats (adult males) were injected STZ-ICV (3 mg/kg)	Diminished protein carbonyls, lipid peroxidation, 8-hydroxy-2-deoxyguanosine, and enhanced antioxidants. A decrease in AChE activity and glutamate levels. γ -aminobutyric acid levels were enhanced.	[99]
<i>Elettaria cardamomum</i> extract	<i>Elettaria cardamomum</i>	Volatile Oils	–	–	–	High fructose and high fat diet coupled with a single small dose of STZ (25 mg/kg) (T2DM rats).	Decreased AChE and caspase-3 activity, reduces elevated cytokines and OS in the hippocampus, enhanced the sensitivity of insulin receptors, and suppressed the expression of glutamate receptors.	[100]
Resveratrol	<i>Veratrum album</i>	Stilbenes	C ₁₄ H ₁₂ O ₃	228.24	501-36-0	STZ-induced SD diabetic rats	Reduced OS in the hippocampus; Decreased the mRNA levels of TNF- α and IL-1 β , enhanced the expression of SYN and GAP-43.	[101]
Resveratrol	<i>Veratrum album</i>	Stilbenes	C ₁₄ H ₁₂ O ₃	228.24	501-36-0	STZ-induced SD diabetic rats	Increased levels of sirtuin1/AChE/MDA/IL-1 β /IL-6 levels, and the decreased levels of ChAT, SOD, and GSH.	[102]
Hyperoside	<i>Hypericum perforatum</i> L	Flavonol Glycosides	C ₂₁ H ₂₀ O ₁₂	464.4	482-36-0	STZ/HFD-induced diabetic rats	Depressed activities of SOD and CAT, and levels of TAC and GSH, whereas levels of IL-1 β , IL-6, TNF- α , NF- κ B, caspase-3 and MDA were increased.	[103]
<i>Agrimonia pilosa</i> Ledeb	<i>Agrimonia pilosa</i> Ledeb	–	–	–	–	A β solutions were infused into the bilateral CA1 regions of SD rats.	Prevented the accumulation of A β in the hippocampus and enhanced insulin signaling; Decreased levels of TNF- α and iNOS in the hippocampus.	[104]
<i>Lonicera japonica</i> Thunb	<i>Lonicera japonica</i> Thunb	–	–	–	–	A β solutions were infused into the bilateral CA1 regions of SD rats.	Prevented the accumulation of A β in the hippocampus and enhanced insulin signaling; Decreased levels of TNF- α and iNOS in the hippocampus.	[104]
Cinnamon oil	<i>Cinnamomum cassia</i> Blume	Phenolic compound	–	–	–	A β solutions were infused into the bilateral CA1 regions of SD rats.	Prevented the accumulation of A β in the hippocampus and enhanced insulin signaling; Decreased levels of TNF- α and iNOS in the hippocampus.	[104]

(Continued)

Table I (Continued).

Natural Products/ Extracts	Natural Products/ Extract Source	Chemical Class	Molecular Formula	Molecular Weight	CAS No.	Models	Mechanism of Action/Effectiveness	References
Dioscin	<i>Polygonatum Zanolancianense</i> Pamp	Steroidal saponins	C ₄₅ H ₇₂ O ₁₆	869.0	19,057-60-4	PC12 cell model and STZ-induced rat models.	The dioscin's anti-DCD effects were associated with the suppression of the P2X7R/NLRP3 pathway	[111]
Tetramethylpyrazine	<i>Ligusticum sinense</i> "Chuanxiong"	Pyrazine-derived nitrogen heterocyclic compound	C ₈ H ₁₂ N ₂	136.19	1124-11-4	HFD followed by a dose of STZ (35 mg/kg) was used to induce diabetes in SD rats.	Treatment with TMP increased BDNF, p-Akt, and p-CREB protein levels, suppressed inflammatory markers (TNF- α , IL-1 β , and NF- κ B), and apoptotic markers (Bcl-2, Bax, caspase-3) in the hippocampus	[112]
Tetramethylpyrazine	<i>Ligusticum sinense</i> "Chuanxiong"	Pyrazine-derived nitrogen heterocyclic compound	C ₈ H ₁₂ N ₂	136.19	1124-11-4	STZ-induced Male wistar rats	Enhanced the phosphorylation of Ser9 in GSK-3 β ; Reduced the protein level of GSK-3 β and implies that the Akt/GSK-3 β pathway may play a role in the neuroprotective effects.	[113]
Salidroside	<i>Rhodiola rosea</i> L.	Phenylethanoid glycosides	C ₁₄ H ₂₀ O ₇	300.30	10,338-51-9	STZ was injected intraperitoneally to induce diabetes.	Suppressed Rho/ROCK/SIRT1 /NF- κ B pathway and protein expression in the diabetic rats.	[114]
Curcumin	<i>Curcuma Longa</i>	Curcuminoids	C ₂₁ H ₂₀ O ₆	368.4	458-37-7	Induced by injection of 50 mg/kg STZ in adult rats	Decreased levels of A β , tau protein, and TOC and the TAC levels were increased.	[132]
<i>Centella asiatica</i>	<i>Centella asiatica</i>	Asiaticoside	–	–	–	Male Wistar rats were injected with STZ (3 mg/kg, i.c.v.) bilaterally	A significant decrease in MDA and an increase in GSH and CAT levels were observed in rats treated with 200 and 300 mg/kg C. asiatica.	[133]
Crocin	<i>Crocus sativus</i> L.	Carotenoid glycosides	C ₄₄ H ₆₄ O ₂₄	977.0	42,553-65-1	A single intraperitoneal injection of 55 mg/kg STZ	A significant increase in the levels of TBARS was observed in the cortex of STZ-induced diabetic rats.	[134]
Quercetin	-	Flavonoids	C ₁₅ H ₁₀ O ₇	302.23	117-39-5	HFD-induced diabetic rats	Attenuate OS through the PI3K/AKT/ Nrf2 signaling pathway.	[135]
Quercetin	-	Flavonoids	C ₁₅ H ₁₀ O ₇	302.23	117-39-5	STZ-induced male diabetic rats	Upregulation of Glo-I.	[136]

Artemisinin	<i>Artemisia caruifolia</i> Buch.-Ham. ex Roxb.	Sesquiterpene Lactones	C ₁₅ H ₂₂ O ₅	282.33	63,968-64-9	STZ-induced diabetic rats	Reduced Aβ plaque formation in the hippocampus, reduced glucose, MDA, ROS, and TNF-α levels, and increased Total Antioxidant Capacity levels.	[137]
Nuciferine and the crude extract of <i>Nelumbo nucifera</i>	Lotus Leaf	Isoquinoline Alkaloid	–	–	–	Alloxan (100 mg/kg body weight)-induced diabetic rats	A recovery of antioxidant enzymes, including SOD, CAT, GPx, and reduced GSH.	[138]
Diosgenin	<i>Dioscorea nipponica</i> Makino; <i>Dioscorea panthaica</i> Prain & Burkill	Steroidal Sapogenin	C ₂₇ H ₄₂ O ₃	414.6	512-04-9	STZ-Induced diabetic Rats	Attenuated hippocampal AChE activity and malon-dialdehyde, along with improvement of antioxidants such as SOD and GSH. Meanwhile, the hippocampal levels of IL-6, NF-κB, TLRs, TNF-α, and astrocyte-specific biomarker glial fibrillary acidic protein, were lower.	[139]
Paeoniflorin	<i>Paeonia albiflora</i> Pall; <i>P. suffruticosa</i> Andr; <i>P. delarayi</i> Franch	Iridoid Glycoside	C ₂₃ H ₂₈ O ₁₁	480.5	23,180-57-6	STZ-Induced diabetic Rats	Increased synaptic density in the CA1 region of the hippocampus; Ameliorated defective insulin signaling by up-regulating p-PI3K and p-Akt protein expression while downregulating p-IRS-1 protein expression.	[140]
Paeoniflorin	<i>Paeonia albiflora</i> Pall; <i>P. suffruticosa</i> Andr; <i>P. delarayi</i>	Iridoid Glycoside	C ₂₃ H ₂₈ O ₁₁	480.5	23,180-57-6	Induced by a high-sucrose, HFD and low dose of STZ	Reducing IL-1β and TNF-α, decreasing SOCS2 expressions and promoting IRS-1 activity and the p-Akt and GSK-3β.	[141]
Matrine	<i>Sophora flavescens</i> Aiton	Quinolizidine Alkaloid	C ₁₅ H ₂₄ N ₂ O	248.36	519-02-8	STZ/HFD-induced diabetic rats	Down regulated ER stress related protein levels (GRP78, CHOP, ATF6 and Caspase-12). Furthermore, administration of matrine enhanced hippocampal protein expressions of PK2, PKR1 and PKR2.	[142]
Oxymatrine	<i>Sophora flavescens</i> Aiton	Quinolizidine Alkaloid	C ₁₅ H ₂₄ N ₂ O ₂	264.36	16,837-52-8	STZ and high-fat and high-cholesterol diet-induced diabetic male SD rats; SH- SY5Y cell model induced by high-glucose	Suppressed ROS levels and NOX2 and NOX4 expression; Decreased caspase-3 expression.	[143]

(Continued)

Table 1 (Continued).

Natural Products/ Extracts	Natural Products/ Extract Source	Chemical Class	Molecular Formula	Molecular Weight	CAS No.	Models	Mechanism of Action/Effectiveness	References
Lychee seed extract	<i>Litchi chinensis</i> Sonn.	Polyphenols	–	–	–	High fat, high sugar and high protein diet-induced diabetic rats	The levels of glucose, insulin, A β , advanced glycation end products and tau protein were significantly increased in the blood and/or hippocampus of T2DM rats, while Lychee seed extract remarkably decreased their levels.	[157]
Calycosin	<i>Astragalus membranaceus</i> (Fisch.) Bunge	Isoflavones	C ₁₆ H ₁₂ O ₅	284.26	20,575-57-9	PC12 cells and AGE-Induced diabetic Rats	Down-regulated the activity of GSK-3 β , inhibited the expression of RAGE products and BACE1 proteins, and regulated the PGC-1 α /TFAM signaling pathway to repair mitochondrial dysfunction.	[161]
Baicalin	<i>Scutellaria baicalensis</i> Georgi	Flavonoids	C ₂₁ H ₁₈ O ₁₁	446.4	21,967-41-9	Goto-Kakizaki rats fed a high-fat and high-glucose diet	The antioxidant defense and anti-inflammatory actions of baicalin were mediated through the Keap1-Nrf2 axis.	[164]

Abbreviations: ChAT, choline acetyltransferase; ER, endoplasmic reticulum; Keap1, kelch-like ECH-associated protein 1; Glo-1, Glyoxalase 1; GPx, glutathione peroxidase; Nrf2, nuclear factor erythroid-2-related factor 2; p-Akt, phosphorylated protein kinase B; p-CREB, phosphorylated cAMP response element-binding; PGC-1 α , peroxisome proliferator-activated receptor- γ coactivator-1 α ; p-IRS, phosphorylated insulin receptor substrate; PKC, protein kinase C; PKR1, prokineticin receptor 1; PK2, Prokineticin 2; PPAR- γ , Peroxisome proliferator-activated receptor- γ ; ROCK, Rho-associated kinase; SIRT1, sirtuin 1; SOCS2, suppressor of cytokine signaling 2; SYN, Synapsin; TBARS, thiobarbituric acid reactive substances; TFAM, mitochondrial transcription factor; TOC, total oxidant capacity; TLRs, Toll-like receptors.

potential mechanisms of action using methods such as spatial transcriptomics and single-cell sequencing. There is a pressing need to strengthen interdisciplinary collaboration, incorporating organoids and gene chips as research subjects to better simulate the *in vivo* micro-environment. Simultaneously, comprehensive studies on the compatibility of formulas specifically for AD combined with T2DM are scarce. Future efforts should involve high-quality clinical studies, such as multicenter, large-sample trials and collaborative analyses of TCM and Western medicine mechanisms, to further explore the potential of these formulas and provide optimized treatment plans for complex comorbidities. Furthermore, it is essential to enhance preclinical and clinical trial research, optimize the extraction, separation, and modification techniques of natural products, and develop efficient and safe natural drugs. Besides, the lack of standardization has made it difficult for TCM to gain widespread recognition internationally, thereby limiting its process of internationalization. Low bioavailability may lead to the insufficient efficacy of medications, affecting clinical treatment outcomes and hindering the translation process from laboratory research to clinical application. Standardization encompasses multiple dimensions, including the quality of medicinal materials, processing techniques, formulation specifications, and efficacy evaluation. For instance, significant differences in the content of active ingredients in medicinal materials from different origins and harvest seasons can lead to unstable drug quality due to the absence of unified standards. Moreover, many active components of TCM exhibit poor water solubility, difficult intestinal absorption, or are easily metabolized by the first-pass effect, which affects their clinical efficacy. In the future, a comprehensive quality traceability system for medicinal materials can be established, along with strict processing and formulation specifications, and the introduction of modern scientific efficacy evaluation indicators. To address bioavailability issues, methods such as nanotechnology, liposome encapsulation, and structural modification can be employed to improve the physicochemical properties of TCM components and enhance their absorption efficiency. These efforts will provide new insights and methodologies for the prevention and treatment of AD and T2DM, thereby promoting the widespread application of TCM in addressing these conditions.

Abbreviations

A β , amyloid β -protein; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; AGEs, advanced glycation end products; Akt, protein kinase B; ApoE, apolipoprotein E; APP, amyloid precursor protein; APP/PS1, APPswe/PSEN1dE9; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; BBB, blood-brain barrier; BBR, Berberine; BDNF, brain-derived neurotrophic factor; CAT, catalase; CNS, central nervous system; DCD, diabetic cognitive dysfunction; EFAA, effects of *Artemisia argyi*; ERK, extracellular signal-regulated kinases; GLUT, Glucose transporter; GSH, glutathione; GSK, glycogen synthase kinase; HFD, high-fat diet; IAPP, islet amyloid polypeptide; ICV, intracerebroventricular; IDE, insulin-degrading enzyme; IGF, insulin-like growth factor; IL, interleukin; iNOS, inducible nitric oxide synthase; IR, insulin resistance; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NF- κ B, nuclear factor- κ B; NFTs, neurofibrillary tangles; NLRP3, NOD-like receptor protein 3; NOX, nicotinamide adenine dinucleotide phosphate hydrogen oxidase; Nrf2, nuclear factor erythroid-2-related factor 2; OS, oxidative stress; PI3K, phosphatidylinositol 3-kinase; PKRs, prokineticin receptors; p-tau, phosphorylated tau; P2X7R, P2X7 receptor; RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; sAD, sporadic AD; SD, Sprague-Dawley; SOD, superoxide dismutase; STZ, streptozotocin; TAC, total antioxidant capacity; TCM, traditional Chinese medicine; TMP, Tetramethylpyrazine; TNF, Tumor Necrosis Factor; T2DM, type 2 diabetes mellitus; 4,5-diCQA, 4,5-dicaffeoylquinic acid.

Data Sharing Statement

All of the data used to support the findings of this study are included within the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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