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REVIEW

Medicinal plants for diabetes associated neurodegenerative diseases: A systematic review of preclinical studies

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Diabetes mellitus is a metabolic defect with many complications for the patients. Deaths due to diabetes and its complications are increasing, and one of the most serious consequences are the neurological disorders. Chemical treatments have irreversible side effect and therefore the aim of this study is to evaluate the medicinal plants used for treatment of cognitive impairments and neurodegenerative diseases associated with diabetes in 2004–2020 period. Electronic databases used were PubMed, Scopus and Cochrane library. The keywords used were "diabetes," "plant," "herb," "neurodegenerative," "neurodegeneration," "cognitive," "cognition," "Alzheimer," "dementia." The non-English articles, repetitive articles and review studies were excluded. From total of 3,590 results, 58 articles are included in the study. The results show that many chemical treatments considered for this disease simply control hyperglycemia, but cannot improve the complications of diabetes. Herbal medicine could be more effective due to the high antioxidant activity of some medicinal plants. Biologically active substances of medicinal plants can improve the neurological disorders caused by diabetes via several pathways. The most important pathway is related to antioxidant properties. Other pathways include antiinflammatory, antiapoptotic, neurotoxicity inhibition, neuronal death, increasing the uptake of glucose by cells and improve neurotransmitters levels involved in learning and memory.

KEYWORDS
cognition, diabetes, herbal medicine, medicinal plants, neurodegeneration, systematic review

1 | INTRODUCTION

Diabetes mellitus (DM) is a common metabolic defect divided into two types: the first type occurs at an early age and it is due to inheritance or deficiency in insulin secretion (defect of the insulin secretion from pancreatic β-cells); the second type occurs at older age and it is due to deficiency in insulin receptors (insulin resistance) in the organs, usually caused by environmental factors such as nutrition and obesity. In both types, in addition to hyperglycemia, the increased oxidative stress causes impairment in the function of various organs (Matsui et al., 2007).

Because the cost for the treatment of diabetes with its complications is high, the use of natural compounds and herbal remedies to prove their therapeutic effects on hyperglycemia and its complications is an important task. Most of these herbal remedies, in addition to their high efficacy, do not have the harmful side effects of chemical drugs (Erukainure, Ijomone, Sanni, Aschner, & Islam, 2019).

1.1 | Diabetes complications

Diabetes is one of the noncommunicable but dangerous diseases that could be considered as an epidemic in many developing countries.

Hosna Khazaei and Mirko Pesce contributed equally to the writing of the manuscript.

Chronic elevation of blood glucose leads to tissue damage. Some of the most common complications of uncontrolled hyperglycemia are diabetic retinopathy, renal failure, blindness, coronary artery and peripheral vascular disease, neuropathy, increased blood pressure, cognitive defects, Alzheimer and dementia (Sima, 2004). Cognitive impairments and memory defects have been reported in both types of diabetes (Reaven, Thompson, Nahum, & Haskins, 1990; Ryan, 1988).

1.2 | Etiology and pathophysiology of neurodegenerative diseases induced by DM

During the uncontrolled diabetes, despite the high blood glucose levels, the glucose transporters in the blood brain barrier are downregulated and that lead to decrease of the brain activity. This reduced activity of the brain is due to its high dependence of glucose. Therefore, one of the complications of diabetes is memory loss (Gejl et al., 2017).

Oxidative damages are another reason for neurodegeneration during diabetes. Fluctuations in blood glucose levels lead to lipid metabolism defect, which ultimately leads to increased oxidative stress and cognitive impairments (Borek, 2006). Indicators of oxidative stress include increased NO levels, MDA, lipid peroxide and decreased SOD, GSH and CAT (White et al., 2002). Indicators of neurotransmitter include decreased ACh, serotonin, dopamine and increased AChE and norepinephrine (Roriz-Filho et al., 2009).

Brain tissue is very sensitive and vulnerable against oxidative stress due to its high metabolic rate and high oxygen consumption; herbs and their derivatives can modulate this damage via their antioxidant and antiinflammatory activities and by this way could reduce the oxidative damages in the brain of diabetic patients (Cambay, Baydas, Tuzcu, & Bal, 2011). Investigations have proven that diabetic patients exhibit greater amounts of cognitive impairment and neurodegenerative disease (Whitmer, 2007). Oxidative damages of the brain lead to morphological and functional damages (atrophy and degeneration of neurons cause memory impairment) usually affected the hippocampus area (Baydas, Nedzvetskii, Tuzcu, Yasar, & Kirichenko, 2003).

Diabetes related to cognitive disorders occurs in two period of life, first during the childhood (5–7 years old) when the brain is growing and forming, and second during the adult period, for which type 2 diabetes is more typical (Roriz-Filho et al., 2009).

Current treatments and industrial drugs only decrease the levels of blood glucose but they cannot improve the oxidative damages caused by diabetes. The use of herbs and natural compound with high antioxidant activity could be more effective than using of chemical drugs (Radhika, Annapurna, & Rao, 2012).

2 | METHODS

2.1 | Study design

For this study, we followed the preferred reporting items for systematic reviews (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2010). The data of the present manuscript were collected by searching three database PubMed, Scopus, and Cochrane library and using "neurodegenerative," "neurodegeneration," "cognitive," "cognition," "dementia," "Alzheimer," and "diabetes" keywords in the title/abstract and "plant," "herb" keywords in the whole text. Search results were entered into the study regardless of time limitation, but the final papers that used in the study were from 2004 to August 2020. The searches were carried out by two researchers separately and the articles were first separated based on title and abstract, then non-English, review and duplicate articles were separated and deleted from the study. The full texts of the remaining articles were studied and included in the study. In the second step, few studies were deleted on the basis of full text. The study design diagram is presented in the results section (Figure 1).

2.2 | Study selection and data extraction

Two investigators selected eligible articles separately by reading titles, abstracts and the full-text of the publications when necessary. Disagreements regarding the study selection process were resolved by discussion with a third researcher. The summary of information including the scientific name of plants, method of induction of diabetes, the model used in the study, effective chemical composition(s) of herbs and finally outcomes of treatment are presented in the Table 1.

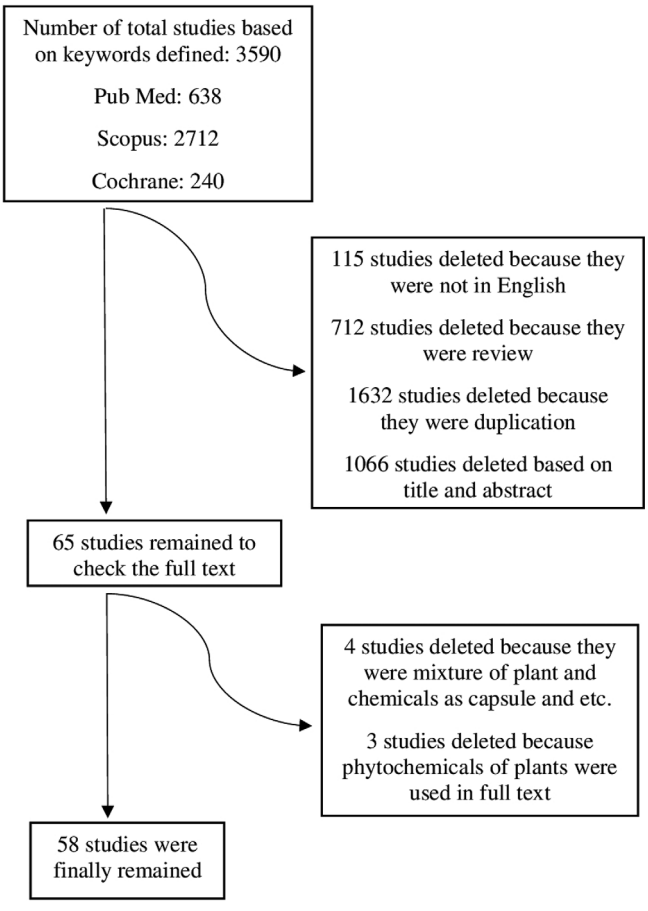

FIGURE 1 Study design diagram

TABLE 1 Medicinal plants used in treatment of neurodegeneration associated with DM

Medicinal plants	Extract/part	Effective chemical composition(s)	Model	Animal/cell	Outcome	References
Aegle marmelos	Aqueous extract/seed	Phenolic and flavonoid compounds	STZ	In vivo- rat	↓Escape latency, ↑Swimming speed	Farshchi, Ghiasi, Farshchi, & Taleb Ghobadi, 2011
Andrographis paniculata	Methanolic extract/leaf	Andrographolide	STZ	In vivo- rat	↓Lymphocyte, ↓Macrophage, ↓MDA, ↑SOD	Radhika et al., 2012
Andrographis paniculata	Hydromethanolic extract/leaf	Andrographolide	STZ	In vivo- rat	↑SOD, ↑CAT, ↓Swimming time, ↓AChE	Thakur, Rai, Chatterjee, & Kumar, 2016
Aralia elata	Aqueous extract/ND	Dihydroxybenzoic acid, chlorogenic acid and caffeic acid	STZ	In vivo-mouse	↓RGC apoptosis, ↓TonEBP, ↓NFkB, ↓AR	Kim et al., 2015
Azadirachta excelsa	Ethanolic extract/leaf	Quercetin	STZ	In vivo- rat	↑Amylin, ↑Insulin, ↑Swimming speed	Zin, Hashim, Samsulrizal, & Azmi, 2019
Camellia sinensis	Methanolic extract/aerial parts	Epigallocatechin gallate	STZ	In vivo- rat	↑TAC, ↓Glu, ↑Thiol groups	Sharifzadeh, Ranjbar, Hosseini, & Khanavi, 2017
Carica papaya	Ether extract/seed	Papain	STZ	In vivo- rat	↓MDA, ↓AChE, ↑SOD, ↑CAT, ↓NO, ↑GSH	Bandaru & Kulandaivelu, 2018
Cola nitida	Acetone extract/seed	Caffeine	STZ	In vivo- rat	↑NA^+/K^+ ATPase	Imam-Fulani, Sanusi, & Owoyele, 2018
Cola nitida	Aqueous extract/ND	Caffeine	STZ + Fructose	In vivo- *rat*	↑GSH, ↑SOD, ↓MDA, ↓AChE, Nrf2↓	Erukainure et al., 2019
Crataegus oxycantha	Aqueous extract/berry	Proanthocyanidins, flavonoids, and polyphenols	STZ	In vivo- rat	↓MDA, ↓AST, ↓ALT, ↑TAC	Zarrinkalam, Ranjbar, Salehi, Kheiripour, & Komaki, 2018
Crocus sativus	Aqueous extract/flower	Crocin	STZ	In vivo- rat	↓Glu, ↓TNF-α, ↓LDL, ↓TG, ↓Cholestrol, ↓AEGs, ↓iNOS, ↑GSP, ↑SOD, ↑GSH, ↑HDL, ↑CAT	Samarghandian, Azimi-Nezhad, & Samini, 2014
EGb 761	_	Ginkgolides	STZ	In vivo-mouse	↑Beclin-1, ↓NF-kB, ↓LC3II/LC3I ratio	Guan et al., 2018
ERPC	Mixture of aqueous and ethanolic extract	Flavonoids, polysaccharide, saponins, alkaloids	STZ	In vivo- rat	↑Oct6, ↑Krox20, ↑MBP, ↑MPZ, ↑Sciatic nerve blood flow	Hao et al., 2017
Evolvulus alsinoides	n-hexane, chloroform, ethyl acetate, methanol, and water extracts/leaf	Tannins, phenolics, flavonoids	-	In vitro/neuroblastoma cell line	↓α-amylase, ↓α-glucosidase, ↓AChE	Mettupalayam Kaliyannan Sundaramoorthy & Kilavan Packiam, 2020
Ficus deltoidea	Methanolic extract/leaf	Vitexin	STZ	In vivo- rat	↑SOD, ↑GPx, ↑Testosterone, ↓TBARS	Nurdiana et al., 2017
Flos puerariae	ND	Puerarin	STZ	In vivo-mouse	↑BW, ↑CAT, ↓MDA, ↑GSH, ↓AChE, ↓Cholestrol, ↓Free fatty acid	Liu et al., 2015

(Continues)

TABLE 1 (Continued)

Medicinal plants	Extract/part	Effective chemical composition(s)	Model	Animal/cell	Outcome	References
Fragaria nilgerrensis	N-butanol extract/leaf	Scutellarin	STZ	In vivo-mouse	↑BW, ↑SOD, ↓Glu, ↑CAT, ↑Memory, ↓MDA	Gao et al., 2018
Garcinia kola	ND/seed	Caffeine	STZ	In vivo- rat	↓Glu, ↓BW, ↓TNF, ↓CD68, ↓GFAP	Etet et al., 2017
Garcinia kola	Aqueous suspension/ND	Caffeine	STZ	In vivo- rat	↓Glu, ↑BW, ↓TNFα, ↓Fas	Farahna et al., 2017
Grape	Proanthocyanidin extract/ seed	Resveratrol	STZ	In vivo- rat	↓NFkBp65, ↓Glu, ↓RAGE	Xu et al., 2008
Guizhi-Fuling-Wan	Aqueous extract/ND	Gallic acid	STZ	In vivo- rat	↓Glu, ↑BW, ↑Bcl2, ↓Bax, ↓Caspase3, ↓Bax, ↓Bax/ Bcl2 ratio	Wu, Chen, Tsai, Wu, & Wood, 2012
Hedera nepalensis	Methanol and chloroform mixture extract/ND	Lupeol	STZ + ALCL3	In vivo- rat	↑CAT, ↑SOD, ↑Dopamine, ↑Serotonin, ↓BG, ↑GSH	Hashmi, Ismail, Mehmood, & Mirza, 2018
He-Ying-Qing-re	Aqueous extract/ND	Chlorogenic acid; Ferulic acid; Rutin	STZ	In vivo-mouse	↑Brn3a, ↑PSD-95, ↑Bcl2, ↑Bcl-XL, ↓CHOP, ↓Caspase, ↓H_2O_2	Zhang et al., 2018b
Hibiscus sabdariffa	Ethyl acetate fraction/flower	Hibiscus acid and quercetin	STZ	In vivo-mouse	↑BW, ↓Glu, ↓AChE, ↓P-JNK, ↓P-tau, ↓MDA, ↑GSH, ↑SOD, ↓c-PAPR	Seung et al., 2018
Hypericum perforatum	Aqueous extract/leaf, flower, stem	Hypericin and hyperforin	STZ	In vivo- rat	↑STL	Hasanein and Shahidi (2011)
Hypericum perforatum	Ethanolic extract/aerial parts	Hypericin and hyperforin	STZ	In vivo- rat	↓Anxiety, ↓Depression, ↑Memory, ↑Locomotor activity	Can, Öztürk, & Özkay, 2011
Jiawei Shengmai san	Aqueous extract/ND	Puerarin	STZ	In vivo- rat	↑ACT, ↑CREB, ↓Escape latency, ↑Memory	Ahmed et al., 2020
Litchi chinesis	Ethanolic extract/seed	Coumaroylquinic acid, procyanidin	STZ	In vivo-rat	↓Glu, ↓Tau, ↓Aβ, ↓AChE, ↓AGEs	Tang et al., 2018
Litsea japonica	Ethanolic extract/aerial parts	Epicatechin, quercitrin and afzelin	ND	In vivo-mouse	↓Glu, ↓NFkB, ↓AGE, ↓RAGE	Kim et al., 2015b
Liuwei dihuang	Ethanolic extract/ND	Gallic acid, morroniside, paeoniflorin, loganin, paeonol	STZ	In vivo-rat	↓Glu, ↑NA^+/K^+ ATPase, ↑GSH, ↑BDNF, ↓AChE, ↓iNOS, ↑IGF-1, ↑ChAT	Liu et al., 2013
Mangifera indica	ND/leaf	Mangiferin	STZ	In vivo-mouse	↓Glu, ↓tau, ↓Caspase, ↓micriglia, ↑BW	Infante-Garcia et al., 2017
Mesembryanthemum crystallinum	ND	D-pinitol	STZ	In vivo-rat/In vitro-C2C12 murine skeletal muscle cell	↑Insulin sensitivity, ↑SOD, ↓Glu, ↓MDA, ↓AChE	Lee, Lee, & Wu, 2014

TABLE 1 (Continued)

Medicinal plants	Extract/part	Effective chemical composition(s)	Model	Animal/cell	Outcome	References
Moringa oliefera	Supplementary diet/leaf	Gallic acid, chlorogenic acid, quercetin and kaempferol	STZ	In vivo-rat	↓AChE, ↓BChE, ↓ACE, ↑CAT, ↑GSH, ↑GST	Oboh, Oyeleye, Akintemi, & Olasehinde, 2018
Morus alba	Ethyl acetate fraction of ethanolic extract/fruit	Polysaccharide and polyphenols	Alloxan	In vivo-mouse	↓Glu, ↓MDA, ↓Amyloid-β, ↓ p-Tau	Min, Yoo, Sok, & Kim, 2020
Myrtus communis	Ethanolic extract/leaf	Myrtucommulone	STZ	In vivo-rat	↓Glu, ↓AChE, ↑ChAT, ↑Neprilysin, ↑α7-nAChR, ↑PSA-NCAM, ↑BDNF	Yaman et al., 2020
Portulaca oleraceae	Aqueous extract/ND	Anthocyanins, antioxidant vitamins, melatonin, flavonoids	STZ	In vivo-rat	↓Glu, ↓Travel distance (MVM), ↑Swimming speed, ↑Time spend on open arms (PMT), ↑Mobility (FST), ↓Escape latency	Tabatabaei, Rashno, Ghaderi, & Askaripour, 2016
Pterocarpus marsupium	Aqueous extract/heart wood	Epicatechin and benzopyran	STZ	In vivo- rat	↓Glu, ↓Escape latency	Vangalapati, Manjrekar, Hegde, & Kumar, 2016
Punica granatum	Supplementary diet/flower	Gallic acid, oleanolic acid, ursolic acid, ellagic acid, triterpenoids	STZ	In vivo- rat	↓Glu, ↓GFAP, ↓MDA, ↓4-HDA, ↑GSH, ↑BW	Cambay et al., 2011
Raphia hookeri	Wine/trunk	Luteic acid, caffeic acid, dihydroxyflavone, protocatechuic acid, gallic acid, flavogallol, gallocatechin gallate	STZ + fructose	In vivo- rat	↓Glu, ↑SOD, ↓MDA, ↓ATPase activity, ↑CAT, ↓Nrf2,↑Glu uptake, ↑GSH	Erukainure, Ijomone, Sanni, et al., 2019
Rubus fruticosus	Hydroethanolic extract/ND	Cyanidin-3-O-glucoside	STZ	In vivo- rat	↓Glu, ↑Step-through latency, ↑BW	Gomar, Hosseini, & Mirazi, 2014
Rumex patientia	Mix in diet/seed	Flavonoids, alkaloids, anthraquinone	STZ	In vivo- rat	↓Glu, ↑BW, ↑Step-through latency	Baluchnejadmojaraand Roghani, 2010
Salacia reticulata and Clitoria ternateae	Alcoholic extract/root	Salacinol and kotalanol	STZ	In vivo- rat	↓Glu, ↓Anxiety, ↑Memory	Rajashree, Patil, Khlokute, & Goudar, 2017
Salvia miltiorrhiza	ND	Phenolic acids	STZ	In vivo- rat	↑BW, ↑MKP-1, ↓Glu, ↓Escape latency	Cai, Lian, Wang, Yu, & Liu, 2014
Salvia officinalis	Hydroalcoholic extract/leaf	Rosmarinic acid	STZ	In vivo- rat	↓MDA, ↓Glu, ↑SOD, ↑CAT, ↑BW	Hasanein, Felehgari, & Emamjomeh, 2016
Solanum melongena	Aqueous extract/fruit	Anthocyanin, hydroxycinnamic acid	ND	In vivo- rat	↓eNTPDase, ↓AChE, ↓BChE, ↓MAO	Nwanna, Ibukun, & Oboh, 2019
Syzygium cumini	Polyphenolic rich extract/leaf	Gallic acid, quercetin, myricetin	Alloxan	In vivo- rat	↓AChE, ↓BChE, ↓MDA, ↑CAT, ↑SOD, ↑GPx	Ajiboye et al., 2018
Teucrium polium	Aqueous extract/aerial parts	Hydroxybenzoic acid, caffeic acid, ferulic acid, luteolin and quercetin	STZ	In vivo- rat	↓Glu, ↑STL, ↓TDC	Hasanein & Shahidi, 2012

(Continues)

TABLE 1 (Continued)

Medicinal plants	Extract/part	Effective chemical composition(s)	Model	Animal/cell	Outcome	References
Trigonella foenum graecum	ND/seed	Trigonelline, gentianine, carpaine, orientin, luteolin, vicentin	STZ	In vivo- rat	↓Blood Glu, ↓MDA, ↑GSH, ↑GPx, ↑SOD, ↑CAT	Kodumuri, Thomas, Jetti, & Pandey, 2019
Urtica dioica	Hydroalcoholic extract/leaf	Scopoletin, quercetin, carvacrol	STZ	In vivo-mouse	↓Glu, ↑STL, ↑BW, ↓Water intake	Patel & Udayabanu, 2013
Urtica dioica	Hydroalcoholic extract/leaf	Scopoletin, quercetin, carvacrol	Dexamethasone	In vivo-mouse	↓Glu, ↓Corticosterone, ↓TBARS, ↑Insulin, ↑BW, ↑CAT, ↑GLUT4	Patel & Udayabanu, 2014
Urtica dioica	Hydroalcoholic extract/leaf	Scopoletin, quercetin, carvacrol	STZ	In vivo- rat	↓Glu, ↑BW, ↓ Escape latency, ↑ Microglial density, ↑GAP43, ↓ CAP1	Keshvari, Rahmati, Mirnasouri, & Chehelcheraghi, 2020
Urtica dioica	Hydroalcoholic extract/leaf	Scopoletin, quercetin, carvacrol	STZ	In vivo- rat	↓Glu, ↑Brain weight, ↑Granule cells density	Fazeli, Gharravi, Ghafari, Jahanshahi, & Golalipour, 2008
Urtica dioica	Hydromethanolic extract/leaf	Scopoletin, quercetin, carvacrol	STZ	In vivo-mouse	↓TBARS, ↓NO, ↑CAT, ↑Thiol	Patel, Parashar, & Udayabanu, 2015
Urtica dioica	Hydromethanolic extract/leaf	Scopoletin, quercetin, carvacrol	STZ	In vivo-mouse	↓Glu, ↓TBARS, ↓NO, ↑Locomotor activity, ↑PPARϒ,↑IRS2, ↑PKB, ↑GLUT4, ↑PI3K	Patel et al., 2016
Vaccinium myrtillus	ND/fruit	Anthocyanin, catechin, Vit C	STZ	In vivo- rat	↑αCaMKII length	Matysek et al., 2017
Withania somnifera and Aloe vera	Aqueous extract/leaves of *A. vera* and roots of *W. somnifera*	Flavonoid compounds	STZ	In vivo-mouse	↓MDA, ↓Glu, ↓Protein carbonyl	Parihar, Chaudhary, Shetty, & Hemnani, 2004
ZiBu PiYin	Aqueous extract/mixture of several herbs	Ginsenosides, senegenin, β-asarone	STZ + high fat diet	In vivo- rat	↓ROS, ↓Glu, ↑IRS1, ↑MAP2, ↑Act, ↑p-GSK3β	Sun et al., 2016
ZiBu PiYin	Aqueous extract/mixture of several herbs	Ginsenosides, senegenin, β-asarone	ND	In vivo-mouse	↑MAP2, ↑PSD95, ↓GSK3β, ↓Glu	Chen et al., 2014

Abbreviations: 4-HDA, 4-hydroxyalkenals; ACE, angiotensin-I converting enzyme; AChE, acetylcholinesterase; AGE, advanced glycation end-products; ALT, alanine aminotransferase; AR, aldose reductase; AST, aspartate aminotransferase; Aβ, amyloid-beta; BChE, butyrylcholinesterase; BDNF, brain-derived neurotrophic factor; BW, body weight; Glu, glucose; CAP1, cyclase-associated protein 1; CAT, catalase; ChAT, cholineacetyltransferase; FST, forced swim test;; GAP43, growth associated protein 43; GFAP, glial–fibrilar acidic protein; Glu, glucose; GLUT4, glucose transporter type 4; GPx, glutathione peroxidase; GSH, glutathione; HDL, high-density lipoproteins; IGF-1, insulin growth factor 1; iNOS, induced nitric oxide synthase; IRS2, insulin receptor substrate 2; LDL, low-density lipoproteins;MAO, monoamine oxidases; MAP2, microtubule-associated protein; MBP, myelin basic protein; MDA, malondialdehyde; MKP-1, mitogen-activated protein kinase phosphatase 1; MPZ, myelin protein zero; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; PKB, Protein kinase B; PMT, plus-maze test; PPARγ, peroxisome proliferator activated receptor gamma; PSD95, postsynaptic density 95; RAGE, receptor advanced glycation end-product; RGC, retinal ganglion cell; SOD, superoxide dismutase; STL, step through latency; STZ, streptozotocin; TAC, total antioxidant capacity;TBARS, thiobarbituric acid reactive substances; TDC, time spent in the dark compartment; TG, triglyceride; TNF, tumor necrosis factor; TonEBP, tonicity-responsive enhancer binding protein; αCaMKII, alpha-Ca2+/calmodulin-dependent protein kinase II.

3 | RESULTS

3.1 | Search results selection and characteristics

From total of 3,590 studies, 1,066 studies were excluded based on their title and abstract, 1,632 studies were deleted because of duplication, 712 studies were excluded because of their review type and 115 studies were deleted because they were not written in English. Sixty-five studies remained to check the full text; therefore, seven studies were excluded based on their full text. Four studies were deleted because they have information about mixture of plant and chemicals as capsule. Three studies were excluded because they were focused on isolated plant compounds but not herbs. Phytochemicals are not considered in the present study. Figure 1 shows the method of the study and criteria for article selection. Table 1 shows the general information of the articles and Figure 2 shows the photos of medicinal plants used in treatment of diabetes associated neurodegenerative diseases (2004–2020).

FIGURE 2 Photos of medicinal plants used in treatment of diabetes associated neurodegenerative diseases (2004–2020) [Colour figure can be viewed at wileyonlinelibrary.com]

3.2 | Medicinal plants used in treatment of neurodegeneration associated with DM

3.2.1 | *Aegle marmelos* (L.) Corrêa

Aegle marmelos (bael, golden apple, Bengal quince, wood apple, bili or bhel) is a member of Rutaceae family. It is a herbal remedy widely used in Asia, native to India. All parts of the plant are utilized in herbal medicine due to their pharmacological activities: antiinflammatory, anti-fever, antioxidant, antitoxic, antidiabetic (Alam, Siddiqui, & Husain, 1990).

Farshchi et al. (2011) demonstrated that the treatment of diabetic rats with *A. marmelos* aqueous extract cause recovery of spatial memory. The experiments were measured by Morris water maze (MVM) method where the treatment with *A. marmelos* causes decrease in swimming time and increase in swimming speed. The authors suggested that improvement of learning and spatial memory is due to decrease lipid peroxidation and oxidative damage (Farshchi et al., 2011).

3.2.2 | *Andrographis paniculata* (Burm.f.) Nees

Andrographis paniculata (green chiretta) is an annual species that belongs to Acanthaceae family, native to India and Sri Lanka. Many studies show that *A. paniculata* has different therapeutic applications due to its antidiabetic, antioxidant, antiviral, antiinflammatory, anti-hepatotoxicity activities (Mishra, Sangwan, & Sangwan, 2007).

Radhika et al. (2012) demonstrated cerebroprotective effect of *A. paniculata* on diabetic rats. The authors suggested that this effect is due to the high antioxidant activity of the herb (Radhika et al., 2012).

Thakur et al. (2016) found that *A. paniculata* causes improvement of cognitive decline and spatial memory of hyperglycemic rats. The authors suggested that the effects observed are due to reducing AChE and raising CAT and SOD levels in the brain tissue of treated animals. That leads to decrease of oxidative damage in the brain and decrease swimming time in MWM test, and finally to improvement of learning and memory (Thakur et al., 2016).

3.2.3 | *Aralia elata* (Miq.) Seem.

Aralia elata (Chinese angelica-tree) is a member of Araliaceae family widely used in Asia. Some of the therapeutic properties of the herb are related to its antiinflammatory, antidiabetic, antioxidant, anticancer activities (Yoshikawa, Shimoda, Nishida, Takada, & Matsuda, 2002).

Kim et al. (2015c) during a study on diabetic mice indicated that *A. elata* could modulate diabetic retinal neurodegeneration by prevention of RGC apoptosis and by decrease of *TonEBP*, *AR* and *NF-κB* expression. Therefore, this herb is a promising agent for treatment of diabetes retinopathy due to its inhibition activity on neuronal toxicity and inflammation, leading to neuronal death (Kim et al., 2015c).

3.2.4 | *Azadirachta excelsa* (Jack) Jacobs

Azadirachta excelsa (marrango tree) is a tree of Meliaceae family. Some of the most important biological activities of this plant are antioxidant, antidiabetic, antiinflammatory, anti-diarrhea (Nurdiana, Mohamad Shukri, Elizabeth Jega, & Nurul Izzati, 2013).

Zin et al. (2019) during a study on diabetic rats treated with *A. excelsa* extracts demonstrated that this herb due to its high antioxidant activity could improve cognitive impairment (Zin et al., 2019). This study shows that quercetin is one of the major active compounds of the ethanolic extract that increases amylin and insulin levels in the brain tissue and improves spatial learning and memory in MWM test compared with diabetic groups. The synthesis and secretion of amylin and insulin is together from the pancreatic β-cells, which are defective in diabetic patients (Kahn et al., 1990). According to these findings, *A. excelsa* can be considered as a potent treatment for cognitive impairments of diabetes (Zin et al., 2019).

3.2.5 | *Camellia sinensis* (L.) Kuntze

Camellia sinensis (green tea) belongs to Theaceae family, used by many peoples all over the world. This plant has many therapeutic activities like antiinflammatory, anticancer, antioxidant, antidiabetic, neuroprotective. Studies demonstrated that polyphenols found in *C. sinensis* are responsible for its pharmacological activities (Guo et al., 2007).

Sharifzadeh et al. (2017) during an investigation on diabetic rats demonstrated that treatment with *C. sinensis* methanolic extracts causes improvement of learning and memory during MVM test, decreases blood glucose and increases thiol groups and total antioxidant capacity (TAC). Therefore, *C. sinensis* can be considered as a potent treatment of neuro-inflammation, learning, and memory disorders in diabetic rats by reducing oxidative stress (Sharifzadeh et al., 2017).

3.2.6 | *Carica papaya* L.

Carica papaya (papaw, pawpaw) is a species of Caricaceae family, native to Mexico and northern part of South America, and naturalized throughout the Caribbean Islands, Florida, Texas, California, Hawaii, and other tropical and subtropical regions of the world. Some of the pharmacological properties of *C. papaya* are due to its high antioxidant, antiinflammatory, neuroprotective, blood glucose, and blood cholesterol lowering, pain lowering, anticancer, memory enhancing activities (Vij & Prashar, 2015).

Bandaru et al. (2018) demonstrated that the treatment of diabetic rats with ether extract of *C. papaya* causes improvement of spatial learning and memory in MVM, also decreases the MDA, AChE, NO and increases GSH and SOD levels in the brain tissue of the laboratory animals. Therefore, based on these findings, *C. papaya* can modulate diabetic neurodegenerative diseases and the majority of the observed effect is due to the decreasing of oxidative stress in the brain (Bandaru & Kulandaivelu, 2018).

3.2.7 | *Cola nitida* (Vent.) Schott & Endl.

Cola nitida (kola nut) is a member of Malvaceae family, native to Africa. This plant affects the CNS due to its high caffeine content. Some of the pharmacological activities of *C. nitida* are antidiabetic, antidepressant, appetite suppressant, aphrodisiac (Adebiyi, Oluyole, & Fagbami, 2009).

Imam-Fulani et al. (2018) during a study on diabetic rats shows that treatment with acetone extract of *C. nitida* causes increase of the Na^+/K^+-ATPase activity in the brain and after that the enhancement of memory. The results obtained are based on Y-maze test (Imam-Fulani et al., 2018). Brain Na^+/K^+-ATPase is one of the important pathway that protect brain from neurodegenerative disease like diabetes (de Lores Arnaiz & Ordieres, 2014).

Erukainure et al. (2019) during a study on diabetic rats demonstrated that treatment with aqueous extract of *C. nitida* could reduce MDA and AChE, and raise GSH, SOD in the brain tissue (Erukainure, Ijomone, Oyebode, et al., 2019). *Nrf2* gene expression increase during oxidative stress. Treatment with *C. nitida* reduces the expression of *Nrf2* in the brain tissue of laboratory rats. Therefore, *C. nitida* is considered as a potent neuroprotective agent against neurodegeneration and oxidative stress in the brain tissue observed in diabetes. These effects are probably due to alkaloid and caffeine content of *C. nitida*.

3.2.8 | *Crataegus rhipidophylla* Gand.

Crataegus rhipidophylla **(Synonym:** *Crataegus oxyacantha*), commonly known as hawthorn, belongs to Rosaceae family. It is a medicinal plant widely used in China and India due to its pharmacological activities on inflammations, cancer, hyperglycemia. The high antioxidant activity of this herb is due to its proanthocyanidins and polyphenols compounds (Swaminathan et al., 2010).

Zarrinkalam et al. (2018) during a study on diabetic rats that received *C. oxyacantha* aqueous extract shows that the treatment with this herb causes improvement of learning and memory during MVM and Shuttle box tests; also increases the TAC and decreases ALT, AST, and MDA levels in the blood of treated animals. Thus, *C. oxycantha* does its neuroprotective effect by reducing oxidative stress (Zarrinkalam et al., 2018).

3.2.9 | *Crocus sativus* L.

Crocus sativus L. (saffron) is a species of Iridaceae family. It is a cultivated medicinal plant used all over the world for treatment of many diseases like neurological disorders, cancer, diabetes, seizure. Some of the biologically active compounds are crocin, crocetin, and safranal (Kanakis, Tarantilis, Tajmir-Riahi, & Polissiou, 2007).

Samarghandian et al. (2014) during an investigation on diabetic rats treated with aqueous extract of *C. sativus* demonstrated improvement of learning and spatial memory during MVM test; also reducing blood sugar and raising the body weight were observed. In the serum analysis, it was observed that the extract increases the HDL and GSP levels and decreases the TNF-α, LDL, TG, cholesterol, and AGEs levels. AGE is an indicator for the diabetic neuropathy progression. The analysis of hippocampus tissue shows increase levels of CAT, SOD, and GSH, and decrease iNOS levels. Therefore, *C. sativus* could protect hippocampus injury induced by hyperglycemia by reducing blood glucose, oxidative stress and inflammation (Samarghandian et al., 2014).

3.2.10 | EGb761

EGb761 is *Ginkgo biloba* L. extract containing flavonoids and terpene lactones. It is widely used in treatment of cognitive and memory disorders (Defeudis, 2002).

Guan et al. (2018) during a study on diabetic mice demonstrated that treatment with EGb761 causes improvement of diabetic neurological disorders identified by MRI. The extract also causes normalization of blood pressure and improvement of learning and memory during Y-maze test. In addition, EGb761 decreases inflammation by reducing NF-kB in the brain tissue, increases beclin-1 protein expression, decreases the LC3-II to LC3-I ratio in the hippocampus. *Beclin-1* and *LC3* genes expression increase in autophagy; so that EGb761 can inhibit autophagy in brain nerve cells. Generally, EGb761 can help to improve neurological disorders in diabetic mice by inhibition of autophagy and inflammation (Guan et al., 2018).

3.2.11 | ERPC

ERPC is a blend of four mixed herbs: *E. alatus* (Gui-Jian-Yu) ethanolic extract, *R. trichosanthis* (Tian-Hua-Fen) aqueous extract, *P. notoginseng* (San-Qi) ethanolic extract and *C. chinensis* (Huang-Lian) aqueous extract flavonoids. This herbal mixture (per g) contains *E. alatus*, *R. trichosanthis* polysaccharide, *P. notoginseng* saponins, and *C. chinensis* alkaloids (Hao et al., 2017).

Hao et al. (2017) during an investigation on diabetic rats that suffering from peripheral neuropathy shows that treatment with ERPC lead to decrease blood glucose levels and latency time during plate test. Also increase in blood flow of sciatic nerve was observed in treated rats. MBP and MPZ decreased in neurodegeneration disease due to diabetes and also Krox20 and Oct6 have important role in MBP and MPZ activation. MBP and MPZ have key roles in myelination. ERPC treatment causes increase of the MBP, MPZ, Oct6, and Karox20 protein expression in the sciatic nerves of animals. Therefore, increase the expression of these proteins caused by ERPC treatment in diabetic rats is a marker to finding the improvement of PNS activity (Hao et al., 2017).

3.2.12 | *Evolvulus alsinoides* (L.) L.

Evolvulus alsinoides (slender dwarf morning glory) is a flowering plant from the family Convolvulaceae that grows in India and other

subtropical regions. This herb is used in folk medicine for treatment of disease associated with oxidative stress, diseases of the respiratory system, memory defects, and neurodegenerative disorders (Nahata, Patil, & Dixit, 2010).

Mettupalayam Kaliyannan Sundaramoorthy and Kilavan Packiam (2020) during an in vitro study on neuroblastoma cell lines showed that treatment with methanolic and aqueous extracts of *E. alsinoides* inhibits AChE, α–amylase and α–glucosidase activity.

Inhibition of α–amylase and α–glucosidase activity controls carbohydrate metabolism and lowers blood glucose levels (Etxeberria, de la Garza, Campión, Martinez, & Milagro, 2012), and AChE hydrolyzes ACh into choline and acetate, this enzyme reduces ACh levels in the brain tissue as a memory enhancer neurotransmitter (Taylor & Radic, 1994).

3.2.13 | *Ficus deltoidea* Jack

Ficus deltoidea (mistletoe fig) is a member of Moraceae family. Its leaves are used in traditional medicine in Malaysia. Some of the pharmacological activities of this plant are antidiabetic, antioxidant, and anti-leucorrhoea. Flavonoids are mainly responsible for the high antioxidant activity and they are the basis in the treatment of diabetes (Farsi et al., 2014).

Nurdiana et al. (2017) during an investigation on diabetic rats show that treatment with *F. deltoidea* methanolic extract causes improvement of learning and memory during MVM test, decreases blood glucose and TBARS and increases SOD, GPx and testosterone (Nurdiana et al., 2017). Previous studies show that the increase of testosterone levels causes improvement of learning and memory (Beauchet, 2006). Consequently, *F. deltoidea* shows neuroprotective effect during diabetic cognitive decline in rats by decreasing oxidative stress and increasing the testosterone levels.

3.2.14 | Flos Puerariae

Pueraria is a genus of Fabaceae family widely used in traditional medicine. The flowers of many species of the genus are used due to their pharmacological activities such as antidiabetic, antiinflammatory, cholesterol reducing, antioxidant, and neuroprotective. Flavonoids are the essential compounds of the *Flos Puerariae* extract (Kamiya et al., 2012).

Liu et al. (2015) during a study in diabetic mice found that treatment with crude extract of *Flos Puerariae* causes improvement of learning and memory in MVM, raises the body weight and decreases hyperglycemia and blood cholesterol levels. In addition, the herb causes decrease the MDA and AChE and increase the CAT and GSH-Px levels in the hippocampus of the brain in laboratory animals. So, *Flos Puerariae* extract does its neuroprotective effect by reducing oxidative stress in the brain and enhances learning and memory in hyperglycemic mice (Liu et al., 2015).

3.2.15 | *Fragaria nilgerrensis* Schltdl. ex J.Gay

Fragaria nilgerrensis is a member of Rosaceae family, native to Asia. This plant is widely used in traditional medicine due to its pharmacological activities such as antidiabetic, anticancer, antiinflammatory, antioxidant (Gao et al., 2018).

Gao et al. (2018) during a study on diabetic rats shows that treatment with n-butanol extract of *F. nilgerrensis* causes improvement of learning and memory during MVM test, decreasing blood glucose and increasing body weight, also reduces MDA and raises CAT and SOD in the liver and hippocampus tissue. *F. nilgerrensis* causes recovery of learning and spatial memory by modulating oxidative stress in the brain of hyperglycemic rats (Gao et al., 2018).

3.2.16 | *Garcinia kola* Heckel

Garcinia kola (Onie or Orogbo) belongs to Clusiaceae family is a herbal remedy utilized in Africa as a cure of many disease especially for treatment of diabetes and oxidative damages due to diabetes (Adedara, Awogbindin, Anamelechi, & Farombi, 2015).

Etet et al. (2017) during a study on diabetic rats shows that *G. kola* seed extract, as a cure, could improve cognitive impairments during hole-board and vertical pole tests, also decreases blood glucose and increases body weight; reduces the expression of inflammatory factors in the brain such as TNF, CD68, and GFAP. Thus, *G. kola* seed extract does its effect by reducing inflammation and following that reducing cognitive impairments (Etet et al., 2017).

Farahna et al. (2016) shows that treatment of hyperglycemic rats with *G. kola* aqueous suspension causes increased body weight and improved hyperglycemia. In the histopathological studies, increased number of Purkinje cells on left cerebellum (cresyl fast violet staining) and decreased inflammation and neurodegeneration factors on right cerebellum (H&E staining) were observed in treated groups. It has been demonstrated that *G. kola* can decrease the inflammation by decreasing the expression of *TNF-α* and *Fas* in the brain of treated animals and can improve neuro-inflammation and neurodegeneration due to diabetes (Farahna et al., 2017).

3.2.17 | Grape seed

Grape seed extract has many pharmacological activities such as antioxidant, neuroprotective, hypocholesterolemic. It has protection role and acts in the treatment of diabetes side effects such as neurodegeneration and diabetes encephalopathy (Zhang et al., 2006).

Xu et al. (2008) during an investigation on diabetic rats with encephalopathy demonstrated that proanthocyanidin extract of grape seeds causes improvement of encephalopathy due to diabetes by inhibition of *NFkBP65* and *RAGE* expression in the hippocampus (Xu et al., 2008). Receptor of advanced glycation end-products (RAGE) is a toxic compound that raises oxidative stress and

inflammation by increasing pro-inflammatory cytokines, also NFkBP65 is a factor for inflammation and it has been shown that increases in the involved organs of diabetic peoples (Haslbeck et al., 2015). Accordingly, Grape seed extract does its effect by reducing oxidative damage and inflammation.

3.2.18 | Guizhi-Fuling-Wan

Guizhi-Fuling-Wan is a herbal composition of aqueous extract of five herbs in 1:1:1:1:1 ratio as follows: *Cinnamomum cassia*, *Poria cocos*, *Paeonia lactiflora*, *Paeonia suffruticosa*, and *Prunus persica*. Guizhi-Fuling-Wan is used in Chinese traditional medicine due to its pharmacological activities such as antidiabetic, anticancer, neuroprotective (Ji et al., 2011).

Wu et al. (2012) demonstrated that treatment of diabetic rats with Guizhi-Fuling-Wan causes improvement of learning and memory impairments during MVM test, also raises *Bcl2* expression and inhibits *Bax* and *Caspase3* expression, reduces *Bax/Bcl2* ratio in hippocampus tissue of treated rats. So, this compound can modulate spatial learning and memory defects and neurological disorders due to hyperglycemia by reducing apoptosis in hippocampus of diabetic rats (Wu et al., 2012).

3.2.19 | *Hedera nepalensis* K.Koch

Hedera nepalensis (chang chun teng) is a member of Araliaceae family, native to Asia, Europe, and Africa. The species is widely used in traditional medicine due to its antioxidant, anticancer, antifungal, antiinflammatory activities (Jafri, Saleem, Ullah, & Mirza, 2017).

Hashmi et al. (2018) demonstrated that treatment of type 3 diabetes rats associated with Alzheimer disease (induced with STZ + $AlCl_3$) with crude extract of *H. nepalensis* causes improvement of learning and memory during MVM test elevated plus maze tests. In addition, decreased blood glucose and oxidative stress confirmed by increase in CAT and SOD levels in the liver and brain tissues were observed. The treatment with *H. nepalensis* raised dopamine and serotonin levels in the midbrain of rats, therefore it can be considered as a cure for Alzheimer disease related to diabetes (Hashmi et al., 2018).

3.2.20 | He-Ying-Qing-Re

He-Ying-Qing-Re formula is a herbal remedy consists of eight plant species: *Arctium lappa*, *Taraxacum mongolicum*, *Polygonatum sibiricum*, *Rehmannia glutinosa*, *Lycium barbarum*, *Scrophularia ningpoensis*, *Angelica sinensis*, *Lonicera japonica*. It is utilized in Chinese traditional medicine for the treatment of many diseases, especially diabetes and its complications on different organs (Zhang et al., 2012).

Zhang, Xu et al. (2018b) during an investigation on diabetic mice with retinopathy shows that treatment with He-Ying-Qing-Re formula can prevent the reduction of retinal ganglion cell, can increase the expression of *Bcl2* and *Bcl-XL* and *Brn3a*, *PSD-95* and can decrease the *CHOP* and Caspase3 expression (cell death indicators) and H_2O_2 levels in the retinae tissue. PSD-95 is a gene that increases neural plasticity in retinal ganglion cells. Therefore, He-Ying-Qing-Re formula does its cure effect by inhibition of apoptosis and decrease of oxidative stress in diabetic mice (Zhang, Xu et al., 2018b).

3.2.21 | *Hibiscus sabdariffa* L.

Hibiscus sabdariffa (Roselle) belongs to Malvaceae family. It is a medicinal plant used in traditional medicine in Asia and Africa due to its wide range of biological activities: antidiabetic, antioxidant, antiaging, reducing blood pressure. Studies show that therapeutic effects of *H. sabdariffa* is mainly due to its flavonoids and anthocyanin's compounds (Agoreyo, Agoreyo, & Onuorah, 2008).

Seung et al. (2018) during a study on diabetic mice demonstrated that treatment with ethyl acetate fraction of *H. sabdariffa* causes improvement of learning and memory during MVM, Y maze and the passive avoidance tests. In addition, it causes reducing the hyperglycemia and raising body weight, causes decrease the expression of p-JNK, p-tau, c-PARP proteins in the brain tissue of treatment with the extract. These proteins have neurotoxic activity lead to neuronal death. *H. sabdariffa* causes decrease the AChE activity and MDA levels and increases the SOD and GSH levels in the serum. Therefore, *H. sabdariffa* by its antioxidant and cholinergic system enhancing activities and inhibition of neuronal death can improve the cognitive declines due to diabetes in mice model (Seung et al., 2018).

3.2.22 | *Hypericum perforatum* L.

Hypericum perforatum (St. John's wort) belongs to *Hypericaceae* family, native to Europe. Studies demonstrated that *H. perforatum* is a potent memory enhancer and widely used for treatment of neurodegenerative disease (Barnes, Anderson, & Phillipson, 2001).

Hasanein and Shahidi (2011) during a study on diabetic rats shows that treatment with *H. perforatum* aqueous extract leads to improvement of passive avoidance learning test (Hasanein & Shahidi, 2011).

Can et al. (2011) during a study on diabetic rats demonstrated that treatment with *H. perforatum* decreases anxiety during plus-maze test and increases locomotor activity during activity cage tests, decreases depression during modified forced swimming test and increases learning during active avoidance tests. It has been suggested that these effects are probably due to antioxidant and cholinergic system enhancing activities of *H. perforatum* (Can et al., 2011).

3.2.23 | Jiawei Shengmai San

Jiawei Shengmai San is a herbal mixture consisting of four herbs: *Panax ginseng*, *Ophiopogon japonicus*, *Schisandra chinensis*, *and Radix*

puerariae. This mixture is used in Chinese traditional medicine for treatment of many diseases such as diabetes, inflammations, cardiovascular diseases, Alzheimer disease, and for improvement of learning and memory (Ni et al., 2011, Zhang, Yu et al., 2018a).

Ahmed et al. (2020) during an investigation on diabetic rats with cognitive failures showed that this formula can improve learning and memory during MVM and NORT tests, also can reduce blood glucose levels and raise AKT and CREB protein expressions that are responsible for learning and memory in the brain tissue. It has been suggested that puerarin is the most effective component of this herbal mixture.

3.2.24 | *Litchi chinensis* Sonn.

Litchi chinensis (Lychee) is a member of Sapindaceae family, native to Asia. It is widely used in Chinese folk medicine. Some of the pharmacological activities of *L. chinensis* are antioxidant, anticancer, antidiabetic and hypolipidemic (Zhang & Zhang, 2015).

Tang et al. (2018) during a study on diabetic rats showed that the treatment with ethanolic extract of *L. chinensis* causes improvement of learning and memory based on tests with MVM. In addition, it reduces blood glucose and expression of AEGs, Tau and Aβ proteins in the hippocampus. Tau has neurotoxic activities, increases oxidative stress, and finally leads to neuronal death. AEGs, Tau and Aβ in the hippocampus, have key roles in progression of diabetic neuropathy and their expression increases during diabetes that leads to neuropathy. So, based on this investigation *L. chinensis* can treated cognitive impairments due to neuronal damage in diabetic rats (Tang et al., 2018).

3.2.25 | *Litsea japonica* (Thunb.) Juss.

Litsea japonica (Thunb) is a species of Lauraceae family, native to Korea. Biological activities of *L. japonica* are not clearly found but antinephropathy has been investigated in previous studies (Sohn et al., 2013).

Kim et al. (2015b) during an investigation on diabetic mice showed that ethanolic extract of *L. japonica*, used as a remedy, reduces the advanced glycation end products (AGEs) and their receptor (RAGE) expression in the neural retinas. In addition, it reduces the *NF-kB* expression in the retina of treated animals. Therefore, *L. japonica* can modulate diabetic retinopathy by inhibition of apoptosis and inflammation in retinae of diabetic mice (Kim, Kim, et al., 2015b).

3.2.26 | Liuwei Dihuang

Liuwei Dihuang is a remedy consists of six herbs: *Rehmannia glutios* roots, *Cornus officinalis* fruits, *Paeonia suffruticosa* root bark, *Dioscorea opposita* rhizome, *Poria cocos* scleorotia, *and Alisma plantago-aquatica* rhizome (Zhou, 2004).

Liu et al. (2013) found that treatment of diabetic rats with Liuwei Dihuang causes improvement of spatial learning and memory during MVM test and reduction of blood glucose levels. In the hippocampus tissue, Liuwei Dihuang causes increase of GSH levels and overexpression of brain neurotrophic factors including BDNF and IGF-1. In addition, the herb remedy decreases AChE and iNOS levels, raises Na^+–K^+-ATP enzyme and ChAT levels. Liuwei Dihuang does its neuroprotective effect by reducing oxidative stress, raising brain neurotrophic factors and inhibition of apoptosis (Liu et al., 2013).

3.2.27 | *Mangifera indica* L.

Mangifera indica (mango) is a member of Anacardiaceae family with many therapeutic applications due to its wide range of biological activities: antioxidant, antiinflammatory, reducing blood glucose levels (Han et al., 2015).

Infante-Garcia et al. (2017) during a study on diabetic mice demonstrated that treatment with *M. indica* extract causes improvement of learning and memory during MVM test, reduction of the *caspase* and *tau* expression, reduction of microglia density and size in the hippocampus. Microglia density is a marker for inflammation. The reduction of its size and density shows the antiinflammatory effect of *M. indica*. The reduction of the *caspase* and *tau* expression shows the neuroprotective effect of the extract (Infante-Garcia et al., 2017).

3.2.28 | *Mesembryanthemum crystallinum* L.

Mesembryanthemum crystallinum (ice plant) belongs to Aizoaceae family and it is a medicinal plant with diverse therapeutic properties due to its wide range of activities: anticancer, antidiabetic, antiaging, antioxidant, antiinflammatory, enhancing memory. It has been suggested that these therapeutic effects of *M. crystallinum* are mainly due to its flavonoids and β-cyanins compounds (Lin et al., 2013).

Lee et al. (2014) shows that the use of *M. crystallinum* extract in C2C12 murine skeletal muscle cells (in vitro) leads to increase the sensitivity to insulin and increase glucose uptake in C2C12 cells. In addition, in vivo treatment of diabetic rats with *M. crystallinum* extract causes decrease of blood glucose and MDA levels in the hippocampus and cortex of treated animals, decreases the AChE activity and increases SOD activity in the hippocampus and cortex tissue of diabetic treated animals. Treatment with *M. crystallinum* extract leads to increase spatial memory during passive avoidance task and MVM tests. Thus, *M. crystallinum* by raising ACh and due to its high antioxidant activity causes improvement of diabetic neurodegenerative disorders (Lee et al., 2014).

3.2.29 | *Moringa oleifera* Lam.

Moringa oleifera (drumstick tree) belongs to Moringaceae family. It is an indigenous plant for South Asia. It is used for treatment of many

diseases such as diabetes, hyperlipidemia, inflammation, oxidative damages. The main compounds of *M. oleifera* are flavonoids, which are responsible for the pharmacological activities observed (Adefegha et al., 2017).

Oboh et al. (2018) showed that treatment of diabetic rats by *M. oleifera* supplementary diet causes increase of the GSH, CAT, GST levels, and decrease of AChE, BChE, and ACE levels in the brain. Therefore, *M. oleifera* does its neuroprotective effect by reducing oxidative stress and enhancing cholinergic system activity in diabetic rats (Oboh et al., 2018).

3.2.30 | *Morus alba* L.

Morus alba (Mulberry) belongs to Moraceae family and has many pharmacological activities which are due mainly to its phenolic content. Some of the biological activities of this herb include antioxidant, antidiabetic, anti-cancer, neuroprotective (Wang, Xiang, Wang, Tang, & He, 2013; Kim et al., 2015a).

Min et al. (2020) during a study on diabetic mice with diabetic dementia demonstrated that the treatment with ethyl acetate fraction of ethanolic extract of *M. alba* fruits reduces AChE activity in the brain tissue and MDA levels, and increases GSH levels in the kidneys, pancreas and brain tissues. In addition, the neuroprotective effect of this extract confirmed by inhibiting the expression of *p-Tau* and increasing *BDNF* and *p-CREB* expression in the brain tissue; in other words, this herb improves neurodegeneration due to diabetes by activation of p-CREB/BDNF pathway in CA1 and CA3 regions of the brain and reduce oxidative stress and blood glucose levels.

3.2.31 | *Myrtus communis* L.

Myrtus communis (myrtus) belongs to *Myrtaceae* family. This herb shows many pharmacological activities such as anti-diabetic, antioxidant, anti-cancer, neuroprotective (Aleksic & Knezevic, 2014; Tumen, Senol, & Orhan, 2012). Phytochemicals that are responsible for these therapeutic properties include hydrolysable tannins, phenolic acids, flavonoids, proanthocyanidins, acylphloroglucinols (Hosseinzadeh, Khoshdel, & Ghorbani, 2011).

Yaman et al. (2020) during an investigation on ovariectomized diabetic rats whit cognitive impairments demonstrated that the treatment with ethanolic extract of *M. communis* reduces AChE levels and increases ChAT activity, and neprilysin, α*7-nAChR*, *PSA-NCAM*, *BDNF* expressions in the hippocampus of treated rats. So this herb can be considered as a potent treatment of neurodegeneration due to diabetes.

3.2.32 | *Portulaca oleracea* L.

Portulaca oleracea (purslane) belongs to Portulacaceae family and it is one of the listed medicinal plants in World Health Organization. It contains flavonoids and other antioxidant compounds. Some of the pharmacological activities of *P. oleracea* are antioxidant, anticancer, hypoglycemic, anti-dementia, and neuroprotective (Dkhil, Moniem, Al-Quraishy, & Saleh, 2011).

Tabatabaei et al. (2016) demonstrated that treatment of hyperglycemic ovariectomized rats with aqueous extract of *P. oleracea* leads to improvement of learning and memory during MVM test, decreases anxiety during plus maze test (PMT), decreases depression measured by forced swimming test (FST) and decreases stress measured by tail pinch stressor test (TPS). It has been demonstrated that therapeutic effects of this plant on the CNS is due to its antioxidant compounds (Tabatabaei et al., 2016).

3.2.33 | *Pterocarpus marsupium* Roxb.

Pterocarpus marsupium (malabar kino or vijayasar) is a medicinal plant of Fabaceae family, widely used in Asia, especially in India for treatment of many diseases such as diabetes and its complications. Studies show that phenolic compounds of *P. marsupium* are responsible for the antidiabetic effect of this plant (Dhanabal, Kokate, Ramanathan, Kumar, & Suresh, 2006).

Vangalapati et al. (2016) during an investigation on diabetic rats found that treatment with aqueous extract of *P. marsupium* causes normalization of blood glucose levels and improvement of spatial learning and memory during MVM test that is probably due to its hypoglycemic activity (Vangalapati et al., 2016).

3.2.34 | *Punica granatum* L.

Punica granatum (pomegranate) belongs to Lythraceae family. It is used mainly in Unani and Ayurvedic medicines. All parts of this plant are used in the treatment of diabetes, atherosclerosis, neurodegenerative disease, for reduction of oxidative stress (Huang et al., 2005).

Cambay et al. (2011) demonstrated that treatment of diabetic rats with *P. granatum* flower mixture in food showed improvement of spatial learning and memory during MVM test, could modulate hyperglycemia and increase of body weight. In the hippocampus tissue of treated animals, increase of the GSH levels and decrease of the MDA and 4-hydroxyalkenals (4-HDA) levels were observed. GFAP is a marker in the hippocampus that becomes increase in neurodegenerative disease and shows glial hyperactivity. Treatment with *P. granatum* flower causes decrease of the GFAP content. Generally, *P. granatum* does its effect by reducing oxidative stress and reducing blood glucose, and follow that leads to improvement of diabetic neurodegeneration (Cambay et al., 2011).

3.2.35 | *Raphia hookeri* G.Mann & H.Wendl.

Raphia hookeri (raffia palm) belongs to Arecaceae family and is a medicinal plant widely used in Asia and Africa. It has many biological

activities: antidiabetic, antioxidant, lactogenic, aphrodisiac. The biologically active substances include hydroxycaffeic acid, luteic acid, caffeic acid, 7,4–dihydroxyflavone (Cunningham & Wehmeyer, 1988).

Erukainure et al. (2019) shows that treatment of diabetic rats with *R. hookeri* wine causes improvement of oxidative damage due to diabetes in the rats' hippocampus by increase in GSH, CAT, SOD levels and decrease in MDA levels in the brain. In addition, the treatment reduces the expression of *Nrf2* that is a marker for oxidative stress during diabetes and increases the myeloperoxidase activity in treated groups that indicate the antiinflammatory effect of *R. hookeri* wine. Consequently, based on the findings *R. hookeri* wine can be considered as a potent cure for neurodegenerative disorders due to diabetes (Erukainure, Ijomone, Sanni, et al., 2019).

3.2.36 | *Rubus fruticosus* L.

Rubus fruticosus (blackberry) is a member of Rosaceae family, native to Europe, Australia and Asia. It is used in traditional medicine for many purposes due to its wide range of pharmacological activities: antioxidant, antidiabetic, antiinflammatory, neuroprotective, anti-diarrhea, antibacterial, and anti-epilepsy (Zia-Ul-Haq, Riaz, De Feo, Jaafar, & Moga, 2014).

Gomar et al. (2014) during an investigation on diabetic rats demonstrated that treatment with *R. fruticosus* hydroethanolic extract causes improvement of learning and memory during passive avoidance learning (PAL) task and increases body weight and modulate hyperglycemia in animals. This extract can be considered as a cure for memory disorders due to diabetes (Gomar et al., 2014).

3.2.37 | *Rumex patientia* L.

Rumex patientia (patience dock) belongs to Polygonaceae family and it is used in traditional medicine due to its pharmacological activities: antioxidant, antiinflammatory, hypoglycemic, gastro-protective (Lone, Kaur, Athar, & Alam, 2007).

Baluchnejadmojarad and Roghani (2010) during a study on diabetic rats shows that treatment with *R. patientia* seeds causes improvement of passive avoidance test, decreases the blood glucose level and increases the body weight. So, it can be considered as a treatment for cognitive impairments due to hyperglycemia.

3.2.38 | *Salacia reticulata* Wight and *Clitoria ternatea* L.

Salacia reticulata (Kothala himbutu) is a member of Celastraceae family. It is utilized in traditional medicine in India and Sri Lanka for improvement of many disease such as diabetes, hyperlipidemia, inflammations (Yoshikawa et al., 2002). *Clitoria ternatea* (Asian pigeonwings) is a member of Fabaceae family and has many pharmacological activities well known in traditional medicine (Taranalli & Cheeramkuzhy, 2000).

Rajashree et al. (2017) shows that combined treatment of diabetic rats with *Salacia reticulata* and *Clitoria ternatea* alcoholic extracts causes improvement of anxiety during elevated plus maze test and also improvement of learning and memory during MVM test. This study shows combined therapy with *Salacia reticulata* and *Clitoria ternatea* on improvement of cognitive impairments of diabetic rats (Rajashree et al., 2017).

3.2.39 | *Salvia miltiorrhiza* Bunge

Salvia miltiorrhiza (red sage) belongs to Lamiaceae family and it is a medicinal plant used in Chinese traditional medicine due to its wide range of biological and therapeutic activities like hypoglycemic, anticancer, antioxidant, neuroprotective, antidiabetic neuropathy (Lee, Kim, Lee, & Lee, 2011).

Cai et al. (2014) during a study on hyperglycemic rats shows that injection of *S. miltiorrhiza* causes improvement of learning and memory tested by MVM; increases body weight and improves hyperglycemia. In the hippocampus, analysis shows increase of *MKP-1*. *MKP-1* overexpression, decreases of the MAPK pathway activity, which leads to improvement of learning and memory via increased neuronal cell viability. Therefore, *S. miltiorrhiza* by its effect on blood glucose levels and MAPK pathway causes improvement of cognitive impairments due to diabetes (Cai et al., 2014).

3.2.40 | *Salvia officinalis* L.

Salvia officinalis (common sage) is a species of Lamiaceae family, native to Iran. It is a medicinal plant utilized in folk medicine all over the world. It has many pharmacological activities including neuroprotective, antidiabetic, anti-Alzheimer, antioxidant (Eidi, Eidi, & Zamanizadeh, 2005).

Hasanein et al. (2016) during a study on hyperglycemic rats found that treatment with hydro-alcoholic leave extract of *S. officinalis* causes improvement of learning and memory, tested with passive avoidance learning and also decreased oxidative damage by decreasing MDA and raising of SOD and CAT levels. In addition, the extract increases body weight and decreases blood glucose levels. Thus, *S. officinalis* does its neuroprotective effect by reducing oxidative damages (Hasanein et al., 2016).

3.2.41 | *Solanum melongena* L.

Solanum melongena (eggplant) is a species of Solanaceae family and it is indigenous of Africa, Australia and New Zealand. Some of the active compounds of this medicinal plant are ascorbic acid, flavonoids and polyphenols with many biological and therapeutic activities. It is used

as a remedy for diabetes, cancer, inflammation, oxidative damages and ulcer (Nwanna, Ibukun, & Oboh, 2016).

Nwanna et al. (2019) demonstrated that this herb could improve neurological disorders in diabetic rats by regulating the enzymes linked to neurodegeneration in the brain such as AChE, BChE, MAO, and decreasing eNTPDase. Therefore, it can improve neurological disorders via enhancing cholinergic system (Nwanna et al., 2019).

3.2.42 | *Syzygium cumini* (L.) Skeels

Syzygium cumini (Jamun) belongs to Myrtaceae family and it is a medicinal plant used in Indian traditional medicine for treatment of diabetes, oxidative stress, inflammation (Sanches et al., 2016).

Ajiboye et al. (2018) during a study on diabetic rats demonstrated that polyphenolic rich extract of *S. cumini* leaves causes improvement of cholinesterase and leads to improvement of brain injury due to oxidative stress in diabetic animals. In details, *S. cumini* causes increase of the CAT, SOD, GPx, and GSH levels, decrease of the MDA, AChE, and BChE levels in the brain of treated rats. In sum, this herb by enhancing the cholinergic system and oxidative stress in the brain tissue do its neuroprotective effects.

3.2.43 | *Teucrium polium* L.

Teucrium polium (felty germander) belongs to Lamiaceae family and it has been utilized in folk medicine during 2000 years ago. Some of the importance biological activities of this medicinal plant are antioxidant, antidiabetic, neuroprotective, anti-dementia, and anti-Alzheimer (Hasani-Ranjbar, Nayebi, Larijani, & Abdollahi, 2010).

Hasanein and Shahidi (2012) showed that diabetic rats treated with aqueous extract of *T. polium* reduces the blood glucose levels and enhances learning and memory during the passive avoidance-learning test. Therefore, this plant enhances learning and memory in hyperglycemic animals but further studies are needed (Hasanein & Shahidi, 2012).

3.2.44 | *Trigonella foenum-graecum* L.

Trigonella foenum-graecum (Fenugreek) belongs to Fabaceae family and used in traditional medicine all over the world. Some of the pharmacological properties of the herb predetermine the use and treatment of disease associated with oxidative damages including diabetes, cancer, inflammation, and others (Goyal, Gupta, & Chatterjee, 2016).

Kodumuri et al. (2019) during a study on diabetic rats demonstrated that treatment with *T. foenum-graecum* extract causes improvement of learning and memory in Y-maze and MWM tests. Also, it modulates the density of neurons in the CA1 and CA3 areas of hippocampus and reduces oxidative damage in the brain measured by increase of CAT, SOD, GPx, GSH, and decrease of MDA levels. *T. foenum-graecum* extract can be considered as a neuroprotective agent in diabetic neurodegenerative defects by modulating hyperglycemia and following that oxidative damage in hippocampus of hyperglycemic animals (Kodumuri et al., 2019).

3.2.45 | *Urtica dioica* L.

Urtica dioica (Stinging nettle) is a perennial plant that belongs to Urticaceae family. It is utilized in folk medicine due to its wide range of biological activities such as antidiabetic, antioxidant, anti-hypercholesterolemia (Bnouham et al., 2003). Carvacrol is one of its active compounds responsible for its therapeutic properties especially for the neuroprotective activity (Yu et al., 2012).

Patel and Udayabanu (2013) showed that treatment of diabetic mice with hydroalcoholic extract of *U. dioica* causes improvement of spatial learning and memory during MVM test. In addition, improvement of STL during passive avoidance step through task, improving the hyperglycemia and increasing of the body weight were observed.

Patel and Udayabanu (2014) showed that treatment of diabetic mice with *U. dioica* causes decreasing the depression in forced swimming and tail suspension test, also improvement of learning and memory during passive avoidance step-through task and MVM test. In addition, it modulates hyperglycemia and reduces corticosterone levels in the plasma, affects the body weight and plasma insulin. In the level of gene expression, it causes reducing of *GLUT4* expression in the hippocampus of treated mice. *GLUT4* is responsible for glucose intake in the brain cells. *U. dioica* reduces oxidative stress measured by reducing TBARS and raising CAT levels.

Fazeli et al. (2008) during a study on diabetic rats demonstrated that *U. dioica* increases the brain/body weight ratio and in the dentate gyrus, raises the number of granule cells, improving the cognitive impairments due to hyperglycemia in animal model (Fazeli et al., 2008).

Patel et al. (2015) showed that diabetic mice treated with hydromethanolic extract of *U. dioica* have reduction of AchR mRNA expression and oxidative damage in the hippocampus by reducing the TBARS and NO levels and raising the CAT and thiol levels. Therefore, the authors confirmed that *U. dioica* improved oxidative damages due to diabetes (Patel et al., 2015).

Patel, Gupta, and Udayabanu (2016) demonstrated that treatment with *U. dioica* hydromethanolic extract causes improvement of memory during novel object recognition task and reducing of the NO and TBARS levels. In addition, the extract increases locomotor activity during peroxisome proliferator activated receptor gamma (PPARγ) and insulin receptor substrate 2 (*IRS2*), *PI3K*, *PKB*, and *GLUT4* expression in the hippocampus tissue. These genes are responsible for glucose homeostasis and apoptosis pathway (Patel et al., 2016).

Keshvari et al. (2020) showed that diabetic rats treated with *U. dioica* hydromethanolic extract reduces escape latency time and improves learning and memory during MVM test. In addition, it raised the expression of GAP43 protein and reduced the expression of CAP1 protein in the hippocampus tissue. GAP-43 protein in hippocampus is responsible for generation of new synapses and neuronal

growth and CAP1 protein is responsible for brain growth, learning, and memory (Rahmati & Kazemi, 2019).

3.2.46 | *Vaccinium myrtillus* L.

Vaccinium myrtillus (bilberry) is a member of Ericaceae family widely used in traditional medicine. Some of the therapeutic applications of this plant are due to its wide range of biological activities such as antioxidant, antiinflammatory, hypoglycemic, anticancer, anti-neurodegeneration, enhancing memory (Subash et al., 2014).

Matysek et al. (2017) during an investigation on diabetic rats demonstrated that treatment with *V. myrtillus* fruits causes increase in αCaMKII-positive nerve fibers length in the hippocampus tissue compared to control group. Calcium/calmodulin-dependent protein kinase II (CaMKII) is a kinase that found in hippocampus and it is a key factor in learning, memory and behavior. The results of the present study suggested that the neuroprotection effect of *V. myrtillus* is due to its high antioxidant potential (Matysek et al., 2017).

3.2.47 | *Withania somnifera* (L.) Dunal and *Aloe vera* (L.) Burm.f.

Withania somnifera (ashwagandha) belongs to Solanaceae family. It is a medicinal plant used in folk medicine due to its antioxidant property. *Aloe vera* is a member of Xanthorrhoeaceae family, native to Arabian Peninsula. It is used for treatment oxidative damage, wounds, diabetes. Mixture of *Withania somnifera* and *Aloe vera* can improve diabetic oxidative damages, neurodegeneration and memory defects (Parihar et al., 2004).

Parihar et al. (2004) found that treatment of diabetic mice with aqueous extracts of *W. somnifera* and *A. vera*, causes improvement of neurodegeneration by reducing oxidative damage. The authors showed that neuroprotective effect and antioxidant potential of *W. somnifera* was stronger than this of *A. vera* and the combination extract of the two herbs showed strongest therapeutic properties than these of any of the herbs individually. Treatment with these medicinal plants causes reduction of the MDA and protein carbonyl content of hippocampus and improvement of motor performance during T-maze test and memory by active avoidance performance test (Parihar et al., 2004).

3.2.48 | ZiBu PiYin

ZiBu PiYin is a herbal mixture of 12 medicinal plants: *Panax ginseng*, *Dioscorea polystachya*, *Wolfiporia extensa*, *Paeonia lactiflora*, *Salvia miltiorrhiza*, *Lablab purpureus*, *Nelumbo nucifera*, *Acorus gramineus*, *Polygala tenuifolia*, *Santalum album*, *Citrus maxima*, *Glycyrrhiza uralensis*, used in Chinese folk medicine for many healing purposes due to its antidiabetic and neuroprotective activities (Shi et al., 2011).

Sun et al. (2016) during a study on diabetic rats demonstrated that treatment with ZiBu PiYin causes improvement of cognitive decline confirmed with hidden platform test, increases the *MAP2*, *ACT* and *P-GSK3β* expression and decreases the ROS levels and *IRS2* expression.

Chen et al. (2014) shows that treatment of diabetic mice with ZiBu PiYin causes improvement of learning and memory during MVM test, also it causes reduce in expression of *GSK* and raises of the expression of *MAP2* and *PSD95*. All of these factors are involved in insulin pathway and lead to glucose homeostasis, so they can lead to inhibition of hyperglycemia and its complications on CNS.

4 | DISCUSSION

The use of herbal remedies with natural sources for treatment of diseases associated with oxidative stress is more necessary than any other disease. DM is a major cause of abnormal hyperglycemia and its secondary complications are due to increased oxidative damage (Kodumuri et al., 2019), changes in the expression of some genes (Hao et al., 2017), reduced glucose uptake (Patel et al., 2016) and increased of neuro-inflammation and apoptosis (Kim et al., 2015).

Synthetic drugs only control blood sugar levels and have no effect on diabetic complications of various organs such as cognitive impairment or neurodegenerative disease of brain tissue due to oxidative damage caused by hyperglycemia. Medicinal plants in addition to the reduction and control of blood glucose levels can improve diabetic complications on other organs due to their antioxidant compounds (Radhika et al., 2012) that may affect the other pathways as mentioned in the results.

In summary, the medicinal plants used for treatment of diabetic complications exert their effects in several ways (Figure 3):

- The predominant part of the studied species does their effects by reducing oxidative stress factors such as MDA and *Nrf2* gene expression and by raising antioxidant indicators such as GSH, GPx, CAT, SOD in the brain, especially in the hippocampus area. Therefore, medicinal plants and their extracts could prevent oxidative damage to the brain and can improve learning and memory in hyperglycemic conditions. Medicinal plants of this group are *C. papaya*, *T. foenum-graecum*, *S. officinalis*, *S. cumini*, *C. nitida* (Ajiboye et al., 2018; Bandaru & Kulandaivelu, 2018; Erukainure, Ijomone, Oyebode, et al., 2019; Hasanein et al., 2016; Kodumuri et al., 2019).
- Another group of plants does their effect by reducing apoptosis indicators and raising neurogenesis in the brain or nervous tissue. The reduction of the expression of Aβ, Tau, NF-kB, RGC, caspase3, and the raising of the expression of MAP2, BCl2 and BCl XL cause improvement of memory and brain activity via reducing or inhibiting neuronal toxicity and neuronal death. Some of these

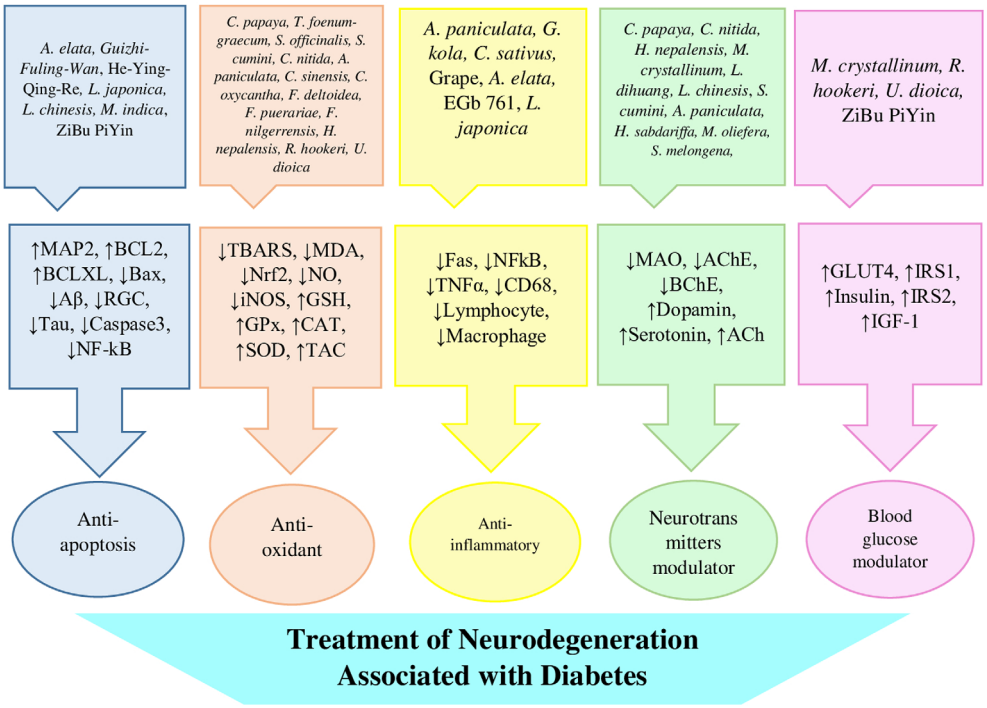

FIGURE 3 Overview of herbal treatment pathways for neurodegeneration associated with diabetes [Colour figure can be viewed at wileyonlinelibrary.com]

plants and herb remedies are *A. elata*, Guizhi-Fuling-Wan, He-Ying-Qing-Re, *L. japonica*, *L. chinesis*, *M. indica* and ZiBu PiYin (Chen et al., 2014; Infante-Garcia et al., 2017; Kim et al., 2015; Sun et al., 2016; Tang et al., 2018; Wu et al., 2012; Zhang et al., 2018b).

- Another group of herbs improves learning and memory by affecting neurotransmitters like dopamine, ACh, AChE, and serotonin. Some of these medicinal plants are *C. papaya*, *C. nitida*, *H. nepalensis*, *M. crystallinum*, *L. dihuang*, *L. chinesis*, and *S. cumini* (Ajiboye et al., 2018; Bandaru & Kulandaivelu, 2018; Erukainure, Ijomone, Oyebode, et al., 2019; Hashmi et al., 2018; Lee et al., 2014; Liu et al., 2013; Tang et al., 2018).
- Inflammation is another complication associated with neurodegenerative damages that can lead to nerve damage and neurodegenerative disorders if not controlled. Medicinal plants and their extracts act by reducing inflammatory factors such as Fas, NFkBP65, TNFα, CD68, lymphocyte and macrophage and by this way could modulate diabetic nervous damages. Some of these herbs are *A. paniculata*, *G. kola*, *C. sativus*, and Grape seed (Etet et al., 2017; Farahna et al., 2017; Radhika et al., 2012; Samarghandian et al., 2014; Xu et al., 2008).
- Another group of plants does their effect by reducing blood glucose and raising glucose uptake by cells. These plants and their extracts increase cellular uptake of glucose by overexpression of proteins such as GLUT4 (brain tissue) and IRS1, and that way they can control DM and its complications on the brain tissue. Some of these plants and herbal remedies are *M. crystallinum*, *R. hookeri*, *U. dioica*, ZiBu PiYin (Erukainure, Ijomone, Sanni, et al., 2019; Lee et al., 2014; Patel et al., 2016; Patel & Udayabanu, 2014; Sun et al., 2016).

The present study demonstrated that 41 medicinal plants species and seven herbal mixtures have scientific evidence in the management of DM associated neurodegenerative diseases. Among these medicinal plants *U. dioica* had the highest scientific evidence (6 scientific papers) demonstrating that it is the most promising natural agent for management of neurodegenerative complications of DM. The most responsible active ingredients of this herb include scopoletin, quercetin, and carvacrol that affect brain tissue, enhance neurogeneration and increase the expression of GLUT4 that leads to increase glucose uptake via brain cells and decrease blood glucose levels and thereby improving DM and its complications on memory and brain tissue. After *U. dioica*, the following herbs include *G. kola* (2 scientific papers), *C. nitida* (2 scientific papers), *H. perforatum* (2 scientific papers), ZiBu PiYin (2 scientific papers) were the most effective with the highest scientific evidence.

Based on the present study, the most responsible active compounds which involve in therapeutic effect of medicinal plants against DM induced neurodegenerative complications include quercetin among flavonoids (12 scientific papers), Gallic acid among phenolic acids (6 scientific papers), caffeine among alkaloids (4 scientific papers) and caffeic acid among hydroxycinnamic acids (3 scientific papers) that had the highest scientific evidence. Therefore, it is suggested that further studies should to be done on these herbs and the active compounds because of their high scientific evidence.

5 | CONCLUSION

Many medicinal plants can be more effective in treating or controlling DM associated neurodegenerative diseases compared to chemical

treatments. Herbal remedies can lower blood glucose levels and improve cognitive defects induced by hyperglycemia through different pathways (discussed above). Moreover, they can increase the activity of antioxidant agents and influence the expression of genes and proteins that are responsible in improving learning and memory via controlling inflammatory and apoptosis pathways, secretion and degradation of neurotransmitters and thus preventing and/or improving neurological disorders induced by DM. As mentioned, all of these pathways are interconnected, but we categorized them for easier access to results for future investigations. Finally, we conclude that medicinal plants and their derivations (especially *U. dioica* and quercetin as the most promising herb and active ingredient, respectively) can be introduced into the industry as an adjunct therapy for hyperglycemia and its complications (especially cognitive declines) and can be used to increase the quality of life in diabetic patients.

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CONFLICT OF INTEREST

No conflicts of interest exist.

STUDY LIMITATIONS

The authors state the lack of registration of the protocol as a limitation in the present study.

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REFERENCES

Adebiyi, S., Oluyole, K., & Fagbami, O. (2009). An assessment of gender involvement in crop production: A case of Kola production in Osun state, Nigeria. *International Journal of Sustainable Crop Production*, *4*, 8–11.

Adedara, I. A., Awogbindin, I. O., Anamelechi, J. P., & Farombi, E. O. (2015). *Garcinia kola* seed ameliorates renal, hepatic, and testicular oxidative damage in streptozotocin-induced diabetic rats. *Pharmaceutical Biology*, *53*, 695–704.

Adefegha, S. A., Oboh, G., Oyeleye, S. I., Dada, F. A., Ejakpovi, I., & Boligon, A. A. (2017). Cognitive enhancing and antioxidative potentials of velvet beans (*Mucuna pruriens*) and horseradish (*Moringa oleifera*) seeds extracts: A comparative study. *Journal of Food Biochemistry*, *41*, e12292.

Agoreyo, F., Agoreyo, B., & Onuorah, M. (2008). Effect of aqueous extracts of *Hibiscus sabdariffa* and *Zingiber officinale* on blood cholesterol and glucose levels of rats. *African Journal of Biotechnology*, *7*, 3949-3951

Ahmed, A., Zeng, G., Azhar, M., Lin, H., Zhang, M., Wang, F., … Wang, Q. (2020). Jiawei Shengmai san herbal formula ameliorates diabetic associate cognitive decline by modulating AKT and CREB in rats. *Phytotherapy Research*, 1–13. https://doi.org/10.1002/ptr.6773

Ajiboye, B. O., Ojo, O. A., Akuboh, O. S., Okesola, M. A., Idowu, O. T., Oyinloye, B. E., & Talabi J. (2018). The protective effect of polyphenol-rich extract of *Syzygium cumini* leaves on cholinesterase and brain antioxidant status in alloxan-induced diabetic rats. *Jordan Journal of Biological Sciences*, *11*, 163–169.

Alam, M., Siddiqui, M., & Husain, W. (1990). Treatment of diabetes through herbal drugs in rural India. *Fitoterapia*, *61*, 240–242.

Aleksic, V., & Knezevic, P. (2014). Antimicrobial and antioxidative activity of extracts and essential oils of *Myrtus communis* L. *Microbiological Research*, *169*, 240–254.

Baluchnejadmojarad, T., & Roghani, M. (2010). Chronic *Rumex patientia* seed feeding improves passive avoidance learning and memory in streptozotocin-diabetic rats. *Basic and Clinical Neuroscience*, *1*, 53–56.

Bandaru, S., & Kulandaivelu, U. (2018). Neuroprotective and nootropic activity of *Carica papaya* seeds on diabetes induced cognitive decline in rats. *Iranian Journal of Pharmaceutical Sciences*, *14*, 107–116.

Barnes, J., Anderson, L. A., & Phillipson, J. D. (2001). St John's wort (*Hypericum perforatum* L.): A review of its chemistry, pharmacology and clinical properties. *Journal of Pharmacy and Pharmacology*, *53*, 583–600.

Baydas, G., Nedzvetskii, V. S., Tuzcu, M., Yasar, A., & Kirichenko, S. V. (2003). Increase of glial fibrillary acidic protein and S-100B in hippocampus and cortex of diabetic rats: Effects of vitamin E. *European Journal of Pharmacology*, *462*, 67–71.

Beauchet, O. (2006). Testosterone and cognitive function: Current clinical evidence of a relationship. *European Journal of Endocrinology*, *155*, 773–781.

Bnouham, M., Merhfour, F. Z., Ziyyat, A., Mekhfi, H., Aziz, M., & Legssyer, A. (2003). Antihyperglycemic activity of the aqueous extract of *Urtica dioica*. *Fitoterapia*, *74*, 677–681.

Borek, C. (2006). Garlic reduces dementia and heart-disease risk. *The Journal of Nutrition*, *136*, 810S–812S.

Cai, H., Lian, L., Wang, Y., Yu, Y., & Liu, W. (2014). Protective effects of *Salvia miltiorrhiza* injection against learning and memory impairments in streptozotocin-induced diabetic rats. *Experimental and Therapeutic Medicine*, *8*, 1127–1130.

Cambay, Z., Baydas, G., Tuzcu, M., & Bal, R. (2011). Pomegranate (*Punica granatum* L.) flower improves learning and memory performances impaired by diabetes mellitus in rats. *Acta Physiologica Hungarica*, *98*, 409–420.

Can, Ö. D., Öztürk, Y., & Özkay, Ü. D. (2011). Effects of insulin and St. John's wort treatments on anxiety, locomotory activity, depression, and active learning parameters of streptozotocin-diabetic rats. *Planta Medica*, *77*, 1970–1976.

Chen, J., Liang, L., Zhan, L., Zhou, Y., Zheng, L., Sun, X., et al. (2014). ZiBuPiYin recipe protects db/db mice from diabetes-associated cognitive decline through improving multiple pathologica changes. *PLoS One*, *9*, e91680.

Cunningham, A., & Wehmeyer, A. (1988). Nutritional value of palm wine from *Hyphaene coriacea* and *Phoenix reclinata* (Arecaceae). *Economic Botany*, *42*(3), 301–306.

de Lores Arnaiz, G. R., & Ordieres, M. G. (2014). Brain Na(+), K(+)-ATPase activity in aging and disease. *International Journal of Biomedical Sciences*, *10*, 85–102.

Defeudis, F. V. (2002). Bilobalide and neuroprotection. *Pharmacological Research*, *46*, 565–568.

Dhanabal, S., Kokate, C., Ramanathan, M., Kumar, E., & Suresh, B. (2006). Hypoglycaemic activity of *Pterocarpus marsupium* Roxb. *Phytotherapy Research*, *20*, 4–8.

Dkhil, M. A., Moniem, A. E. A., Al-Quraishy, S., & Saleh, R. A. (2011). Antioxidant effect of purslane (*Portulaca oleracea*) and its mechanism of action. *Journal of Medicinal Plants Research*, *5*, 1589–1593.

Eidi, M., Eidi, A., & Zamanizadeh, H. (2005). Effect of *Salvia officinalis* L. leaves on serum glucose and insulin in healthy and streptozotocin-induced diabetic rats. *Journal of Ethnopharmacology*, *100*, 310–313.

Erukainure, O. L., Ijomone, O. M., Oyebode, O. A., Chukwuma, C. I., Aschner, M., & Islam, M. S. (2019). Hyperglycemia-induced oxidative brain injury: Therapeutic effects of *Cola nitida* infusion against redox

imbalance, cerebellar neuronal insults, and upregulated Nrf2 expression in type 2 diabetic rats. *Food and Chemical Toxicology*, *127*, 206–217.

Erukainure, O. L., Ijomone, O. M., Sanni, O., Aschner, M., & Islam, M. S. (2019). Type 2 diabetes induced oxidative brain injury involves altered cerebellar neuronal integrity and elemental distribution, and exacerbated Nrf2 expression: Therapeutic potential of raffia palm (*Raphia hookeri*) wine. *Metabolic Brain Disease*, *34*, 1–15.

Etet, P. F. S., Farahna, M., Satti, G. M., Bushara, Y. M., El-Tahir, A., Hamza, M. A., … Vecchio, L. (2017). *Garcinia kola* seeds may prevent cognitive and motor dysfunctions in a type 1 diabetes mellitus rat model partly by mitigating neuroinflammation. *Journal of Complementary and Integrative Medicine*, *14*.

Etxeberria, U., de la Garza, A. L., Campión, J., Martinez, J. A., & Milagro, F. I. (2012). Antidiabetic effects of natural plant extracts via inhibition of carbohydrate hydrolysis enzymes with emphasis on pancreatic alpha amylase. *Expert Opinion on Therapeutic Targets*, *16*, 269–297.

Farahna, M., Etet, P. F. S., Osman, S. Y., Yurt, K. K., Amir, N., Vecchio, L., … Adem, A. (2017). *Garcinia kola* aqueous suspension prevents cerebellar neurodegeneration in long-term diabetic rat—A type 1 diabetes mellitus model. *Journal of Ethnopharmacology*, *195*, 159–165.

Farshchi, A., Ghiasi, G., Farshchi, S., & Taleb Ghobadi, A. (2011). The effect of chronic administration of *Aegle marmelos* seed extract on learning and memory in diabetic rats. *Iranian Journal of Basic Medical Sciences*, *14*, 42–48.

Farsi, E., Ahmad, M., Hor, S. Y., Ahamed, M. B. K., Yam, M. F., & Asmawi, M. Z. (2014). Standardized extract of *Ficus deltoidea* stimulates insulin secretion and blocks hepatic glucose production by regulating the expression of glucose-metabolic genes in streptozitocin-induced diabetic rats. *BMC Complementary and Alternative Medicine*, *14*, 220.

Fazeli, S., Gharravi, A., Ghafari, S., Jahanshahi, M., & Golalipour, M. (2008). The granule cell density of the dentate gyrus following administration of *Urtica dioica* extract to young diabetic rats. *Folia Morphologica*, *67*, 196–204.

Gao, L., Wang, X., Lin, Z., Song, N., Liu, X., Chi, X., & Shao, T. (2018). Antidiabetic and neuroprotective effect of the N-butanol extract of *Fragaria nilgerrensis* Schlecht. In STZ-induced diabetic mice. *Evidence-Based Complementary and Alternative Medicine*.

Gejl, M., Brock, B., Egefjord, L., Vang, K., Rungby, J., & Gjedde, A. (2017). Blood-brain glucose transfer in Alzheimer's disease: Effect of GLP-1 analog treatment. *Scientific Reports*, *7*, 17490.

Gomar, A., Hosseini, A., & Mirazi, N. (2014). Preventive effect of *Rubus fruticosus* on learning and memory impairment in an experimental model of diabetic neuropathy in male rats. *Pharma Nutrition*, *2*, 155–160.

Goyal, S., Gupta, N., & Chatterjee, S. (2016). Investigating therapeutic potential of *Trigonella foenum-graecum* L. as our defense mechanism against several human diseases. *Journal of Toxicology*, *2016*, 1250387.

Guan, Z. F., Zhang, X. M., Tao, Y. H., Zhang, Y., Huang, Y. Y., Chen, G., … Zhou, H. G. (2018). EGb761 improves the cognitive function of elderly db/db−/− diabetic mice by regulating the beclin-1 and NF-κB signaling pathways. *Metabolic Brain Disease*, *33*, 1887–1897.

Guo, S., Yan, J., Yang, T., Yang, X., Bezard, E., & Zhao, B. (2007). Protective effects of green tea polyphenols in the 6-OHDA rat model of Parkinson's disease through inhibition of ROS-NO pathway. *Biological Psychiatry*, *62*, 1353–1362.

Han, J., Yi, J., Liang, F., Jiang, B., Xiao, Y., Gao, S., … Chen, W. (2015). X-3, a mangiferin derivative, stimulates AMP-activated protein kinase and reduces hyperglycemia and obesity in db/db mice. *Molecular and Cellular Endocrinology*, *405*, 63–73.

Hao, G. M., Liu, Y. G., Wu, Y., Xing, W., Guo, S. Z., Wang, Y., … Han, J. (2017). The protective effect of the active components of ERPC on diabetic peripheral neuropathy in rats. *Journal of Ethnopharmacology*, *202*, 162–171.

Hasanein, P., Felehgari, Z., & Emamjomeh, A. (2016). Preventive effects of *Salvia officinalis* L. against learning and memory deficit induced by diabetes in rats: Possible hypoglycaemic and antioxidant mechanisms. *Neuroscience Letters*, *622*, 72–77.

Hasanein, P., & Shahidi, S. (2011). Effects of *Hypericum perforatum* extract on diabetes-induced learning and memory impairment in rats. *Phytotherapy Research*, *25*, 544–549.

Hasanein, P., & Shahidi, S. (2012). Preventive effect of *Teucrium polium* on learning and memory deficits in diabetic rats. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *18*, BR41.

Hasani-Ranjbar, S., Nayebi, N., Larijani, B., & Abdollahi, M. (2010). A systematic review of the efficacy and safety of Teucrium species, from antioxidant to anti-diabetic effects. *International Journal of Pharmacology*, *6*, 315–325.

Hashmi, W. J., Ismail, H., Mehmood, F., & Mirza, B. (2018). Neuroprotective, antidiabetic and antioxidant effect of Hedera nepalensis and lupeol against STZ+ AlCl 3 induced rats model. *DARU Journal of Pharmaceutical Sciences*, *26*, 179–190.

Haslbeck, K. M., Schleicher, E., Bierhaus, A., Nawroth, P., Haslbeck, M., Neundörfer, B., & Heuss, D. (2015). The AGE/RAGE/NF-κB pathway may contribute to the pathogenesis of polyneuropathy in impaired glucose tolerance (IGT). *Experimental and Clinical Endocrinology & Diabetes*, *113*(5), 288–291.

Hosseinzadeh, H., Khoshdel, M., & Ghorbani, M. (2011). Antinociceptive, anti-inflammatory effects and acute toxicity of aqueous and ethanolic extracts of *Myrtus communis* L. aerial parts in mice. *Journal of Acupuncture and Meridian Studies*, *4*, 242–247.

Huang, T. H. W., Peng, G., Kota, B. P., Li, G. Q., Yamahara, J., Roufogalis, B. D., & Li, Y. (2005). Pomegranate flower improves cardiac lipid metabolism in a diabetic rat model: Role of lowering circulating lipids. *British Journal of Pharmacology*, *145*, 767–774.

Imam-Fulani, A. O., Sanusi, K. O., & Owoyele, B. V. (2018). Effects of acetone extract of *Cola nitida* on brain sodium-potassium adenosine triphosphatase activity and spatial memory in healthy and streptozotocin-induced diabetic female Wistar rats. *Journal of Basic and Clinical Physiology and Pharmacology*, *29*, 411–416.

Infante-Garcia, C., Jose Ramos-Rodriguez, J., Marin-Zambrana, Y., Teresa Fernandez-Ponce, M., Casas, L., Mantell, C., & Garcia-Alloza, M. (2017). Mango leaf extract improves central pathology and cognitive impairment in a type 2 diabetes mouse model. *Brain Pathology*, *27*, 499–507.

Jafri, L., Saleem, S., Ullah, N., & Mirza, B. (2017). In vitro assessment of antioxidant potential and determination of polyphenolic compounds of *Hedera nepalensis* K. Koch. *Arabian Journal of Chemistry*, *10*, S3699–S3706.

Ji, X., Gao, J., Cai, X., Lu, W., Hu, C., Wang, Z., & Zhang, S. (2011). Immunological regulation of Chinese herb Guizhi Fuling capsule on rat endometriosis model. *Journal of Ethnopharmacology*, *134*, 624–629.

Kahn, S. E., D'Alessio, D. A., Schwartz, M. W., Fujimoto, W. Y., Ensinck, J. W., Taborsky GJ, & Porte, D. Jr. (1990). Evidence of cosecretion of islet amyloid polypeptide and insulin by β-cells. *Diabetes*, *39*, 634–638.

Kamiya, T., Takano, A., Matsuzuka, Y., Kusaba, N., Ikeguchi, M., Takagaki, K., & Kondo, K. (2012). Consumption of Pueraria flower extract reduces body mass index via a decrease in the visceral fat area in obese humans. *Bioscience Biotechnology and Biochemistry*, *76*, 1511–1517.

Kanakis, C. D., Tarantilis, P. A., Tajmir-Riahi, H. A., & Polissiou, M. G. (2007). Crocetin, dimethylcrocetin, and safranal bind human serum albumin: Stability and antioxidative properties. *Journal of Agricultural and Food Chemistry*, *55*, 970–977.

Keshvari, M., Rahmati, M., Mirnasouri, R., & Chehelcheraghi, F. (2020). Effects of endurance exercise and *Urtica dioica* on the functional, histological and molecular aspects of the hippocampus in STZ-induced diabetic rats. *Journal of Ethnopharmacology*, *256*, 112801.

Kim, H. G., Park, G., Lim, S., Park, H., Choi, J. G., Jeong, H. U., … Oh, M. S. (2015a). Mori Fructus improves cognitive and neuronal dysfunction induced by beta-amyloid toxicity through the GSK-3β pathway in vitro and in vivo. *Journal of Ethnopharmacology*, *171*, 196–204.

Kim, J., Kim, C. S., Lee, Y. M., Sohn, E., Jo, K., & Kim, J. S. (2015b). Litsea japonica extract inhibits neuronal apoptosis and the accumulation of advanced glycation end products in the diabetic mouse retina. *Molecular Medicine Reports*, *12*, 1075–1081.

Kim, S. J., Yoo, W. S., Kim, H., Kwon, J. E., Hong, E. K., Choi, M., … Choi, W. S. (2015c). *Aralia elata* prevents neuronal death by down-regulating tonicity response element binding protein in diabetic retinopathy. *Ophthalmic Research*, *54*, 85–95.

Kodumuri, P. K., Thomas, C., Jetti, R., & Pandey, A. K. (2019). Fenugreek seed extract ameliorates cognitive deficits in streptozotocin-induced diabetic rats. *Journal of Basic and Clinical Physiology and Pharmacology*, *30*(4).

Lee, B. H., Lee, C. C., & Wu, S. C. (2014). Ice plant (*Mesembryanthemum crystallinum*) improves hyperglycaemia and memory impairments in a Wistar rat model of streptozotocin-induced diabetes. *Journal of the Science of Food and Agriculture*, *94*, 2266–2273.

Lee, S. H., Kim, Y. S., Lee, S. J., & Lee, B. C. (2011). The protective effect of salvia miltiorrhiza in an animal model of early experimentally induced diabetic nephropathy. *Journal of Ethnopharmacology*, *137*, 1409–1414.

Lin, T. H., Tan, T. W., Tsai, T. H., Chen, C. C., Hsieh, T. F., Lee, S. S., … Tang, C. H. (2013). D-pinitol inhibits prostate cancer metastasis through inhibition of αVβ3 integrin by modulating FAK, c-Src and NF-κB pathways. *International Journal of Molecular Sciences*, *14*, 9790–9802.

Liu, J. P., Feng, L., Zhang, M. H., Ma, D. Y., Wang, S. Y., Gu, J., … Ma, S. P. (2013). Neuroprotective effect of Liuwei Dihuang decoction on cognition deficits of diabetic encephalopathy in streptozotocin-induced diabetic rat. *Journal of Ethnopharmacology*, *150*, 371–381.

Liu, Z. H., Chen, H.G., Wu, P. F., Yao, Q., Cheng, H. K., Yu, W., & Liu, C. (2015). Flos puerariae extract ameliorates cognitive impairment in streptozotocin-induced diabetic mice. *Evidence-Based Complementary and Alternative Medicine*. *2015*, 873243.

Lone, I. A., Kaur, G., Athar, M., & Alam, M. S. (2007). Protective effect of *Rumex patientia* (English Spinach) roots on ferric nitrilotriacetate (Fe-NTA) induced hepatic oxidative stress and tumor promotion response. *Food and Chemical Toxicology*, *45*, 1821–1829.

Matsui, T., Tanaka, T., Tamura, S., Toshima, A., Tamaya, K., Miyata, Y., … Matsumoto, K. (2007). α-Glucosidase inhibitory profile of catechins and theaflavins. *Journal of Agricultural and Food Chemistry*, *55*, 99–105.

Matysek, M., Mozel, S., Szalak, R., Zacharko-Siembida, A., Obszańska, K., & Arciszewski, M. (2017). Effect of feeding with bilberry fruit on the expression pattern of αCaMKII in hippocampal neurons in normal and diabetic rats. *Polish Journal of Veterinary Sciences*, *20*, 313–319.

Mettupalayam Kaliyannan Sundaramoorthy, P., & Kilavan Packiam, K. (2020). In vitro enzyme inhibitory and cytotoxic studies with *Evolvulus alsinoides* (Linn.) Linn. Leaf extract: A plant from Ayurveda recognized as Dasapushpam for the management of Alzheimer's disease and diabetes mellitus. *BMC Complementary Medicine and Therapies*, *20*, 1–12.

Min, A. Y., Yoo, J. M., Sok, D. E., & Kim, M. R. (2020). Mulberry fruit prevents diabetes and diabetic dementia by regulation of blood glucose through upregulation of antioxidative activities and CREB/BDNF pathway in alloxan-induced diabetic mice. *Oxidative Medicine and Cellular Longevity*, *2020*, 1298691.

Mishra, S. K., Sangwan, N. S., & Sangwan, R. S. (2007). Phcog rev.: Plant review *Andrographis paniculata* (Kalmegh): A review. *Pharmacognosy Reviews*, *1*, 283–298.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg*, *8*(5), 336–341.

Nahata, A., Patil, U. K., & Dixit, V. K. (2010). Effect of *Evolvulus alsinoides* Linn. on learning behavior and memory enhancement activity in rodents. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *24*, 486–493.

Ni, Q., Wang, J., Li, E.Q., Zhao, A.B., Yu, B., Wang, M., & Huang, C.R. (2011). Study on the protective effect of the Mixture of Shengmai Powder and Danshen Decoction on the myocardium of diabetic cardiomyopathy in the rat model. *Chin J Integr Med.*, *17*(2), 116–125.

Nurdiana, S., Goh, Y., Hafandi, A., Dom, S.M., Nur Syimal'ain, A., Syaffinaz, N. M., & Ebrahimi, M. (2017). Improvement of spatial learning and memory, cortical gyrification patterns and brain oxidative stress markers in diabetic rats treated with Ficus deltoidea leaf extract and vitexin. *Journal of Traditional and Complementary Medicine*, *8*(1), 190–202.

Nurdiana, S., Mohamad Shukri, K., Elizabeth Jega, J., & Nurul Izzati, S. (2013). Antidiabetic activity of Azadirachta excelsa extract on alloxan induced diabetic rats. *The Open Conference Proceedings Journal*, *4*, 49–52.

Nwanna, E. E., Ibukun, E. O., & Oboh, G. (2016). Effect of some tropical eggplant fruits (solanum Spp) supplemented diet on diabetic neuropathy in experimental male Wistar rats in-vivo. *Functional Foods in Health and Disease*, *6*, 661–676.

Nwanna, E. E., Ibukun, E. O., & Oboh, G. (2019). Eggplant (solanum spp) supplemented fruits diet modulated the activities of ectonucleoside triphosphate diphosphohydrolase (ENTPdase), monoamine oxidase (MAO), and cholinesterases (AChE/BChE) in the brain of diabetic Wistar male rats. *Journal of Food Biochemistry*, *43*(8), e12910.

Oboh, G., Oyeleye, S. I., Akintemi, O. A., & Olasehinde, T. A. (2018). *Moringa oleifera* supplemented diet modulates nootropic-related biomolecules in the brain of STZ-induced diabetic rats treated with acarbose. *Metabolic Brain Disease*, *33*, 457–466.

Parihar, M., Chaudhary, M., Shetty, R., & Hemnani, T. (2004). Susceptibility of hippocampus and cerebral cortex to oxidative damage in streptozotocin treated mice: Prevention by extracts of Withania somnifera and *Aloe vera*. *Journal of Clinical Neuroscience*, *11*, 397–402.

Patel, S. S., Gupta, S., & Udayabanu, M. (2016). *Urtica dioica* modulates hippocampal insulin signaling and recognition memory deficit in streptozotocin induced diabetic mice. *Metabolic Brain Disease*, *31*, 601–611.

Patel, S. S., Parashar, A., & Udayabanu, M. (2015). *Urtica dioica* leaves modulates muscarinic cholinergic system in the hippocampus of streptozotocin-induced diabetic mice. *Metabolic Brain Disease*, *30*, 803–811.

Patel, S. S., & Udayabanu, M. (2013). Effect of *Urtica dioica* on memory dysfunction and hypoalgesia in an experimental model of diabetic neuropathy. *Neuroscience Letters*, *552*, 114–119.

Patel, S. S., & Udayabanu, M. (2014). *Urtica dioica* extract attenuates depressive like behavior and associative memory dysfunction in dexamethasone induced diabetic mice. *Metabolic Brain Disease*, *29*, 121–130.

Radhika, P., Annapurna, A., & Rao, S. N. (2012). Immunostimulant, cerebroprotective & nootropic activities of *Andrographis paniculata* leaves extract in normal & type 2 diabetic rats. *The Indian Journal of Medical Research*, *135*, 636.

Rahmati, M., & Kazemi, A. (2019). Various exercise intensities differentially regulate GAP-43 and CAP-1 expression in the rat hippocampus. *Gene*, *692*, 185–194.

Rajashree, R., Patil, R., Khlokute, S. D., & Goudar, S. S. (2017). Effect of Salacia reticulata W. and *Clitoria ternatea* L. on the cognitive and behavioral changes in the streptozotocin-induced young diabetic rats. *Journal of Basic and Clinical Physiology and Pharmacology*, *28*, 107–114.

Reaven, G. M., Thompson, L. W., Nahum, D., & Haskins, E. (1990). Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes Care*, *13*, 16–21.

Roriz-Filho, J. S., Sà-Roriz, T. M., Rosset, I., Camozzato, A. L., Santos, A. C., Chaves, M. L., & Roriz-Cruz, M. (2009). (Pre) diabetes, brain aging, and cognition. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1792*(5), 432–443.

Ryan, C. M. (1988). Neurobehavioral complications of type I diabetes: Examination of possible risk factors. *Diabetes Care*, *11*, 86–93.

Samarghandian, S., Azimi-Nezhad, M., & Samini, F. (2014). Ameliorative effect of saffron aqueous extract on hyperglycemia, hyperlipidemia, and oxidative stress on diabetic encephalopathy in streptozotocin induced experimental diabetes mellitus. *BioMed Research International*, *2014*, 920857

Sanches, J. R., Franca, L. M., Chagas, V. T., Gaspar, R. S., dos Santos, K. A., Goncalves, L. M., … Paes, A.M. (2016). Polyphenol-rich extract of *Syzygium cumini* leaf dually improves peripheral insulin sensitivity and pancreatic islet function in monosodium L-glutamate-induced obese rats. *Frontiers in Pharmacology*, *7*, 48.

Seung, T. W., Park, S. K., Kang, J. Y., Kim, J. M., Park, S. H., Kwon, B. S., … Heo, H. J. (2018). Ethyl acetate fraction from *Hibiscus sabdariffa* L. attenuates diabetes-associated cognitive impairment in mice. *Food Research International*, *105*, 589–598.

Sharifzadeh, M., Ranjbar, A., Hosseini, A., & Khanavi, M. (2017). The effect of green tea extract on oxidative stress and spatial learning in Streptozotocin-diabetic rats. *Iranian Journal of Pharmaceutical Research*, *16*, 201.

Shi, X., Lu, X., Zhan, L., Qi, X., Liang, L., Hu, S., … Zhang, F. L. (2011). The effects of the Chinese medicine ZiBu PiYin recipe on the hippocampus in a rat model of diabetes-associated cognitive decline: A proteomic analysis. *Diabetologia*, *54*(7), 1888–1899.

Sima, A. A. (2004). Diabetes underlies common neurological disorders. *Annals of Neurology*, *56*, 459–461.

Sohn, E., Kim, J., Kim, C. S., Lee, Y. M., Jo, K., Shin, S. D., & Kim, J. S. (2013). The extract of Litsea japonica reduced the development of diabetic nephropathy via the inhibition of advanced glycation end products accumulation in db/db mice. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 769416

Subash, S., Essa, M. M., Al-Adawi, S., Memon, M. A., Manivasagam, T., & Akbar, M. (2014). Neuroprotective effects of berry fruits on neurodegenerative diseases. *Neural Regeneration Research*, *9*, 1557.

Sun, Z., Zhan, L., Liang, L., Sui, H., Zheng, L., Sun, X., & Xie, W. (2016). ZiBu PiYin recipe prevents diabetes-associated cognitive decline in rats: Possible involvement of ameliorating mitochondrial dysfunction, insulin resistance pathway and histopathological changes. *BMC Complementary and Alternative Medicine*, *16*, 200.

Swaminathan, J. K., Khan, M., Mohan, I. K., Selvendiran, K., Devaraj, S. N., Rivera, B. K., & Kuppusamy, P. (2010). Cardioprotective properties of Crataegus oxycantha extract against ischemia-reperfusion injury. *Phytomedicine*, *17*, 744–752.

Tabatabaei, S. R. F., Rashno, M., Ghaderi, S., & Askaripour, M. (2016). The aqueous extract of *Portulaca oleracea* ameliorates neurobehavioral dysfunction and hyperglycemia related to streptozotocin-diabetes induced in ovariectomized rats. *Iranian Journal of Pharmaceutical Research*, *15*, 561.

Tang, Y., Yu, C., Wu, J., Chen, H., Zeng, Y., Wang, X., … Qin, D. (2018). Lychee seed extract protects against neuronal injury and improves cognitive function in rats with type II diabetes mellitus with cognitive impairment. *International Journal of Molecular Medicine*, *41*(1), 251–263.

Taranalli, A., & Cheeramkuzhy, T. (2000). Influence of *Clitoria ternatea* extracts on memory and central cholinergic activity in rats. *Pharmaceutical Biology*, *38*, 51–56.

Taylor, P., & Radic, Z. (1994). The cholinesterases: From genes to proteins. *Annual Review of Pharmacology and Toxicology*, *34*, 281–320.

Thakur, A. K., Rai, G., Chatterjee, S. S., & Kumar, V. (2016). Beneficial effects of an *Andrographis paniculata* extract and andrographolide on cognitive functions in streptozotocin-induced diabetic rats. *Pharmaceutical Biology*, *54*, 1528–1538.

Tumen, I., Senol, F. S., & Orhan, I. E. (2012). Inhibitory potential of the leaves and berries of *Myrtus communis* L.(myrtle) against enzymes linked to neurodegenerative diseases and their antioxidant actions. *International Journal of Food Sciences and Nutrition*, *63*, 387–392.

Vangalapati, B., Manjrekar, P. A., Hegde, A., & Kumar, A. (2016). *Pterocarpus marsupium* heartwood extract restores learning, memory and cognitive flexibility in a STZ-NA induced diabetes animal model. *International Journal of Pharmacy and Pharmaceutical Sciences*, *8*, 339–343.

Vij, T., & Prashar, Y. (2015). A review on medicinal properties of *Carica papaya* Linn. *Asian Pacific Journal of Tropical Disease*, *5*, 1–6.

Wang, Y., Xiang, L., Wang, C., Tang, C., & He, X. (2013). Antidiabetic and antioxidant effects and phytochemicals of mulberry fruit (*Morus alba* L.) polyphenol enhanced extract. *PLoS One*, *8*, e71144.

White, L., Petrovitch, H., Hardman, J., Nelson, J., Davis, D. G., Ross, G. W., … Markesbery, W.R. (2002). Cerebrovascular pathology and dementia in autopsied Honolulu-Asia aging study participants. *Annals of the new York Academy of Sciences*, *977*, 9–23.

Whitmer, R. A. (2007). Type 2 diabetes and risk of cognitive impairment and dementia. *Current Neurology and Neuroscience Reports*, *7*, 373–380.

Wu, K. J., Chen, Y. F., Tsai, H. Y., Wu, C. R., & Wood, W. G. (2012). Guizhi-Fuling-Wan, a traditional Chinese herbal medicine, ameliorates memory deficits and neuronal apoptosis in the streptozotocin-induced hyperglycemic rodents via the decrease of Bax/Bcl2 ratio and caspase-3 expression. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 656150

Xu, L., Li, B., Cheng, M., Zhang, W., Pan, J., Zhang, C., & Gao, H. (2008). Oral administration of grape seed proanthocyanidin extracts down-regulate RAGE dependant nuclear factor-kappa BP65 expression in the hippocampus of streptozotocin induced diabetic rats. *Experimental and Clinical Endocrinology & Diabetes*, *116*, 215–224.

Yaman, B. K., Çevik, Ö., Yalman, K., Ertaş, B., Şen, A., & Şener, G. (2020). *Myrtus communis subsp. communis* improved cognitive functions in ovariectomized diabetic rats. *Gene*, *744*, 144616.

Yoshikawa, M., Shimoda, H., Nishida, N., Takada, M., & Matsuda, H. (2002). Salacia reticulata and its polyphenolic constituents with lipase inhibitory and lipolytic activities have mild antiobesity effects in rats. *The Journal of Nutrition*, *132*, 1819–1824.

Yu, H., Zhang, Z. L., Chen, J., Pei, A., Hua, F., Qian, X., … Xu, X. (2012). Carvacrol, a food-additive, provides neuroprotection on focal cerebral ischemia/reperfusion injury in mice. *PLoS One*, *7*(3), e33584.

Zarrinkalam, E., Ranjbar, K., Salehi, I., Kheiripour, N., & Komaki, A. (2018). Resistance training and hawthorn extract ameliorate cognitive deficits in streptozotocin-induced diabetic rats. *Biomedicine & Pharmacotherapy*, *97*, 503–510.

Zhang, A. H., Yu, J. B., Sun, H., Kong, L., Wang, X. Q., Zhang, Q. Y., & Wang, X. J. (2018a). Identifying quality-markers from Shengmai San protects against transgenic mouse model of Alzheimer's disease using chinmedomics approach. *Phytomedicine*, *45*, 84–92.

Zhang, C., Xu, Y., Tan, H. Y., Li, S., Wang, N., Zhang, Y., & Feng, Y. (2018b). Neuroprotective effect of He-Ying-Qing-Re formula on retinal ganglion cell in diabetic retinopathy. *Journal of Ethnopharmacology*, *214*, 179–189.

Zhang, F. L., Gao, H. Q., Wu, J. M., Ma, Y. B., You, B. A., Li, B. Y., & Xuan, J. H. (2006). Selective inhibition by grape seed proanthocyanidin extracts of cell adhesion molecule expression induced by advanced glycation end products in endothelial cells. *Journal of Cardiovascular Pharmacology*, *48*, 47–53.

Zhang, J., & Zhang, C. (2015). Research progress on the antineoplastic pharmacological effects and mechanisms of Litchi seeds. *Chinese Medicine*, *6*, 20–26.

Zhang, Y., Su, J., Li, H., Ruan, W., Liu, X., Ye, C., & Zou, J. (2012). Combination of 'Heying Prescription' and laser therapy for diabetic retiopathy. *Shanghai Journal of Traditional Chinese Medicine*, *46*, 50–52.

Zhou, W. (2004). *Progress in the pharmacological study on Chinese traditional medicine prescriptions in neurodegenerative disease treatment. New studies in Chinese traditional medicine pharmacology* (pp. 272–315). Beijing, China: *People Health Press*.

Zia-Ul-Haq, M., Riaz, M., De Feo, V., Jaafar, H. Z., & Moga, M. (2014). *Rubus fruticosus* L.: Constituents, biological activities and health related uses. *Molecules*, *19*(8), 10998–11029.

Zin, N. S. N. M., Hashim, N., Samsulrizal, N., & Azmi, N. S. A. (2019). The protective effect of Azadirachta excelsa leaves extract and quercetin treatment on the learning and memory impairments in relation with insulin and amylin levels in the brain of streptozotocin-induced diabetic rats. *Journal of King Saud University-Science*, *31*, 299–307.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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