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Cognitive Impairment by Type 2 Diabetes and Therapy Opportunities with Natural Medicines*

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Abstract Type 2 Diabetes Mellitus (T2DM) is the most prevalent type of diabetes worldwide, and usually affects elder population. Clinical and basic studies have highlighted its involvement in cognition decline especially learning and memory. T2DM individuals are at high risk to develop dementia as compare to normal population. This paper reviews the recent studies which demonstrated cognitive decline among T2DM individuals and in animal models, including the related mechanisms and the therapies, to make a better knowledge on T2DM cognitive complication.

Key words diabetes mellitus type 2, cognition, insulin receptor, neuro-inflamation/neurotransmitter, memory loss, Chinese herbal medicine
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1 Introduction

Diabetes mellitus is one of the most devastating metabolic disorder, stands fourth among non-communicable diseases. The estimates of 2014 suggested that 422 million peoples are living with diabetes and the global prevalence has been doubled since 1980[1]. Diabetes mellitus Type 2 (T2DM) is a condition preceded by a pre-diabetic condition characterized by insulin resistance, obesity, dyslipidemia, hypertension etc. It affects different organs and aggravates complications such as nephropathy, retinopathy, atherosclerosis, cardiovascular, and stroke. In the last few decades, influence of T2DM on the functional outcome of nervous system has been an area of immense interest. These studies have highlighted strong connections of T2DM with cognitive functions[2-4].

The influence of T2DM on cognitive functions ranges from mild impairment to extreme clinical condition known as dementia[5-6]. Cognitive impairment affects daily life activities including memory loss, self-care behavior and affects patients

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themselves, their careers, and society. According to the estimates of World Health Organization, globally around 50 million peoples were suffering from different form of cognitive impairment, out of which 60%−70% cases were owed to Alzheimer's disease. Population based study showed the increased incidence of mild to complex cognitive impairments in diabetic patients[7-9]. In the presence of T2DM, there is a 60% increased risk of getting dementia and diabetic women are more sensitive to develop cognitive decline as compared to diabetic men[10].

This review was aimed to highlight the cognitive impairments among T2DM functions and involvement of insulin resistance, oxidative stress and inflammation in promoting cognitive decline.

2 Animal and human studies suggesting cognitive decline in diabetes

Diabetes accelerates the brain aging and affects different cognitive domains including information processing, mental flexibility, psychomotor efficiency, attention etc. T2DM usually affect psychomotor speed, executive function, visuo-spatial problems and memory[11-14]. These complications will ultimately affect the quality of daily life with increased imbalance and Gait disturbances[15-16]. The mechanism of T2DM associated central nervous system disorder is still not completely investigated and under extensive research. Different studies conducted so far, among humans and various animal models which revealed decreased cognitive ability among T2DM and were summarized in following sections as well as in Figure 1.

2.1 In humans

Patients with uncontrolled diabetes was found to have low scores in mini-mental state examination score (MMSE) with reduced performances in perceptual speed, category fluency, digit span backward and episodic memory in a Sweden-based population study. These cognitive declines were directly proportional to the presence of vascular disorder and apo-lipoprotein E4 APOe4[17]. A twin pair study among T2DM individual demonstrated task related deactivation of the default mode network especially reduced activation of the left hemisphere temporoparietal regions (includes angular gyrus, supramarginal gyrus, and middle temporal gyrus)[18]. Elder individuals have more compromised efficacy in task oriented test, working memory, lower verbal and visuospatial speeds as compared to healthy controls. These cognitive decline were more in females and in patients with increased Hb1Ac level[19-20]. In a recent ten-year follow up study among Mexican population (1 634 individuals) confirmed the accelerated cognitive decline among T2DM patients *i.e.* 3 MSE score of 4.3 as compared to healthy control (2.3) within 6 years[21]. The impaired cognitive decline was also reported among early diagnosed T2DM patients (<3 years) and the decline become more prominent with aging (>60 years). Other inflammatory diseases such as rheumatoid arthritis and asthmas further aggravate the conditions[22].

Espeland *et al*.[23] further confirmed that diabetic women are at high risk to develop dementia and cognitive impairments and postmenopausal hormone treatment (*i. e*. estrogen) further aggravate the condition. Races within populations also play its part

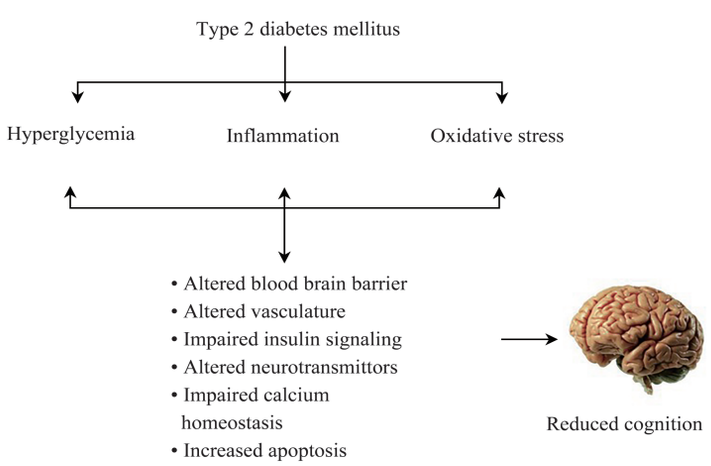

Fig. 1 Impact of type 2 diabetes on brain physiology responsible for reduced cognition

in the age related cognitive decline. The cognitive decline among T2DM Afro-American (age group (59 ± 8) years) was more prevalent as compared to Caucasian (age group (65 ± 8.7) years) population. They showed the positive correlation among race and advancing age on Trial B and Digit Symbol tests[24]. Attenuated nitric oxide signaling cascade and accelerated cognitive decline among non-diabetic individuals due to hypertension also highlights the race related cognitive decline among African[25].

Hyperglycemia has detrimental effect in the cognition. Study showed that 1% rise in the hemoglobin A1C (HbA1C) level is responsible for lower scores in various cognitive tests[26]. Increased HbA1C is responsible for reduced neural network efficacy with longer network path length suggesting altered structural integration. It also negatively correlates with the fractional anisotropy (FA) values used to measure the directional coherence for the fiber tracts[27-28]. A population based study among adult individual (Age≤ 60 years) further validated the involvement of increased fasting plasma glucose and Hb1Ac with reduced mini mental score *i.e*. 3 MSE score < 79[29-30]. Elevated postprandial blood glucose and Hb1AC were responsible for low score in Rey complex figure copy test, verbal learning test, Digit span and MMSE[28]. Pre-diabetic persons with higher FPG also showed impaired decision making with intact working memory[31]. Fluctuation in the blood glucose level is also responsible for cognitive decline even before the hypoglycemic condition was achieved[32].

Type 2 diabetic patients to overcome hyperglycemia related complication were encouraged to achieve optimal glycemic level *via* anti diabetic therapy. To achieve normal glucose level usually leads to hypoglycemia. Hypoglycemia with its severity also accounts for different life threatening complications. As brain which only utilizes glucose as a source of energy, thus hypoglycemia also affects the central nervous system and associated with brain damage and dementia[33]. The molecular mechanism by which it causes alteration in the brain and dementia is still a dilemma. Several studies showed the increased risk of developing dementia among hypoglycemic individuals *i.e.* almost three time more[3, 34-35]. Edinburgh study showed that T2DM individuals with history of and/or incident hypoglycemia demonstrate poor performances in MR, DSC, and TMT-B cognitive tests and become more prominent with the passage time[34]. Moreover, dementia related to hypoglycemia is directly proportional to the duration of diabetes, other vascular complications and use of the drug to maintain optimal glycemic control. Thus, type 2 diabetes in terms of hyperglycemia and hypoglycemia has negative correlated with cognition functions.

2.2 In animal models

Various T2DM animal models either genetic (OLETF, GK, Zucker diabetic fatty rats, db/db mouse etc) or experimentally induced (High fat diet with Streptozotocin administration) have been used extensively to study brain aging and cognitive decline. Different studies showed the presence of cognitive decline in different T2DM models[2, 36-38]. Otsuka Long-Evans Tokushima Fatty (OLETF) rats a T2DM model displayed anxiety like symptoms, cognitive impairments with reduced brain derived neutropenic factor (*i.e*. responsible for intact neuronal function), and it also synergize the pathology of vascular dementia[39-41]. Neurogenesis that is the central point in intact neuronal function was also found to be impaired in diabetic GK rats (Goto-Kakizaki GK rats). Enhanced proliferation with reduced survival of the neural progenitor cells was observed and these cells were failed to respond toward different growth factors such as FGF2 and IGF1. In addition, these rats in the age of eighteen week showed abnormal vasculature with reduced blood vessel area and branching within dentate gyrus responsible for neurological disorders[42]. Reduced locomotion, exploration and memory was also observed in 10−20 weeks old GK rats in open field and passive avoidance tests[43]. On the other hand, Zucker obese rats (T2DM model) also displayed reduced hippocampus associated tasks *i.e*. learning and memory on delayed alternation task with a variable interval between trials. Destabilized vasculature was positively correlated with ß amyloid deposition, insulin signaling impairment, reduced glucose metabolism (*i.e*. reduced GLUT 4) and cognitive decline[44]. As T2DM is preceded by prediabetic stage, which also negatively affect the cognition as observed by poor performance on hippocampal dependent tasks like memory and learning assessed by Morris water

maze and Y-maze tests in sucrose fed rats[45].

Thus aforementioned reported evidences clearly suggest the profound effects of type 2 diabetes in the impairment of cognitive abilities and increases the risk of dementia especially in elderly population. These changes also attributed to a complicated daily life routine.

3 Molecular mechanism in diabetes associated cognitive decline

The presence of insulin receptor in the brain neglected the fact that brain is insulin insensitive organ[46-47]. Hyperglycemia, hyperinsulinemia and insulin resistance together affect the cerebrovascular moiety by reducing the vascular tone, leakage of the blood-brain barrier (BBB) and elevated oxidation and inflammation.

3.1 Type 2 diabetes and blood brain barrier

Blood brain barrier (BBB) is crucial for the integrity of brain and intact neurological functions[48-49]. Beside barrier function, it also provides mode of communication between central nervous system (CNS) and its periphery[50-51]. Selective permeability of the BBB is provided by the presence of tight junctions between the endothelial cells by virtue of trans-membrane protein claudin, occludins and in combination with other scaffolding proteins[52]. Its disruption alters its barrier property and allows the passage of substances that are neurotoxic which resulted in enhanced inflammation and oxidation ultimately leads towards cognition decline and dementia[53-54].

The two important features of T2DM (*i.e*. hyperglycemia and insulin resistance) was found to disrupt BBB and responsible for several CNS pathologies[55-57]. Diabetic patients showed enhanced BBB permeability as observed by diffusion of administered gadolinium diethylenetriamine penta acetic acid (Gd-DTPA) and captured images by using magnetic resonance imaging (MRI). Diffusion rate is elevated as compared to healthy control and the vulnerability increase with the increase of white matter lesions. Down regulation of occludin and claudin-5 proteins further strengthen the disrupted BBB permeability in Zucker diabetic fatty rats (ZDF) and structurally altered vasculature surrounded by phagocytes[58]. Takechi *et al*.[59] showed that high fat and high fructose diet in C57BL/6J mice significantly impaired cognition with elevated BBB permeability and neuro-inflammation. Activated protein kinase C β (PKCβ) was found to destabilize the BBB and its inhibition (by Enzastaurin a PKCβ inhibitor) enhances the BBB permeability by up regulating the expression of claudin and occuldin 5 proteins and resulted in reduced microglial activation and inflammation in db/db rats[57]. Diabetic Rhesus monkeys also displayed disrupted BBB as compared to their healthy controls, down regulated BBB proteins with elevated oxidative stress (*e. g*. translocation of Nrf2 from cytoplasm to nuclei) and intracranial lesions[60]. Furthermore, disrupted BBB and its related microglial activation, inflammation and oxidative stress further worsen the brain environment. Thus, it can also serve as a therapeutic target to avoid cognitive decline in diabetes and its associated neuro-pathological complications.

3.2 Structural and functional changes in the T2DM brain

In the light of different imaging technologies such as diffusion tensor imaging (DTI), magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission topography (PET) *etc*. T2DM was found to induce structural and functional changes in the brain[61-64]. Hyperglycemia directly correlated with the disruption of vasculature leading to reduced microcirculation of the brain, arterial stiffness and functional changes in the regional cerebral perfusion[65-66]. Brain atrophies with enhanced lateral ventricular volumes with slightly enhanced brain aging was evident among T2DM individuals[67-69]. Different population-based studies have correlated the age, higher BMI, Hb1Ac, FPG and duration of disease with the reduced brain volume, increased levels of cerebrospinal fluid (CSF), reduced white matter integrity, cortical and sub cortical atrophy with reduced axial diffusivity[70-72].

Diabetic and pre-diabetic stages also affects hippocampus the area responsible for learning and memory characterized by reduced size and decreased cortical thickness of medial temporal lobe. The mean diffusivity in T2DM brain was also increased with reduced glucose metabolism, and functional connectivity. Xiong *et al.*[73] by using DTI showed 36.6% reduced brain connectivity and 58.5%

increased brain diffusivity among the diabetic group with mild cognitive impairments (MCI) as compared to healthy controls. Functional MRI studies demonstrate that T2DM patients with microangiopathy and impaired cognition functions displayed reduced brain activity (decreased regional homogeneity ReHo) values as compared to diabetic individuals without microangiopathy[74]. Reduced volumes of caudate nucleus, thalamus with white matter integrity was also found among youth T2DM individuals[75]. With the combination of imaging technology and graph theory based analysis, Cui *et al.*[76-77] showed altered brain connectivity in term of decreased degree centrality (DC, common measure for brain global connectivity) and functional connectivity (FC) of each region of brain of T2DM individuals. They further suggested that reduced visual memory and vision dependent task (Rey-Osterrieth Complex Figure Test (CFT) delayed recall trial) among diabetic individuals might be due to reduced functional connectivity in the lingual gyrus. On the other hand, T2DM individual perform better in executive function as analyzed by trial making test part B (TMT-B) which is positively correlated with increased DC and network connectivity in 2 important hubs *i.e.* right anterior insula and dACC (dorsal anterior cingulate cortex). This suggesting the compensatory mechanism in younger diabetic population *i.e*. more neuronal resources were required to successfully accomplish the relevant task. Although this study includes small population size but provides the information regarding altered brain connectivity among T2DM individuals. Cerebral vessels stiffness will promote reduced cerebrovascular responsiveness (CVR) among T2DM individuals which also have negative influence on the cognition. About 14% increased pulsatility index with reduced CVR especially was noted in three cognition tasks *i. e*. Digital symbol coding, Symbol digit coding and digit letter switching[78].

Cumulatively, these imaging techniques will help to determine the brain damages but fails to depict the mechanism behind T2DM related cognition decline.

3.3 Insulin directed mechanism related to cognitive decline in diabetic brain

In the last few decades, the role of insulin in brain and its involvement in cognition was extensively highlighted. Earlier brain was considered as insulin privileged organ but the presence of insulin and its receptor in different portion of the brain nullified this concept and suggested the role of insulin in neurological processes[79]. The presence of insulin, its mRNA and c-peptide (*i. e*. pro-insulin molecule) further confirms that brain is an insulin sensitive organ[80-81]. Insulin resistance in the Alzheimer's brain also pinpointed the involvement of it in the cognition functions[82-84]. Insulin secreted in the periphery was transferred to brain by crossing BBB in a regulated fashion and exert its function. Its transport is dependent on the peripheral insulin while prolonged hyperinsulinemia hampered the insulin transport in the brain[85]. Thus, the insulin resistance among T2DM individuals might be responsible for cognitive decline and make the condition more prone towards dementia in elderly population[55, 86].

Insulin receptor is a trans-membrane protein with two extracellular α subunits (insulin binding) and two intracellular β subunits responsible to initiate the downstream pathway. Insulin signaling cascade is similar to the periphery. Insulin secreted in the periphery will cross the BBB and bind to α unit of the receptor. This binding will facilitate the auto phosphorylation by activating the tyrosine kinase of the β subunits domain which phosphorylates the insulin receptor substrate (IRS). This auto phosphorylation will activate two downstream pathways *i.e*. phosphoinositol 3 kinase (PI3K) or Akt pathway and MAPK/ERK pathway. Phosphorylated insulin receptor activates PI3K resulting in the formation of phosphatidylinositol tri phosphate which further activate the phosphoinositide dependant protein kinase to phosphorylate and activate Akt. After activation it performs different functions: a. It maintains glucose homeostasis by maintaining the glucose transporters (GLUT4) in the plasma membrane; b. Down regulation of forkhead box B is responsible for oxidative stress; c. Inhibit the glycogen synthase kinase 3 β responsible for tau deposition. Insulin also found to activate mTOR pathways responsible for synapses.

Different studies revealed the involvement of insulin signaling responsible for long term potentiation and its alteration will lead to cognitive decline. Reduced translocated GLUT4 was observed in Zucker obese rats with reduced cognition[44, 77]. PIVUS study showed the involvement of insulin

resistance in reduced verbal cognitive function, reduced grey matter and brain size[87]. Diabetic and pre diabetic patients with insulin resistance demonstrated reduced glucose metabolism in different regions of the brain[88]. Impairments in the different steps of insulin signaling pathway was found in type 2 diabetic individuals with reduced cognition. Different studies showed the positive effect of insulin on cognition[89]. Activated GSK3 β which is responsible for tau phosphorylation also promotes insulin resistance by negative feedback and by serine phosphorylation of insulin receptor substrate[90]. An impaired insulin signaling cascade was responsible for altered mitochondrial biogenesis, oxidative stress, neuro-inflammation which negatively affect cognition among diabetic individuals.

3.4 Metabolic impairments in type 2 diabetic brain

Inhibition of insulin signals will be responsible for the deposition of β amyloid aggregates which is turns elevates oxidative stress and inflammation and resulted in impaired cognition[55, 91]. Soares et al showed impaired glycogen metabolism in diabetic brain as evident by changes in the glycogen synthase phosphorylation rate among GK rats thus hindering learning and memory[38].

Dyslipidemia is one of the common features of type 2 diabetes patients, which promotes mitochondrial injury and impaired oxidative system[92]. Dyslipidemia itself responsible for cognitive decline and different studies have reported the altered composition of saturated and unsaturated fatty acids *e.g.* docosahexaenoic acid (DHA), Stearic acid, ceramide and very long chain fatty acids (VLCFAs) in patients with cognitive decline[93-97]. Thus, dyslipdemia with hyperglycemia plays a synergistic role to demolish cognition. They also showed the accumulation of VLCFA and enhanced amyloid β deposition with reduced β peroximal oxidation in the T2DM rat model (high fat diet and STZ). These rats showed reduced learning and memory on Morris water maze[98]. T2DM patients with cognitive decline also showed altered pathways of sphingolipids, bile acid and uric acid metabolism[99]. Ceramide (sphingolipids family) involved in cellular signal cascade, responsible for elevated proinflammatory cytokines and insulin resistance. It also impairs brain insulin signaling by crossing the breaching BBB and hampers the insulin receptor signaling and Akt pathway. This can also be a possible candidate responsible for declined cognition among T2DM patients[100]. Cholesteryl ester transfer protein (CETP) which promotes dyslipidemia was also found in increased concentration in the serum of diabetic patients with cognitive impairments[101]. Adiponectin, a protein responsible for insulin sensitivity and glucose homeostasis is also reduced in the T2DM patients[102]. Leptin, a pro-inflammatory hormone responsible for the production of IL-1β and its resistance is responsible for enhanced inflammation in the brain[103]. Moreover, the concentration of leptin was also elevated in T2DM with poor performances in different cognitive domains[102, 104].

3.5 Oxidative stress in type 2 diabetic brain

Brain solely utilizes glucose as an energy source; T2DM brain was evident for impaired insulin functions responsible for altered glucose metabolism and transport *via* glucose transporter. As brain cells are unable to store glucose, thus only rely on its transport to perform neuronal functions which was hampered T2DM and might be responsible for reduced cognition[88, 105-107]. Mitochondria the central organelle in energy biogenesis is also responsible for oxidative stress as a producer and target of reactive free radicals. Its energy turnover was significantly impaired in various neurodegenerative diseases. Oxidative stress was characterized by elevated reactive oxygen and nitrogen species with reduced antioxidant enzymes[108-109]. Type 2 diabetes was also reported for impaired antioxidant system responsible for oxidative stress[110-111]. Sucrose fed mice and transgenic Alzheimer's mice model (3xTg-AD) showed swollen and altered mitochondrial structure with depleted energy (ATP)[112]. This insult of antioxidant system and oxidative stress was responsible for neuro-degeneration and altered synaptic plasticity, ultimately cognitive decline. GK diabetic rats showed disrupted electron transport chain which further aggravated with aging and Aβ deposition[113]. Mitochondrial dysfunction in the brain is responsible for oxidative stress related cognitive abnormalities[114]. Utilizing a rat model, Shi *et al*.[98] showed the accumulation of VLCFA in the diabetic rat which is correlated with increased oxidative stress (increased expression of NOX4, p47phox and HO-1 protein) in the diabetic brain. Elevated oxidative stress is a common etiology of both AD and T2DM brain[115-116]. Auto oxidation of glucose, increased polyol pathway,

glycation of proteins resulted in the production of advance glycation endproducts (AGEs). In a STZ induced diabetic rats the level of antioxidant enzymes catalase, superoxide dismutase and glutathione peroxidase decreases with increased MDA. This failure will lead to the accumulation of reactive oxygen species in the hippocampus. Oxidative stresss was also found to down regulate the expression of GluR2 subunit of the AMPA receptor and inhibit long term potentiation and promote cognitive impairments. These results were further verified by administrating Bacopa monnieri fraction CDRI-08 (rich in Bacoside A & B) which was resulted in the reduced hyperglycemia, restored insulin resistance and oxidative stress related cognitive decline as determined by Morris water maze[117]. Advance glycation end products (AGEs) and their receptor (RAGEs) are other important markers responsible for cognitive decline. Both contribute cognitive deficiencies either *via* AGEs-RAGE pathway or by releasing oxygen radicals, diminishing mitochondrial activity, and glucose metabolism[118-119]. RAGE was involved in the Alzheimer's brain injury and the microglial cell activation leading to neuro-inflammation[120]. Recently, Wang *et al*.[121] demonstrated the presence of increased RAGE in the serum of diabetic patients with moderate cognitive decline (MCI), with enhanced AGE-P level which is positively correlated with the reduced executive functions. They further deduced that a unit increase in the AGE-P was responsible for 74% increased risk of MCI. On the other hand, each unit rise in RAGE reduced the MCI risk by 54%. Another study showed the positive correlation with the increased HbA1C level and increased serum AGEs, RAGE and inflammatory molecules (C reactive protein) in T2DM individuals and negatively correlated with cognition[102]. Interestingly, edaravone a free radical scavenger significantly ameliorates the oxidative stress in an intracerebrovascular injected STZ diabetic model and reverse the cognitive decline[122]. Various other studies also showed the use of antioxidant will reverse the oxidative stress related cognitive decline human and animal models [90, 122-124].

3.6 The inflammation in type 2 diabetic brain

The promotion of obesogenic and dibetogenic environment with the modernization of the world makes the situation more problematic with the passage of time. T2DM usually precedes pre-diabetic condition *i. e*. obesity which is responsible for increased level of pro inflammatory cytokines[125-126]. The involvement of these pro-inflammatory cytokines (TNF-α and IL-6) already developed in the Alzheimer's patients[127-128]. In the presence of altered BBB among obese and T2DM individuals the pro-inflammatory cytokines take entry into the brain and hampers insulin signaling in the brain[129-130]. A cross sectional study highlighted the elevated TNF-α and IL-6 among T2DM individuals with cognitive impairments[131]. Chuang *et al*.[132-133] showed the impaired global and regional cerebral vaso-reactivity with increased inflammatory markers (C reactive protein) was associated with declined cognition especially executive functions. In a zebra fish diabetic model, Dorsemans *et al*.[134] illustrate the elevated gene expression of inflammatory cytokines including TNF-α, IL-1β and IL-6 in the brain with reduced expression of genes responsible for maintaining BBB and altered neurogenesis. TNF-α was reported to activate the c-jun N- terminal kinase (JNK) pathway which was responsible for insulin resistance in the periphery[135]. In a time-dependent manner TNF-α, IL-1β was found to positively correlated with cognitive insult in STZ induces diabetic rats as evident in Morris water maze and New object recognition test[2]. Whereas, in the brain it also promotes serine phosphorylation of the insulin receptor substrate and hampers the insulin signaling in the demented individuals[136-137]. Recently, Jawale *et al*.[138] showed the increased level of TNF-α and IL-6 in the diabetic rats with reduced cognition. They further showed that anti-inflammatory effect of cinnamaldehyde which amoleraites cognitive impairments in the diabetic rats. Proliferation of the activated microglial cells is one of the characteristic features of diabetic brain which is responsible for increased inflammation[139]. Asiaticoside a triterpenoid isolated from *Centella asiatica* (L.) was found to be anti-inflammatory and restore the cognitive decline by reducing the oxidative stress and activating the insulin signaling in the diabetic rats[140].

3.7 The neurotransmitters， amino acid and calcium in type 2 diabetic brain

With dyslipidemia, oxidative stress and neuro-inflammation altered hyopthalmic pituitary adrenal axis (HPA) axis was also featured in diabetic brain[141]. This alteration will also play important role in the altered neurogenesis and cognitive decline. Increased corticosterone and reduced glucocorticoid receptors was evident in the GK diabetic rats which is responsible for altered neurogenesis in the diabetic brain[42, 141]. Insulin resistance in the diabetic brain

also modulates neurotransmitters usually excitatory and inhibitory receptors (g-aminobutyric acid (GABA) and glutamate receptors (GluR)) which affect cognition[142-143]. Increased concentration of GABA among diabetic individuals with cognitive decline was associated with high Hb1Ac level[144]. Sickmann *et al*. [145] showed the increased level of GABA in the Zucker diabetic fatty rats. NF- κB inhibitor (BAY) was found to reverse the cognitive decline in the type 2 diabetic rats by restoring the glutamate and GABA levels with reduced oxidative stress and neuro-inflammation[146].

Calcium the intracellular messenger also exerts its effect on numerous neuronal functions responsible for long term potentiation, and learning and memory. Impaired calcium homeostasis was evident in the STZ induced diabetic rats. Impaired calcium homeostasis especially in the endoplasmic reticulum and mitochondria were responsible for imbalance neurotransmitters. Likewise, elevated level of calcium in the endoplasmic reticulum was found to promote caplain 2 (pro-apoptotic proteases) responsible for cell death. Calpain 2 was also evident in the type 2 diabetic B pancreatic cells as well as in the AD brain. In STZ induced hyperglycemic rat showed impaired calcium homeostasis in the dorsal root ganglion neurons[147]. Increased in L-type voltage gated calcium channel is correlated with impaired learning in the aged neurons[148]. Impaired VOCCs is a hallmark of different neurodegenerative diseases. Singhal *et al*.[149] showed impaired learning and memory in STZ induced diabetic rats with increased CaV1.2 expression suggesting its role in the increased calcium uptake. They further demonstrated that reduced Ca^{2+}-ATPase activity in the plasma membrane and sarcoplasmic reticulum decreased mitochondrial calcium uptake with increased lipid peroxidation and oxidative stress. Nimodipine (a known calcium channel blocker) was found to reverse the calcium homeostasis towards normal and restores cognitive functions in the diabetic animal.

4 Possible therapies to treat diabetes associated cognitive decline

World Diabetic Council classified diabetes as a risk responsible for cognitive decline or dementia. Different studies stated above highlight the prevalence of impaired cognition among T2DM patients. Type 2 diabetes mellitus being the fastest growing disease which effecting the elderly population worldwide needs to be taken care of. In type 2 diabetes, hyperglycemia, insulin resistance, neuro-inflammation and oxidative stress contributes toward cognitive decline. By understanding the insulin resistance mechanism in the brain pave the pathway to use different anti-diabetic drugs which might be helpful to restore cognition. Different anti-diabetic agents were found to restore cognition (Figure 2). The table in supplementary file will over view the different medication used to reduce cognitive decline among diabetic individuals (Supplementary Table S1).

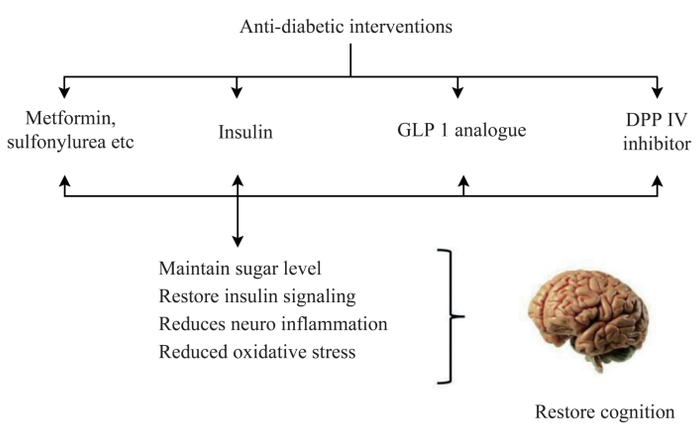

Fig. 2 Pharmacological intervention strategies to delay cognition decline among T2DM individuals

4.1 Natural products

Since the origin of humankind, natural product as medicine used to cure various health concerns. These practice of natural products were traced back 60 000 years. The use of natural medicines was well reported in the scripture of traditional Chinese medicine (TCM), Unani Medicine, Ayurveda and still practiced in the recent times. The secondary metabolite within floral diversity provide a great shelf of compounds to be explored as novel medicine[150-151]. These natural product has been exploring for various pharmacological activities such as anticancer, anti-bacterial and antidiabetic *etc*. The proper biological activities of these compounds will further expand their use in different disease condition. Advancement in sciences clarified with evidence the use of natural medicine to cure various health complications. Out of different practices, TCM acquires great attention and recognized worldwide. Chinese herbal formulation has been used in China as well as in Europe and other countries to combat various health complications. Food and drug regulation authorities categorize Chinese herbal formulation as food supplements if provide evidence of their nontoxic nature. Different researcher used these TCM herbal formulations or their ingredient to revert cognitive decline among various animal models of cognitive decline as well as in humans. Huatuo Zaizao pills are TCM reported to cure Alzheimer's by reversing long term potentiation and reducing amyloid beta deposition is the hippocampus[152]. Feng *et al*. [153] showed that Dendrobium polysaccharides reduced inflammation and reverted cognitive decline in senescence associated microglial activation mouse model. As diabetic brain was characterized by increased oxidative stress, inflammation and reduced neurogenesis there are studies which highlighted the importance of natural compounds to reverse these conditions to restore cognitive declines. Some of the studies are mentioned in Table 1.

4.2 Future of natural product to be explored to overcome DACD

The above stated studies clearly suggest the modulation of brain inflammation and oxidative stress is a key to overcome diabetes associated cognitive decline. In Table 2, a few natural products which ameliorate diabetes insults and can be a possible candidate to test to overcome DACD.

5 Conclusion

The adapted modern life style and rising ageing population increases the prevalence of type 2 diabetes globally. Different epidemiological and clinical studies strongly linked T2DM with cognitive decline. It speeds up brain aging and T2DM individuals are at higher risk to develop mild cognitive decline to dementia. Hyperglycemia, hypoglycemia and altered insulin signaling are the characteristic features of diabetes impair blood brain barrier and vasculature in brain leading towards low blood circulation. Different atrophies were found in the diabetic brain. With the understanding of insulin resistant in the diabetic brain affecting learning and memory, still the complete understanding of molecular mechanism is yet to be elucidated. Insulin resistance, increased oxidative stress, neuro-inflammation synergistically or alone were responsible for reduced cognition. Different anti-diabetic drug, antioxidant and anti-inflammatory drug was found to ameliorate the cognitive decline in animal models but still their positive impact on human is still debatable. Only insulin was found to restore cognition both in diabetic animals as well as human. Beside FDA Approved Medication of diabetes literature reported bundles of natural compounds which showed positive impact on DACD.

In future prospective there is an immense need to understand the complete mechanism behind T2DM related cognitive decline. Different programs should be launched to train the diabetic individuals toward exercise and to cut of extra calories from their meals. By understanding the mechanism will pave the way to develop new neural protective drugs with better efficacy which will slow down the cognition reduction among diabetic patients.

Table 1 Traditional Chinese medicine used to ameliorate DACD

Natural Product	Animal Used	Outcomes
Grape seed Proanthocy anidin[154]	STZ Induced diabetes in Wistar rats	· Improved cognition · Improved neuronal survivlal · Improved pancreatic β cells · Significantly reduced apoptosis in neuronal and pancreatic β cells · Increased insulin secretion and sensitivity
Total Saponins from *Rhizoma Anemarrhenae*[155]	STZ Induced diabetes in SD rats	· Treatment at 200mg/kg significantly improves cognition in Morris water maze · Reduced expression of Amyloid β [Aβ(1-40) and Aβ(1-42)] and TNF-α in the diabetic brain · Reduced expression of TNFα in the serum of diabetic rats · Reduced fasting glucose level with improved body weight
Lychee seed extract[156]	High fat diet plus STZ induced diabetes in SD Rats	· Improves learning and memory in Morris water maze · Reduced neuronal injury · Significantly reduces the concentration of Amyloid β, glucose, Advance glycation end product and Tau protein in the blood or hippocampi of diabetic rats · Improved insulin resistance
Polyphenol-rich Boswellia Serrata Gum[157]	High fat and high fructose diet with STZ induced diabetes in Wistar rats	· Improves learning and memory in Morris water maze and Passive avoidance test · Significantly reduced Amyloid β and Tau protein in the diabetic brain · Reduced inflammation by downregulating the expression of caspase 3, GSK 3β, TNF-α, IL-1β, Il-6 and MDA · Significantly enhanced the expression of hippocampal GSH, SOD and glutamate receptors · Improved insulin resistance and hyperlipidemia
Fenugreek Seed Extract[158]	STZ induced diabetes in Wistar rats	· Improves learning and memory in Morris water maze and T- maze · Significantly reduced blood glucose level · Increased neurons in the CA1 and CA3 region of hippocampus · Significantly reduce oxidative stress by downregulating MDA, and glutathione and upregulating SOD, CAT level
ZiBuPiYin[159-161]	· db/db mice · STZ induced · Zucker diabetic fatty rats (psychological stress induced diabetes associated cognitive decline)	· Improved learning and memory in Morris water maze · Strengthen brain leptin concentration · Revert insulin resistance · Down regulate GSK3β · Restore PI3K-Akt signaling pathways · Improves protein processing in endoplasmic reticulam · Increased growth receptor binind protein 2 (Grb2) thus stimulating PI3k-Akt and its downstream pathway · Normalize depression or anxiety behavior in open field · Improved learning and memory outcomes in Morris water maze · Increased dendritic spine density with increased expression of MAP2 (marker for dendritic cytoskeleton) and PSD95 (Post synaptic density) · Reverts Microbiome imbalance in diabetic rats thus reduces anxiety and depression like behavior · Increased butyrate producing bacteria (*Roseburia*) and *Coprococcus* which is responsible for increased LPS in plasma thus favor insulin resistance, inflammation · Maintain glucose homeostasis
Astragalus Polysaccherin (APS)[162]	STZ induced	· Improved learning and memory in Morris water maze · Increased activation of CREB. NMDA and CaMK II

Continued to Table 1

Natural Product	Animal Used	Outcomes
Nigella Sativa Oil Alone or in combination with antidiabetic drugs[90,163]	High fat with STZ induced diabetes in albino Wistar and SD rats	· Reduced oxidative stress by decreasing TBRAS, NO, XO and increasing GSH, GST and SOD levels · Reduced neuronal inflammation by reducing levels of TNF-α, IL-1β, IL-6 and INOS · Restore cholinergic function by reducing AChE levels · Reduced the level of AGEs, Insulin degrading enzymes and Amyloid β in the blood or brain of diabetic rats · Reduced the expression of Amyloid precursor protein (APP), Beta site AβPP cleaving enzyme (BACE), Receptors for advance glycation end product (RAGE), p53, Nuclear factor κ B · Increased expression of NAD dependent deacetylase sirtuin (SIRT1), A disintegrin and metalloprotease 10 (ADAM10), Insulin receptor (IR), Insulin like growth factor (IGF)
Terpenoid-rich Elettaria Cardamomum Extract[164]	High fat and high fructose diet with STZ induced diabetes in Wistar rats	· Improves learning and memory in Morris water maze and Passive avoidance test · Significantly reduced Amyloid β and Tau protein in the diabetic brain · Reduced inflammation by downregulating the expression of caspase 3, acetylcholinesterase (AChE), GSK 3β, TNF-α, IL-1β, Il-6 and MDA · Significantly enhanced the expression of hippocampal GSH, SOD and glutamate receptors · Increased expression of glutamate receptor expression (AMPA, GluR1, NMDA Receptor subunit NR1, NR2A, NR2B)
Mangiferin[36]	STZ induced diabetes in SD rats	· Improved learning and memory in Morris water maze · Reduced AGEs, RAGEs, TNF-α, IL-1β and MDA level in cortex and hippocampus of diabetic rats · Elevated expression of GSH, SOD, Glyoxalase 1
Ginsenoside Re[155]	STZ induced diabetes in SD rats	· Improved learning and memory in Morris water maze · Reduced AGEs, RAGEs, TNF-α, IL-1β and MDA level in cortex and hippocampus of diabetic rats · Elevated expression of GSH · Reduced sugar level in serum of diabetic rats
Jinzhida[165]	High fat diet and STZ induced diabetes SD rats	· Enhanced learning and memory in Morris water maze and step down test · Increased insulin sensitivity by down regulating endoplasmic reticulum stress (ERS) markers phosphorylation (PERK, e1F2α, IRE1α), Insulin resistance marker phosphorylation (JNK, IR) · Increase protein kinase B (AKT) expression
Urtica Dioica[166]	STZ induced diabetes in Swiss albino rats	· Restore memory, learning and locomotion in NORT and open field arena · Improved insulin sensitivity and glucose tolerance by enhancing IR, PI3K, AKT, GLUT4 and MAPK expression · Reduced oxidative stress by downregulating TBRAS, NO levels and upregulating catalase, total thiol levels
Withania Somnifera And Aloe vera[167-168]	STZ induced diabetes in Swiss albino rats	· Improved motor activities and memory in T-Maze and active avoidance test · In combination they significantly reduce oxidative insult by reducing lipid peroxidation and protein carbonyl in diabetic brain · In combination it also significantly blood sugar level
Chotosan[169]	STZ induced diabetes in SD rats	· Improved memory in Y maze task · Upregulate glutamate receptor (NR2B) · Improved Long term depression
Andrographis Paniculata Extract[170]	STZ induced diabetes in Charles Foster albino rats	· Improved learning and memory in Morris water maze · Reduced AChE activity, SOD and CAT activities · Reduced blood sugar and promote insulin sensitivity
Jiawei Shengmai san formulation[171]	STZ induced diabetes in SD rats	· Improved reference and working memory in Morris water maze and NORT · Improved histological changes of diabetic brain · Improved expression of Akt and CREB

Table 2 Possible candidate natural compounds to ameliorate DACD

Natural Product	Animal Used	Outcomes
Astragaloside IV[172]	High fat diet and STZ induced diabetic nephropathy	· Inhibited glomerulosclerosis, mesangial proliferation, tubular cells edema and interstitial fibrosis · Reduced oxidative stress by reducing MDA, IL-1β, IL-4, IL-6 and enhancing SOD
Salvianolic Acid A[173]	Zucker Diabetic Fatty Rats	· Improved body weight and glucose tolerance · Reduced Total cholesterol and LDL-C at higher dose · Improved histological feature of aortic tissues after diabetes insult i.e. fewer cholesterol crystal, foam cells and calcification, macrophages · Reduced the expression of high sensitive C reactive protein · Reduced expression of NLPR3, Caspase 1, IL-1β, NF-κB
Polysaccharides from *Cordyceps Taii*[174]	STZ Induced diabetes in Kunming mice	· Increased body weight, insulin level with reduced blood sugar · Reduced total cholesterol, total glyceride, LDL-C with increased HDL-C · Restores pancreatic pathology and β cells after diabetic insults · Reduced inflammation by downregulating TNF-α, IL-6 and CRP levels
Dietary Hesperidin Exerts[175]	STZ induced diabetes in Wistar Rats	· Reduced glucose level with increased insulin secretion · Reduced total cholesterol, total glyceride, LDL-C with increased HDL-C
Baicalin[176]	STZ Induced diabetes in Kunming mice	· Reduced cell apoptosis in chicken embryonated eggs after hyperglycemia · Inhibited ROS production · Improved oxidative stress by enhancing SOD · Reduced blood glucose
Cassiae Semen Extract[177]	STZ induced diabetes in Wistar Rats	· Increased body weight, glucose tolerance with reduced blood sugar levels · Reduced total cholesterol, total glyceride, LDL-C with increased HDL-C · Reduced oxidative stress by upregulating SOD, CAT activity and downregulating MDA level · Reduced inflammation as evident by reduced IL-1β, IL-6 and TNF-α · Reduced RAGE expression
Salidroside[178-179]	STZ induced diabetes model or bone loss	· Increased body weight with reduced blood sugar · Reduced Alkaline phosphatase · Reduced inflammation by reducing RANKL · Improving bone density
Kirenol[180]	Goto-Kakizaki (GK) rats	· Decrease Fasting Plasma Glucose · Reduced apoptosis in cardiomyocytes · Reduced inflammation by downregulating the translocation of NF-κB from cytoplasm to nucleas, reduced level of TNF-α, IL-1β and IL-6 · Enhance AKT phosphorylation
Curcumin[181]	High fat diet and STZ induced diabetes in SD rats	· Improved body weight with reduced fasting blood glucose · Improved oral glucose and insulin tolerance · Restores pancreatic pathology and β cells after diabetic insults · Reduced apoptosis in pancreatic cells · Reduced inflammation as evident by reduced IL-1β, IL-6 and TNF-α · Reduced oxidative stress by increasing SOD and downregulating MDA
Urolithin A[182]	High fat diet and STZ induced diabetes in C57BL/6 mice	· Improved body weight with reduced fasting blood glucose · Improved oral glucose and insulin tolerance · Reduced inflammation as evident by reduced IL-1β, IL-10 and TNF-α · Reduced oxidative stress by increasing GSH and downregulating MDA · Restores pancreatic pathology and β cells after diabetic insults · Enhanced expression of AKT, PI3K and reduced expression of caspase 3

Supplementary materials 20200265_Table S1.pdf is available at paper online (http://www.pibb.ac.cn or http://www.cnki.net).

References

[1] (WHO) WHO. Global Reports on Diabetics. 2016

[2] Ahmed A, Zeng G, Jiang D, *et al*. Time-dependent impairments in learning and memory in Streptozotocin-induced hyperglycemic rats. Metabolic Brain Disease, 2019, **34**(5): 1431-1446

[3] Feinkohl I, Price J F, Strachan M W, *et al*. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimers Res Ther, 2015, **7**(1): 46

[4] Nooyens A C, Baan C A, Spijkerman A M, *et al*. Type 2 diabetes and cognitive decline in middle-aged men and women: the Doetinchem Cohort Study. Diabetes Care, 2010, **33**(9):1964-1969

[5] No authors listed. 2020 Alzheimer's disease facts and figures. Alzheimers Dement, 2020, doi:10.1002/alz.12068

[6] Callisaya M L, Beare R, Moran C, *et al*. Type 2 diabetes mellitus, brain atrophy and cognitive decline in older people: a longitudinal study. Diabetologia, 2019, **62**(3): 448-458

[7] Biessels G J, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol, 2018, **14**(10): 591-604

[8] Biessels G J, Whitmer R A. Cognitive dysfunction in diabetes: how to implement emerging guidelines. Diabetologia, 2020, **63**(1): 3-9

[9] Teixeira M M, Passos V M A, Barreto S M, *et al*. Association between diabetes and cognitive function at baseline in the Brazilian Longitudinal Study of Adult Health (ELSA- Brasil). Scientific Reports, 2020,**10**(1):1596

[10] Chatterjee S, Peters S A, Woodward M, *et al*. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care, 2016, **39**(2): 300-307

[11] Ryan C M, Williams T M, Finegold D N, *et al*. Cognitive dysfunction in adults with type 1 (insulin-dependent) diabetes mellitus of long duration: effects of recurrent hypoglycaemia and other chronic complications. Diabetologia, 1993, **36**(4): 329-334

[12] Ohmann S, Popow C, Rami B, *et al*. Cognitive functions and glycemic control in children and adolescents with type 1 diabetes. Psychol Med, 2010, **40**(1): 95-103

[13] Perantie D C, Lim A, Wu J, *et al*. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. Pediatric Diabetes, 2008, **9**(2): 87-95

[14] van Duinkerken E, Ryan C M. Diabetes mellitus in the young and the old: Effects on cognitive functioning across the life span. Neurobiol Dis, 2020, **134**:104608

[15] Chung C C, Pimentel Maldonado D A, Jor'dan A J, *et al*. Lower cerebral vasoreactivity as a predictor of gait speed decline in type 2 diabetes mellitus. J Neurol, 2018, **265**(10): 2267-2276

[16] Rucker J L, McDowd J M, Mahnken J D, *et al*. Multitasking in older adults with type 2 diabetes: a cross-sectional analysis. Plos One, 2017,**12**(10): e0186583

[17] Marseglia A, Fratiglioni L, Laukka E J, *et al*. Early cognitive deficits in type 2 diabetes: a population-based study. J Alzheimers Dis, 2016, **53**(3): 1069-1078

[18] Wood A G, Chen J, Moran C, *et al*. Brain activation during memory encoding in type 2 diabetes mellitus: a discordant twin pair study. J Diabetes Res, 2016, **2016**: 3978428

[19] Palta P, Carlson M C, Crum R M, *et al*. Diabetes and cognitive decline in older adults: the ginkgo evaluation of memory study. J Gerontol A Biol Sci Med Sci, 2017, **73**(1): 123-130

[20] Redondo M T, Beltran-Brotons J L, Reales J M, *et al*. Executive functions in patients with Alzheimer's disease, type 2 diabetes mellitus patients and cognitively healthy older adults. Exp Gerontol, 2016, **83**: 47-55

[21] Mayeda E R, Haan M N, Yaffe K, *et al*. Does type 2 diabetes increase rate of cognitive decline in older Mexican Americans? Alzheimer Dis Assoc Disord, 2015, **29**(3): 206-212

[22] Lavielle P, Talavera J O, Reynoso N, *et al*. Prevalence of cognitive impairment in recently diagnosed type 2 diabetes patients: are chronic inflammatory diseases responsible for cognitive decline? Plos One, 2015, **10**(10): e0141325

[23] Espeland M A, Brinton R D, Hugenschmidt C, *et al*. Impact of type 2 diabetes and postmenopausal hormone therapy on incidence of cognitive impairment in older women. Diabetes Care, 2015, **38**(12): 2316-2324

[24] Obidi C S, Pugeda J P, Fan X, *et al*. Race moderates age-related cognitive decline in type 2 diabetes. Exp Aging Res, 2008, **34**(2): 114-125

[25] Moody-Ayers S Y, Stewart A L, Covinsky K E, *et al*. Prevalence and correlates of perceived societal racism in older African-American adults with type 2 diabetes mellitus. J Am Geriatr Soc, 2005, **53**(12): 2202-2208

[26] Cukierman-Yaffe T, Gerstein H C, Williamson J D, *et al*. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care, 2009, **32**(2): 221-226

[27] Silverman J M, Schmeidler J, Lee P G, *et al*. Associations of hemoglobin A1c with cognition reduced for long diabetes duration. Alzheimers Dement(N Y), 2019, **5**: 926-932

[28] Kim D J, Yu J H, Shin M S, *et al*. Hyperglycemia reduces efficiency of brain networks in subjects with type 2 diabetes. Plos One, 2016, **11**(6): e0157268

[29] Roy S, Kim N, Desai A, *et al*. Cognitive function and control of type 2 diabetes mellitus in young adults. N Am J Med Sci, 2015, **7**(5): 220-226

[30] Yu Z B, Zhu Y, Li D, *et al*. Association between visit-to-visit variability of HbA1c and cognitive decline: a pooled analysis of two prospective population-based cohorts. Diabetologia, 2020, **63**(1): 85-94

[31] Hawkins M A, Gunstad J, Calvo D, *et al*. Higher fasting glucose is associated with poorer cognition among healthy young adults. Health Psychol, 2016, **35**(2): 199-202

[32] Kinoshita T, Shimoda M, Sanada J, *et al*. Association of GA/HbA1c ratio and cognitive impairment in subjects with type 2 diabetes mellitus. J Diabetes Complications, 2016, **30**(8): 1452-1455

[33] Rhee S Y. Hypoglycemia and Dementia. Endocrinol Metab (Seoul), 2017, **32**(2): 195-199

[34] Feinkohl I, Aung P P, Keller M, *et al*. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. Diabetes Care, 2014, **37**(2): 507-515

[35] Meneilly G S, Tessier D M. Diabetes, dementia and hypoglycemia. Can J Diabetes, 2016, **40**(1): 73-76

[36] Liu Y W, Zhu X, Yang Q Q, *et al*. Suppression of methylglyoxal hyperactivity by mangiferin can prevent diabetes-associated cognitive decline in rats. Psychopharmacology(Berl), 2013, **228**(4): 585-594

[37] Rom S, Zuluaga-Ramirez V, Gajghate S, *et al*. Hyperglycemia-driven neuroinflammation compromises BBB leading to memory loss in both diabetes mellitus (DM) type 1 and type 2 mouse models. Mol Neurobiol, 2019, **56**(3): 1883-1896

[38] Soares A F, Nissen J D, Garcia-Serrano A M, *et al*. Glycogen metabolism is impaired in the brain of male type 2 diabetic Goto-Kakizaki rats. J Neurosci Res, 2019, **97**(8): 1004-1017

[39] Cho J A, Park S H, Cho J, *et al*. Exercise and curcumin in combination improves cognitive function and attenuates ER stress in diabetic rats. Nutrients, 2020, **12**(5): 1309

[40] Kwon K J, Lee E J, Kim M K, *et al*. Diabetes augments cognitive dysfunction in chronic cerebral hypoperfusion by increasing neuronal cell death: implication of cilostazol for diabetes mellitus-induced dementia. Neurobiol Dis, 2015, **73**:12-23

[41] Li X L, Aou S, Hori T, *et al*. Spatial memory deficit and emotional abnormality in OLETF rats. Physio Behav, 2002, **75**(1-2): 15-23

[42] Beauquis J, Homo-Delarche F, Giroix M H, *et al*. Hippocampal neurovascular and hypothalamic-pituitary-adrenal axis alterations in spontaneously type 2 diabetic GK rats. Exp Neurol, 2010, **222**(1): 125-134

[43] Matsunaga Y, Negishi T, Hatakeyama A, *et al*. Impairment of synaptic development in the hippocampus of diabetic Goto-Kakizaki rats. Int J Dev Neurosci, 2016, **53**: 58-67

[44] Winocur G, Greenwood C E, Piroli G G, *et al*. Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. Behav Neurosci, 2005, **119**(5): 1389-1395

[45] Soares E, Prediger R D, Nunes S, *et al*. Spatial memory impairments in a prediabetic rat model. Neuroscience, 2013, **250**: 565-577

[46] Blazquez E, Velazquez E, Hurtado-Carneiro V, *et al*. Insulin in the brain: its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. Front Endocrinol(Lausanne), 2014, **5**:161

[47] Pomytkin I, Costa-Nunes J P, Kasatkin V, *et al*. Insulin receptor in the brain: mechanisms of activation and the role in the CNS pathology and treatment. CNS Neurosci Ther, 2018, **24**(9): 763-774

[48] Liebner S, Dijkhuizen R M, Reiss Y, *et al*. Functional morphology of the blood-brain barrier in health and disease. Acta Neuropathol, 2018, **135**(3): 311-336

[49] Zhao Z, Nelson A R, Betsholtz C, *et al*. Establishment and dysfunction of the blood-brain barrier. Cell, 2015, **163**(5): 1064-1078

[50] Abbott N J, Patabendige A A, Dolman D E, *et al*. Structure and function of the blood-brain barrier. Neurobiol Dis, 2010, **37**(1): 13-25

[51] Xu Z, Zeng W, Sun J, *et al*. The quantification of blood-brain barrier disruption using dynamic contrast-enhanced magnetic resonance imaging in aging rhesus monkeys with spontaneous type 2 diabetes mellitus. Neuroimage, 2017, **158**: 480-487

[52] Obermeier B, Daneman R, Ransohoff R M. Development, maintenance and disruption of the blood-brain barrier. Nat Med, 2013, **19**(12): 1584-1596

[53] Kamat P K, Kyles P, Kalani A, *et al*. Hydrogen sulfide ameliorates homocysteine-induced Alzheimer's disease-like pathology, blood-brain barrier disruption, and synaptic disorder. Mol Neurobiol, 2016, **53**(4): 2451-2467

[54] Patel J P, Frey B N. Disruption in the blood-brain barrier: the missing link between brain and body inflammation in bipolar disorder? Neural plast, 2015, **2015**: 708306

[55] Garcia-Serrano A M, Duarte J M N. Brain metabolism alterations in type 2 diabetes: what did we learn from diet-induced diabetes models? Front Neurosci, 2020, **14**: 229

[56] Salameh T S, Mortell W G, Logsdon A F, *et al*. Disruption of the hippocampal and hypothalamic blood-brain barrier in a diet-induced obese model of type II diabetes: prevention and treatment by the mitochondrial carbonic anhydrase inhibitor, topiramate. Fluids Barriers CNS, 2019, **16**(1): 1

[57] Stranahan A M, Hao S, Dey A, *et al*. Blood-brain barrier breakdown promotes macrophage infiltration and cognitive impairment in leptin receptor-deficient mice. J Cereb Blood Flow Metab, 2016, **36**(12): 2108-2121

[58] Yoo D Y, Yim H S, Jung H Y, *et al*. Chronic type 2 diabetes reduces the integrity of the blood-brain barrier by reducing tight junction proteins in the hippocampus. J Vet Med Sci, 2016, **78**(6): 957-962

[59] Takechi R, Lam V, Brook E, *et al*. Blood-brain barrier dysfunction precedes cognitive decline and neurodegeneration in diabetic insulin resistant mouse model: an implication for causal link. Front Aging Neurosci, 2017, **9**: 399

[60] Xu P, Xu S P, Wang K Z, *et al*. Cognitive-enhancing effects of hydrolysate of polygalasaponin in SAMP8 mice. J Zhejiang Uni Sci B, 2016, **17**(7): 503-514

[61] Brundel M, Kappelle L J, Biessels G J. Brain imaging in type 2 diabetes. Eur Neuropsychopharmacol, 2014, **24**(12): 1967-1981

[62] Macpherson H, Formica M, Harris E, *et al*. Brain functional alterations in type 2 diabetes - a systematic review of fMRI studies. Front Neuroendocrinol, 2017, **47**: 34-46

[63] Younis F M, Blumenthal-Katzir T, Hollander K, *et al*. Telmisartan-mediated metabolic profile conferred brain protection in diabetic

hypertensive rats as evidenced by magnetic resonance imaging, behavioral studies and histology. Eur J Pharmacol, 2016, **789**: 88-97

[64] Zhang J, Liu Z, Li Z, Wang Y, *et al*. Disrupted white matter network and cognitive decline in type 2 diabetes patients. J Alzheimers Dis, 2016, **53** (1): 185-195

[65] Ferguson S C, Blane A, Perros P, *et al*. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. Diabetes, 2003, **52**(1): 149-156

[66] Ryan C M, Geckle M O, Orchard T J. Cognitive efficiency declines over time in adults with Type 1 diabetes: effects of micro- and macrovascular complications. Diabetologia, 2003, **46**(7): 940-948

[67] Falvey C M, Rosano C, Simonsick E M, *et al*. Macro- and microstructural magnetic resonance imaging indices associated with diabetes among community-dwelling older adults. Diabetes Care, 2013, **36**(3): 677-682

[68] Lee J H, Yoon S, Renshaw P F, *et al*. Morphometric changes in lateral ventricles of patients with recent-onset type 2 diabetes mellitus. Plos One, 2013, **8**(4): e60515

[69] Wisse L E, de Bresser J, Geerlings M I, *et al*. Global brain atrophy but not hippocampal atrophy is related to type 2 diabetes. J Neurol Sci, 2014, **344**(1-2): 32-36

[70] Sato K, Satoh S, Muraoka T, *et al*. Evidence of brain atrophy detected on magnetic resonance imaging is associated with failure of acquisition of the ability for insulin self-injection. Endocr J, 2014, **61**(11): 1125-1130

[71] van Bloemendaal L, Ijzerman R G, Ten Kulve J S, *et al*. Alterations in white matter volume and integrity in obesity and type 2 diabetes. Metab Brain Dis, 2016, **31**(3): 621-629

[72] van Elderen S G, de Roos A, de Craen A J, *et al*. Progression of brain atrophy and cognitive decline in diabetes mellitus: a 3-year follow-up. Neurology, 2010, **75**(11): 997-1002

[73] Xiong Y, Sui Y, Xu Z, *et al*. A diffusion tensor imaging study on white matter abnormalities in patients with type 2 diabetes using tract-based spatial statistics. AJNR Am J Neuroradiol, 2016, **37**(8): 1462-1469

[74] Peng J, Qu H, Peng J, *et al*. Abnormal spontaneous brain activity in type 2 diabetes with and without microangiopathy revealed by regional homogeneity. Eur J Radiol, 2016, **85**(3): 607-615

[75] Rofey D L, Arslanian S A, El Nokali N E, *et al*. Brain volume and white matter in youth with type 2 diabetes compared to obese and normal weight, non-diabetic peers: a pilot study. Int J Dev Neurosci, 2015, **46**: 88-91

[76] Cui Y, Li S F, Gu H, *et al*. Disrupted brain connectivity patterns in patients with type 2 diabetes. AJNR Am J Neuroradiol, 2016, **37**(11): 2115-2122

[77] Cui Y, Liang X, Gu H, *et al*. Cerebral perfusion alterations in type 2 diabetes and its relation to insulin resistance and cognitive dysfunction. Brain Imaging Behav, 2017, **11**(5): 1248-1257

[78] Nealon R S, Howe P R, Jansen L, *et al*. Impaired cerebrovascular responsiveness and cognitive performance in adults with type 2 diabetes. J Diabetes Complications, 2017, **31**(2): 462-467

[79] Goodner C J, Berrie M A. The failure of rat hypothalamic tissues to take up labeled insulin *in vivo* or to respond to insulin *in vitro*. Endocrinology, 1977, **101**(2): 605-612

[80] Ghasemi R, Haeri A, Dargahi L, *et al*. Insulin in the brain: sources, localization and functions. Mol Neurobiol, 2013, **47**(1): 145-171

[81] Havrankova J, Schmechel D, Roth J, *et al*. Identification of insulin in rat brain. Proc Natl Acad Sci USA, 1978, **75**(11): 5737-5741

[82] de la Monte S M, Longato L, Tong M, *et al*. Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. Curr Opin Investig Drugs, 2009, **10**(10): 1049-1060

[83] Sims-Robinson C, Kim B, Rosko A, *et al*. How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol, 2010, **6**(10): 551-559

[84] Spinelli M, Fusco S, Grassi C. Brain insulin resistance and hippocampal plasticity: mechanisms and biomarkers of cognitive decline. Front Neurosci, 2019, **13**: 788

[85] Wallum B J, Taborsky G J, Jr. Porte D, *et al*. Cerebrospinal fluid insulin levels increase during intravenous insulin infusions in man. J Clin Endocrinol Metab, 1987, **64**(1): 190-194

[86] Koekkoek P S, Kappelle L J, van den Berg E, *et al*. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol, 2015, **14**(3): 329-340

[87] Benedict C, Brooks S J, Kullberg J, *et al*. Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. Diabetes Care, 2012, **35**(3): 488-494

[88] Baker L D, Cross D J, Minoshima S, *et al*. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol, 2011, **68**(1): 51-57

[89] Reger M A, Watson G S, Green P S, *et al*. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. J Alzheimers Dis, 2008, **13**(3): 323-331

[90] Balbaa M, Abdulmalek S A, Khalil S. Oxidative stress and expression of insulin signaling proteins in the brain of diabetic rats: role of Nigella sativa oil and antidiabetic drugs. Plos One, 2017, **12**(5): e0172429

[91] Brewer G J. Epigenetic oxidative redox shift (EORS) theory of aging unifies the free radical and insulin signaling theories. Exp Gerontol, 2010, **45**(3): 173-179

[92] Biessels G J, Staekenborg S, Brunner E, *et al*. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol, 2006, **5**(1): 64-74

[93] Fernandes M F, Matthys D, Hryhorczuk C, *et al*. Leptin suppresses the rewarding effects of running *via* STAT3 signaling in dopamine neurons. Cell Metab, 2015, **22**(4): 741-749

[94] He Q, Li Q, Zhao J, *et al*. Relationship between plasma lipids and mild cognitive impairment in the elderly Chinese: a case-control study. Lipids Health Dis, 2016, **15**(1): 146

[95] Kou J, Kovacs G G, Hoftberger R, *et al*. Peroxisomal alterations in Alzheimer's disease. Acta Neuropathol, 2011, **122**(3): 271-283

[96] Yurko-Mauro K, Alexander D D, Van Elswyk M E.

Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. Plos One, 2015, **10**(3): e0120391

[97] Yurko-Mauro K, McCarthy D, Rom D, *et al*. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement, 2010, **6**(6): 456-464

[98] Shi Y, Sun X, Sun Y, *et al*. Elevation of cortical C26: 0 due to the decline of peroxisomal beta-oxidation potentiates amyloid beta generation and spatial memory deficits *via* oxidative stress in diabetic rats. Neuroscience, 2015, **315**: 125-135

[99] Zhang L, Li M, Zhan L, *et al*. Plasma metabolomic profiling of patients with diabetes-associated cognitive decline. Plos One, 2015, **10**(5): e0126952

[100] Jones E E, Dworski S, Canals D, *et al*. On-tissue localization of ceramides and other sphingolipids by MALDI mass spectrometry imaging. Anal Chem, 2014, **86**(16): 8303-8311

[101] Sun J, Cai R, Huang R, *et al*. Cholesteryl ester transfer protein intimately involved in dyslipidemia-related susceptibility to cognitive deficits in type 2 diabetic patients. J Alzheimers Dis, 2016, **54**(1): 175-184

[102] Gorska-Ciebiada M, Saryusz-Wolska M, Borkowska A, *et al*. Adiponectin, leptin and IL-1 beta in elderly diabetic patients with mild cognitive impairment. Metab Brain Dis, 2016, **31**(2): 257-266

[103] Misiak B, Leszek J, Kiejna A. Metabolic syndrome, mild cognitive impairment and Alzheimer's disease--the emerging role of systemic low-grade inflammation and adiposity. Brain Res Bull, 2012, **89**(3-4): 144-149

[104] Labad J, Price J F, Strachan M W, *et al*. Serum leptin and cognitive function in people with type 2 diabetes. Neurobiol Aging, 2012, **33**(12): 2938-2941.e2

[105] de la Monte S M, Tong M, Wands J R. The 20-year voyage aboard the journal of Alzheimer's disease: docking at 'type 3 diabetes', environmental/exposure factors, pathogenic mechanisms, and potential treatments. J Alzheimers Dis, 2018, **62**(3): 1381-1390

[106] Pugazhenthi S, Qin L, Reddy P H. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis, 2017, **1863**(5): 1037-1045

[107] Sripetchwandee J, Chattipakorn N, Chattipakorn S C. Links between obesity-induced brain insulin resistance, brain mitochondrial dysfunction, and dementia. Front Endocrinol (Lausanne), 2018, **9**: 496

[108] Montane J, Klimek-Abercrombie A, Potter K J, *et al*. Metabolic stress, IAPP and islet amyloid. Diabetes Obes Metab, 2012, **14 Suppl 3**: 68-77

[109] Westermark P, Andersson A, Westermark G T. Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. Physiol Rev, 2011, **91**(3): 795-826

[110] Maciejczyk M, Zebrowska E, Chabowski A. Insulin resistance and oxidative stress in the brain: what's new? Int J Mol Sci, 2019, **20**(4): 874

[111] Oguntibeju O O. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol, 2019, **11**(3): 45-63

[112] Carvalho C, Cardoso S, Correia S C, *et al*. Metabolic alterations induced by sucrose intake and Alzheimer's disease promote similar brain mitochondrial abnormalities. Diabetes, 2012, **61**(5): 1234-1242

[113] Moreira P I, Santos M S, Moreno A M, *et al*. Increased vulnerability of brain mitochondria in diabetic (Goto-Kakizaki) rats with aging and amyloid-beta exposure. Diabetes, 2003, **52**(6): 1449-1456

[114] Moreira P I. Alzheimer's disease and diabetes: an integrative view of the role of mitochondria, oxidative stress, and insulin. J Alzheimers Dis, 2012, **30 Suppl 2**: S199-215

[115] Guglielmotto M, Giliberto L, Tamagno E, *et al*. Oxidative stress mediates the pathogenic effect of different Alzheimer's disease risk factors. Front Aging Neurosci, 2010, **2**: 3

[116] Tan J L, Li Q X, Ciccotosto G D, *et al*. Mild oxidative stress induces redistribution of BACE1 in non-apoptotic conditions and promotes the amyloidogenic processing of Alzheimer's disease amyloid precursor protein. Plos One, 2013, **8**(4): e61246

[117] Pandey S P, Singh H K, Prasad S. Alterations in hippocampal oxidative stress, expression of AMPA receptor GluR2 subunit and associated spatial memory loss by bacopa monnieri extract (CDRI-08) in streptozotocin-induced diabetes mellitus type 2 mice. Plos One, 2015, **10**(7): e0131862

[118] Carubelli R, Schneider J E, Jr. Pye Q N, *et al*. Cytotoxic effects of autoxidative glycation. Free Radic Biol Med, 1995, **18**(2): 265-269

[119] Win M T, Yamamoto Y, Munesue S, *et al*. Regulation of RAGE for attenuating progression of diabetic vascular complications. Exp Diabetes Res, 2012, **2012**: 894605

[120] Lue L F, Andrade C, Sabbagh M, *et al*. Is There inflammatory synergy in type II diabetes mellitus and Alzheimer's disease? Int J Alzheimers Dis, 2012, **2012**: 918680

[121] Wang P, Huang R, Lu S, *et al*. RAGE and AGEs in mild cognitive impairment of diabetic patients: a cross-sectional study. Plos One, 2016, **11**(1): e0145521

[122] Zhou S, Yu G, Chi L, *et al*. Neuroprotective effects of edaravone on cognitive deficit, oxidative stress and tau hyperphosphorylation induced by intracerebroventricular streptozotocin in rats. Neurotoxicology, 2013, **38**: 136-145

[123] Kuhad A, Chopra K. Effect of sesamol on diabetes-associated cognitive decline in rats. Exp Brain Res, 2008, **185**(3): 411-420

[124] Zhou J, Du X, Long M, *et al*. Neuroprotective effect of berberine is mediated by MAPK signaling pathway in experimental diabetic neuropathy in rats. Eur J Pharmacol, 2016, **774**: 87-94

[125] Reinehr T, Karges B, Meissner T, *et al*. Inflammatory markers in obese adolescents with type 2 diabetes and their relationship to hepatokines and adipokines. J Pediatr, 2016, **173**: 131-135

[126] Spranger J, Kroke A, Mohlig M, *et al*. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective

population-based European Prospective Investigation into Cancer and Nutrition (EPIC) -Potsdam Study. Diabetes, 2003, **52**(3): 812-817

[127] Forlenza O V, Diniz B S, Talib L L, *et al*. Increased serum IL-1beta level in Alzheimer's disease and mild cognitive impairment. Dement Geriatr Cogn Disord, 2009, **28**(6): 507-512

[128] Jia J P, Meng R, Sun Y X, *et al*. Cerebrospinal fluid tau, Abeta1-42 and inflammatory cytokines in patients with Alzheimer's disease and vascular dementia. Neurosci Lett, 2005, **383**(1-2): 12-16

[129] Arnoldussen I A, Kiliaan A J, Gustafson D R. Obesity and dementia: adipokines interact with the brain. Eur Neuropsychopharmacol, 2014, **24**(12): 1982-1999

[130] Sonnen J A, Larson E B, Brickell K, *et al*. Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol, 2009, **66**(3): 315-322

[131] Marioni R E, Deary I J, Murray G D, *et al*. Associations between polymorphisms in five inflammation-related genes and cognitive ability in older persons. Genes Brain Behav, 2010, **9**(3): 348-352

[132] Chung C C, Pimentel D, Jor'dan A J, *et al*. Inflammation-associated declines in cerebral vasoreactivity and cognition in type 2 diabetes. Neurology, 2015, **85**(5): 450-458

[133] Kawamura T, Umemura T, Umegaki H, *et al*. Effect of renal impairment on cognitive function during a 3-year follow up in elderly patients with type 2 diabetes: association with microinflammation. J Diabetes Investig, 2014, **5**(5): 597-605

[134] Dorsemans A C, Soule S, Weger M, *et al*. Impaired constitutive and regenerative neurogenesis in adult hyperglycemic zebrafish. J Comp Neurol, 2017, **525**(3): 442-458

[135] Hirosumi J, Tuncman G, Chang L, *et al*. A central role for JNK in obesity and insulin resistance. Nature, 2002, **420**(6913): 333-336

[136] Chang R C, Suen K C, Ma C H, *et al*. Involvement of double-stranded RNA-dependent protein kinase and phosphorylation of eukaryotic initiation factor-2alpha in neuronal degeneration. J Neurochem, 2002, **83**(5): 1215-1225

[137] Lourenco M V, Clarke J R, Frozza R L, *et al*. TNF-alpha mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's beta-amyloid oligomers in mice and monkeys. Cell Metab, 2013, **18**(6): 831-843

[138] Jawale A, Datusalia A K, Bishnoi M, *et al*. Reversal of diabetes-induced behavioral and neurochemical deficits by cinnamaldehyde. Phytomedicine, 2016, **23**(9): 923-930

[139] Nagayach A, Patro N, Patro I. Astrocytic and microglial response in experimentally induced diabetic rat brain. Metab Brain Dis, 2014, **29**(3): 747-761

[140] Yin Z, Yu H, Chen S, *et al*. Asiaticoside attenuates diabetes-induced cognition deficits by regulating PI3K/Akt/NF-kappaB pathway. Behav Brain Res, 2015, **292**: 288-299

[141] Stranahan A M, Lee K, Mattson M P. Central mechanisms of HPA axis regulation by voluntary exercise. Neuromolecular Med, 2008, **10**(2): 118-127

[142] Karczewska-Kupczewska M, Tarasow E, Nikolajuk A, *et al*. The effect of insulin infusion on the metabolites in cerebral tissues assessed with proton magnetic resonance spectroscopy in young healthy subjects with high and low insulin sensitivity. Diabetes Care, 2013, **36**(9): 2787-2793

[143] Kleinridders A, Ferris H A, Cai W, *et al*. Insulin action in brain regulates systemic metabolism and brain function. Diabetes, 2014, **63**(7): 2232-2243

[144] van Bussel F C, Backes W H, Hofman P A, *et al*. Increased GABA concentrations in type 2 diabetes mellitus are related to lower cognitive functioning. Medicine(Baltimore), 2016, **95**(36): e4803

[145] Sickmann H M, Waagepetersen H S, Schousboe A, *et al*. Brain glycogen and its role in supporting glutamate and GABA homeostasis in a type 2 diabetes rat model. Neurochem Int, 2012, **60**(3): 267-275

[146] Datusalia A K, Sharma S S. NF-kappaB inhibition resolves cognitive deficits in experimental type 2 diabetes mellitus through CREB and glutamate/GABA neurotransmitters pathway. Curr Neurovasc Res, 2016, **13**(1): 22-32

[147] Biessels G J, ter Laak M P, Hamers F P, *et al*. Neuronal Ca2+ disregulation in diabetes mellitus. Eur J Pharmacol, 2002, **447**(2-3): 201-209

[148] Landfield P W. Increased hippocampal Ca^{2+} channel activity in brain aging and dementia. Hormonal and pharmacologic modulation. Ann N Y Acad Sci, 1994, **747**: 351-364

[149] Singhal K, Sandhir R. L-type calcium channel blocker ameliorates diabetic encephalopathy by modulating dysregulated calcium homeostasis. J Neurosci Res, 2015, **93**(2): 296-308

[150] Li X, Liang Z, Du J, *et al*. Herbal decoctosome is a novel form of medicine. Science China Life Sciences, 2019, **62**(3): 333-348

[151] Chen Y, Yu L X, Wei Y, *et al*. D-ribose increases triglyceride *via* up-regulation of DGAT in the liver. Science China Life Sciences, 2019, **62**(6): 858-861

[152] Zhang J H, Yu L J, Yang H, *et al*. Huatuo Zaizao pill ameliorates cognitive impairment of APP/PS1 transgenic mice by improving synaptic plasticity and reducing Abeta deposition. BMC complement Altern Med, 2018, **18**(1): 167

[153] Feng C Z, Cao L, Luo D, *et al*. Dendrobium polysaccharides attenuate cognitive impairment in senescence-accelerated mouse prone 8 mice *via* modulation of microglial activation. Brain Res, 2019,**1704**: 1-10

[154] Sanna R S, Muthangi S, Sagar B K C, *et al*. Grape seed proanthocyanidin extract and insulin prevents cognitive decline in type 1 diabetic rat by impacting Bcl-2 and Bax in the prefrontal cortex. Metab Brain Dis, 2019, **34**(1): 103-117

[155] Liu Y W, Zhu X, Lu Q, *et al*. Total saponins from Rhizoma Anemarrhenae ameliorate diabetes-associated cognitive decline in rats: involvement of amyloid-beta decrease in brain. J Ethnopharmacol, 2012, **139**(1): 194-200

[156] Tang Y, Yu C, Wu J, *et al*. Lychee seed extract protects against neuronal injury and improves cognitive function in rats with type II diabetes mellitus with cognitive impairment. Int J Mol Med, 2018, **41**(1): 251-263

[157] Gomaa A A, Makboul R M, Al-Mokhtar M A, *et al*. Polyphenol-rich Boswellia serrata gum prevents cognitive impairment and insulin resistance of diabetic rats through inhibition of GSK3beta

activity, oxidative stress and pro-inflammatory cytokines. Biomed Pharmacother, 2019, **109**: 281-292

[158] Kodumuri P K, Thomas C, Jetti R, *et al*. Fenugreek seed extract ameliorates cognitive deficits in streptozotocin-induced diabetic rats. J Basic Clin Physiol Pharmacol, 2019, **30**(4): /j/jbcpp.2019.30.issue-4/jbcpp-2018-0140/jbcpp-2018-0140.xml

[159] Bi T, Zhan L, Zhou W, *et al*. Effect of the ZiBuPiYin recipe on diabetes-associated cognitive decline in Zucker diabetic fatty rats after chronic psychological stress. Front Psychiatry, 2020, **11**: 272

[160] Chen J, Liang L, Zhan L, *et al*. ZiBuPiYin recipe protects db/db mice from diabetes-associated cognitive decline through improving multiple pathological changes. Plos One, 2014, **9**(3): e91680

[161] Chen J, Zhan L, Lu X, *et al*. The alteration of ZiBuPiYin recipe on proteomic profiling of forebrain postsynaptic density of db/db mice with diabetes-associated cognitive decline. J Alzheimers Dis, 2017, **56**(2): 471-489

[162] Zhang G, Fang H, Li Y, *et al*. Neuroprotective effect of astragalus polysacharin on streptozotocin (STZ)-induced diabetic rats. Med Sci Monit, 2019, **25**: 135-141

[163] Balbaa M, El-Zeftawy M, Ghareeb D, *et al*. Nigella sativa relieves the altered insulin receptor signaling in streptozotocin-induced diabetic rats fed with a high-fat diet. Oxid Med Cell Longev, 2016, **2016**: 2492107

[164] Gomaa A A, Makboul R M, El-Mokhtar M A, *et al*. Terpenoid-rich Elettaria cardamomum extract prevents Alzheimer-like alterations induced in diabetic rats *via* inhibition of GSK3beta activity, oxidative stress and pro-inflammatory cytokines. Cytokine, 2019, **113**: 405-416

[165] Chang X H, Liang L N, Zhan L B, *et al*. The effect of Chinese Jinzhida recipe on the hippocampus in a rat model of diabetes-associated cognitive decline. BMC complement Altern Med, 2013, **13**: 161

[166] Patel S S, Gupta S, Udayabanu M. Urtica dioica modulates hippocampal insulin signaling and recognition memory deficit in streptozotocin induced diabetic mice. Metab Brain Dis, 2016, **31**(3): 601-611

[167] Parihar M S, Chaudhary M, Shetty R, *et al*. Susceptibility of hippocampus and cerebral cortex to oxidative damage in streptozotocin treated mice: prevention by extracts of Withania somnifera and Aloe vera. J Clin Neurosci, 2004, **11**(4): 397-402

[168] Parihar P, Shetty R, Ghafourifar P, *et al*. Increase in oxidative stress and mitochondrial impairment in hypothalamus of streptozotocin treated diabetic rat: antioxidative effect of Withania somnifera. Cell Mol Biol, 2016, **62**(1): 73-83

[169] Sasaki-Hamada S, Tamaki K, Otsuka H, *et al*. Chotosan, a Kampo formula, ameliorates hippocampal LTD and cognitive deficits in juvenile-onset diabetes rats. J Pharmacol Sci, 2014, **124**(2): 192-200

[170] Thakur A K, Rai G, Chatterjee S S, *et al*. Beneficial effects of an Andrographis paniculata extract and andrographolide on cognitive functions in streptozotocin-induced diabetic rats. Pharm Biol, 2016, **54**(9): 1528-1538

[171] Ahmed A, Zeng G, Azhar M, *et al*. Jiawei Shengmai San herbal formula ameliorates diabetic associate cognitive decline by modulating AKT and CREB in rats. Phytother Res, 2020, doi: 10.1002/ptr.6773

[172] Wang E, Wang L, Ding R, *et al*. Astragaloside IV acts through multi-scale mechanisms to effectively reduce diabetic nephropathy. Pharmacol Res, 2020, **157**: 104831

[173] Ma Q, Yang Q, Chen J, *et al*. Salvianolic acid A ameliorates early-stage atherosclerosis development by inhibiting NLRP3 inflammasome activation in Zucker diabetic fatty rats. Molecules, 2020, **25**(5): 1089

[174] Liu R M, Dai R, Luo Y, *et al*. Glucose-lowering and hypolipidemic activities of polysaccharides from Cordyceps taii in streptozotocin-induced diabetic mice. BMC complement Altern Med, 2019, **19**(1): 230

[175] Akiyama S, Katsumata S, Suzuki K, *et al*. Dietary hesperidin exerts hypoglycemic and hypolipidemic effects in streptozotocin-induced marginal type 1 diabetic rats. J Clin Biochem Nutr, 2010, **46**(1): 87-92

[176] Wang G, Liang J, Gao L R, *et al*. Baicalin administration attenuates hyperglycemia-induced malformation of cardiovascular system. Cell Death Dis, 2018, **9**(2): 234

[177] Wang Q, Zhou J, Xiang Z, *et al*. Anti-diabetic and renoprotective effects of Cassiae Semen extract in the streptozotocin-induced diabetic rats. J Ethnopharmacol, 2019, **239**: 111904

[178] Chen X F, Li X L, Yang M, *et al*. Osteoprotective effects of salidroside in ovariectomized mice and diabetic mice. Eur J Pharmacol, 2018, **819**: 281-288

[179] Zheng H, Qi S, Chen C. Salidroside improves bone histomorphology and prevents bone loss in ovariectomized diabetic rats by upregulating the OPG/RANKL ratio. Molecules, 2018, **23**(9): 2398

[180] Wu B, Huang X Y, Li L, *et al*. Attenuation of diabetic cardiomyopathy by relying on kirenol to suppress inflammation in a diabetic rat model. J Cell Mol Med, 2019, **23**(11): 7651-7663

[181] Qihui L, Shuntian D, Xin Z, *et al*. Protection of curcumin against Streptozocin-induced pancreatic cell destruction in T2DM rats. Planta Med, 2020, **86**(2): 113-120

[182] Tuohetaerbaike B, Zhang Y, Tian Y, *et al*. Pancreas protective effects of Urolithin A on type 2 diabetic mice induced by high fat and streptozotocin *via* regulating autophagy and AKT/mTOR signaling pathway. J Ethnopharmacol, 2020, **250**: 112479

糖尿病所致认知障碍与中药防治概况*

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摘要　2型糖尿病（T2DM）通常影响老年人群，也是世界上最普遍的糖尿病类型. 临床研究表明，T2DM与认知损害，尤其是学习记忆能力下降有关. 与正常人群相比，T2DM患者继发痴呆症的风险较高. 本文综述了近年来有关T2DM患者认知损害和动物模型方面的研究，包括相关机制和中药治疗的可能性，以期对T2DM并发认知损害有更深入的认识.

关键词　2型糖尿病，认知，胰岛素受体，神经炎症/神经递质，记忆丢失，中草药
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