Journal of Young Pharmacists, 2024; 16(4):620-632.
https://www.jyoungpharm.org

Review Article

Potential of Medicinal Plants to Inhibit Neurodegenerative Activities in Diabetes: A Systematic Review

Phaik Har Yong[1], Wong Xue Yi[1], Meram Azzani[2,*], Rhanye Mac Guad[3,4], Zhi Xiang Ng[5]

[1]School of Bioscience, Faculty of Pharmacy and Biomedical Sciences, MAHSA University, Selangor, MALAYSIA.
[2]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Sungai Buloh, Selangor, MALAYSIA.
[3]Department of Biomedical Science, Faculty of Medicine and Health Science, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, MALAYSIA.
[4]Borneo Medical and Health Research Centre, Faculty of Medicine and Health Sciences, Universiti Malaysia, Kota Kinabalu, Sabah, MALAYSIA.
[5]School of Biosciences, Faculty of Science and Engineering, University of Nottingham Malaysia, Selangor, MALAYSIA.

ABSTRACT

Several studies have established that diabetes can exacerbate the neurodegeneration process. Some studies have reported the potential use of medicinal plants to inhibit neurodegenerative activities in diabetes. Therefore, this systematic review aims to evaluate the potential of medicinal plants to ameliorate neurodegenerative activities in diabetes. This systematic review was reported according to PRISMA guidelines. A systematic search was performed in four databases which were PubMed, Scopus, Google Scholar and Science Direct. Seven articles that fulfilled the inclusion criteria were selected for reporting this review. The medicinal plants reported in these articles were studied for their blood glucose lowering effect, acetylcholinesterase inhibitory activity and cognitive improvement ability through a behavioural test known as the Morris water maze. The medicinal plants such as Liuwei Dihuang Decoction (LWDHD), *Flos Puerariae* Extract (FPE), methanolic leaf extract of *Peristrophe bicalyculata* (MEPb), Ethanol Extract of *Clitorea ternatea* (EECT), Lychee Seed Extract (LSE) *Andrographis paniculata* extract (AP), andrographolide and Petroleum Ether Extract of *Carica papaya* Seeds (PEECPS) have shown significant result in Morris water maze test and acetylcholinesterase inhibitory activity, suggesting their ability to improve cognitive behaviour. They were also reported to have blood glucose lowering effect except for MEPb. LWDHD, FPE, MEPb, EECT, LSE, AP, andrographolide and PEECPS reported in these articles have shown potential in improving cognitive behaviour of diabetic animals. They were also reported to have anti-diabetic effects except for MEPb. However, more studies and research should be conducted to ensure the potential and safe use of these medicinal plants.

Keywords: Medicinal plants, Neurodegenerative activities, Diabetes, Cognitive, Acetylcholinesterase, Systematic review.

Correspondence:
Dr. Meram Azzani
Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus-47000, Sungai Buloh, Selangor, MALAYSIA.
Email: dr_memeazzani@yahoo.com/ meram@uitm.edu.my
ORCID: 0000-0002-7939-1539

Received: 31-01-2024;
Revised: 31-03-2024;
Accepted: 11-06-2024.

INTRODUCTION

Diabetes Mellitus (DM) is a rapidly spreading global disease that has been related to economic growth and urbanisation[1,2] with a substantial effect on human morbidity and mortality.[3] According to a recent report by the International Diabetes Federation (IDF), approximately 425 million people were diagnosed with DM in 2017, with the figure predicted to rise to 552 million by 2020.[4,5] Furthermore, the World Health Organization (WHO) estimates that China, India and the United States continue to have the highest numbers of people with DM.[2] Within a certain population, several variations in the prevalence of DM occurred with respect to age, gender, geographical location and ethnicity.[4]

DM is a metabolic condition characterised by a rise in blood glucose levels caused by an alteration in insulin production, insulin use, or both.[5] According to the WHO classification of DM (2019), DM can be classified into Type 1 DM (T1DM) and Type 2 DM (T2DM), hybrid forms of diabetes, idiopathic, unclassified and gestational DM.[6,7] T1DM or Insulin Dependent Diabetes Mellitus (IDDM) resulted when autoimmune system mediates the destruction of beta pancreatic cells, causing insulin secretion deficiency. More common type of DM is T2DM or Non-Insulin Dependent Diabetes Mellitus (NIDDM) with the primary defects in inadequate compensatory insulin secretion or insulin resistance, with a declining of insulin level in long term.[8] Hybrid form of DM includes slowly evolving immune-mediated diabetes (also known as "Latent Autoimmune Diabetes in Adults" or LADA) and ketosisprone T2DM (affected present with ketosis and evidence of severe insulin deficiency but later go into remission and do not require insulin treatment.[9] Idiopathic DM may be genetic (monogenic forms such as maturity onset diabetes

OPEN ACCESS

Manuscript TECHNOMEDIA

DOI: 10.5530/jyp.2024.16.80

of the young) or secondary to drugs, pancreatic factors or other illnesses, due to no clear-cut diagnostic category at the time of diabetes diagnosis.[6] For example, T2DM has been diagnosed in children and young adults as a result of the worldwide rise in obesity incidence and children and young adults with T1DM are more likely to be overweight or obese than in the past. Furthermore, ketosis or frank ketoacidosis is not limited to people with T1DM. Gestational DM can occur in any form of glucose intolerance at the first recognition or onset of pregnancy.[3]

Of concern, a person's risk of developing degenerative diseases including atherosclerosis, coronary artery disease, hypertension, kidney disease, nephropathy, neuropathy, stroke and the accelerated ageing of the brain will rise with DM.[1,2] Aside from lifestyle modification and proper nutrition, DM patients are often prescribed with different formulations of antidiabetic medications.[10] As of most drugs, they are often called double-edge sword in terms of its effects,[11] despite of careful assessment prior to initiation by medical practitioners or endocrinologists. In recent years, increasing evidence on the benefits of several plants for the treatment of DM including *Artemisia herba-alba*,[12] *Morinda citrifollia* L.,[13] *Caralluma awdeliana* (Deflers) A. Berger[14] and *Momordica charantia*[15] have been reported across different parts of the world and populations. Not surprisingly, some of these plants have been used as an adjuvant or as favorable alternative therapy for DM including Diabecon®,[16] Glyoherb®[17] and Diabeta Plus®.[18] This review aims to highlight the scientific evidence of medicinal plants used as for the prevention and treatment of DM based on *in vitro* efficacy and mechanisms of action.

MATERIALS AND METHODS

This systematic review was reported according to Preferred Reporting Items for Systemic Review and Meta-Analyses (PRISMA) guidelines.[19]

Data Source

Systematic search was performed in four databases: PubMed, Science Direct, Google Scholar and Scopus for relevant and reliable literatures. Manual search was also performed on the bibliography of the included articles.

Search Strategy

The process of search criteria and study selection was outlined in the flowchart shown in Figure 1. The searches were performed through catalogued descriptors in Medical Subject Headings-MeSH in English, contained in the title and summary of the studies. The search terms were used in combination or separately in the respective databases, as follows: medicinal plants AND (diabetes OR hyperglycaemia) AND neurodegeneration.

Study Selection

The title and abstract of each article were initially screened for the relevant keywords. Those that were not relevant were discarded. The articles that considered relevant were then proceed to full text screening and analysis. The retrieved abstract and full text articles were assessed independently to determine for their eligibility using the predefined inclusion and exclusion criteria.

Inclusion Criteria

The searches were performed among articles published within January 2011 to May 2020. Searches were limited to English language. The studies were only included if diabetic animal model was used and related to neurodegeneration study with both Acetylcholinesterase (AChE) inhibitory activity and Morris Water Maze (MWM) overlapped.

Exclusion Criteria

Review articles, clinical trials, case reports and articles not related to animal study were excluded before they were further screened in detail. During the first screening, articles without diabetic animal model used and not related to neurodegeneration study were excluded. While in second screening, full text articles were screened and those did not meet the inclusion criteria were then excluded from reporting this review.

Data Extraction

After screening for the full text papers based on inclusion and exclusion criteria, data extraction was performed. Family name or surname of the first author and the year of publication for each paper were extracted. In addition, the information extracted included of animal population, characteristic of animal, induction of diabetic animal, study design, intervention or treatment, control vintage, measurement, findings and results as well as the conclusion.

Quality Assessment

The quality assessment was conducted based on a validated Risk of Bias (RoB) tool that was specifically designed for animal intervention studies.[20]

RESULTS

A total of 196 articles were identified through database searches and 1540 articles were identified through manual searches. Following this, 186 articles from database searches and 1521 articles from manual searches were discarded after screening the titles and abstracts as they were not related to diabetes and neurodegeneration. The remaining 10 articles from database searches and 19 articles from manual searches proceeded to eligibility analysis. Nine articles from database searches and 13 articles from manual searches were then discarded as they did not fulfill the inclusion criteria. As a result, only 7 articles remained

and were included in this systematic review. The flowchart shown in Figure 1 outlines the process and results of the search criteria and study selection and the findings of the selected studies are summarized in Table 1. Some articles expressed all values as mean±Standard Deviation (SD),[22,26] whereas others expressed all values as mean±Standard Error of the Mean (SEM).[21,23-25,27]

Effect of Medicinal Plants on Morris Water Maze

The Morris Water Maze (MWM) was used as a behavioral parameter to assess the cognitive function, learning and spatial memory ability of diabetic animals. The test was carried out in a pool partially filled with water. Various cues and spatial signs were used and consistently kept in the same position to guide the animals to the target platform during the training period. During the probe trial for the retention test, the platform was removed from the pool or tank. The escape or Transfer Latency (TL) of the animals searching for the target platform was determined. All seven articles reported that medicinal plants can improve the cognitive behavior of diabetic animals.[21-27] This potential was determined by the *p*-value for their latency time, with $p<0.001$ indicating high potential, $p<0.05$ indicating moderate potential and $p<0.01$ indicating low potential.

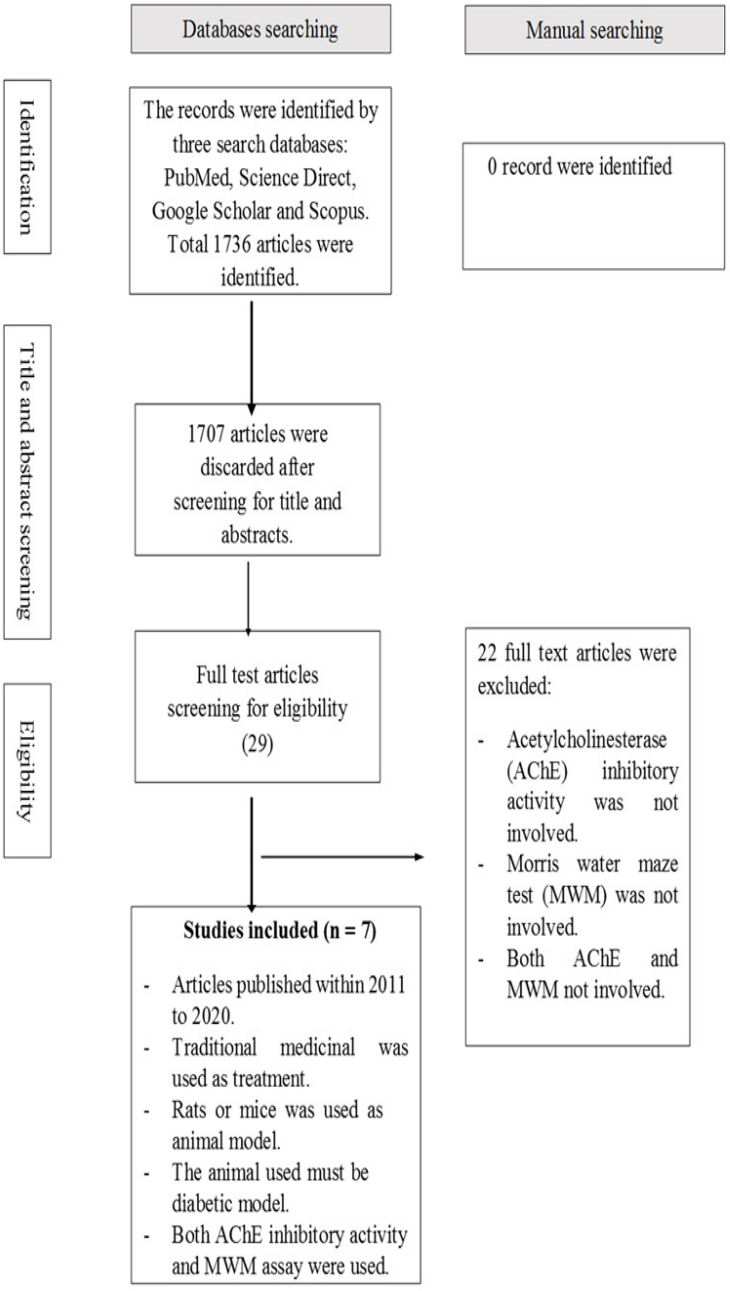

Figure 1: Process and result of search criteria and study selection.

Table 1: Summary of the findings in selected studies.

References	Name of medical plants	Extract/part	Effective chemical composition	Animal/cell	Outcome
Liu *et al.*, 2013[22]	Liuwei Dihuang	Ethanol extract/root of *Rehmannia glutinosa* Libosch/fruit of *Cornus officinalis* Sieb/tubers of *Dioscorea oppositifolia* L/rhizomes of *Alisma orientale* (G. Samuelsson) Juz/dried sclerotia of *Poria cocos* (Schw.) Wolf/ root cortex of *Paoenia ostii*.	Gallic acid, morroniside, paeoniflorin, loganin, paeonol.	STZ-induced rat	Morris water maze test (mean latency and path length were shortened remarkedly, compared with model group (p<0.05); improving the cognitive deficits. Treatment with LWDHD (1 g/kg and 2 g/kg) significantly decreased the AChE activity in the hippocampus of STZ-treated rats (p<0.05, n=6). LWDHD (1 g/kg and 2 g/kg), rosiglitazone (5 mg/kg) and donepezil (3 mg/kg) remarkably attenuated the neuron apoptosis of STZ-treated rats with the integrity of the nuclei morphology (p<0.01, n=9). Following the treatment with LWDHD (1 g/kg and 2 g/kg), the expression of caspase-3 protein was remarkably reduced as compared to the model rats (p<0.01, n=9). Reduced expressions of the BDNF and IGF-1 were prevented by the oral administration of LWDHD of 1 g/kg and 2 g/kg and rosiglitazone (5 mg/kg). Treatment with LWDHD (1 g/kg and 2 g/kg), rosiglitazone (5 mg/kg) and donepezil (3 mg/kg) significantly attenuated the accumulation of Aβ (1-40) amyloids on neurons in the hippocampus and cerebral cortex of DE rats (p<0.01 or p<0.05, n=9).
Liu, *et al.*, 2015[23]	Flos Puerariae	Methanolic extract/leaf.	---	STZ-induced mice.	Morris water maze test: FPE-treated diabetic mice significantly reduced the prolonged escape latency in a dose dependent manner. FPE-treated diabetic mice markedly increased the time in searching the platform in the target quadrant. Decrease the blood glucose level and normalize the body weight in experimental diabetic mice (p<0.05) Reversed AChE activity in cerebral cortex of experimental diabetic mice.

References	Name of medical plants	Extract/part	Effective chemical composition	Animal/cell	Outcome
Njan, *et al.*, 2020[24]	*Peristrophe bicalyculata*	Methanolic extract/leaf.	----	High-fat diet and STZ-induced rat.	Morris water maze test: There was significant increase ($p<0.05$) in escape latency in untreated diabetic rats compared to normal control. The extract significantly decreased ($p<0.05$) escape latency similar to pioglitazone treatment in treated diabetic rats compared to the diabetic control. Total time spent in non-targeted quadrants significantly increased ($p<0.05$) in untreated diabetic rats compared to normal control. Effect of Methanolic leaf extract of *Peristrophe bicalyculata* (MEPb) on brain Acetylcholinesterase (AchE) activity in HFD/STZ-induced diabetic rats: Brain AchE levels significantly ($p<0.05$) increased in untreated diabetic rats compared to normal control. Both the extract and pioglitazone treatment produced significant ($p<0.05$) decreased of these levels in treated rats compared to diabetic control.
Talpat e, *et al.*, 2014[25]	*Clitorea ternatea* Linn. (Fabaceae)	Ethanol extract/leaf.	Alkaloids, glycosides, steroids and flavonoids.	STZ-induced rat.	Nootropic study: Effects of EECT on spontaneous alterations (%) in Y maze arm: EECT (200 and 400 mg/kg), metformin (200 mg/kg) and piracetam (200 mg/kg) treated diabetic animals showed significant ($p<0.05$), increase in % spontaneous alterations in retention trial as compared to diabetic controls. Effects of EECT on spatial working and reference memory in Radial arm maze: Diabetic animals, treated with EECT (200 and 400 mg/kg) showed dose dependent ($p<0.001$) increase in spatial working-reference memory in retention trial as compared to diabetic controls. Effects of EECT on transfer latency in Morris water maze: Two weeks repeated treatment with EECT (200 and 400 mg/kg) and piracetam (200 mg/kg) significantly ($p<0.001$) decreased TL in retention trial as compared to diabetic controls. Neurochemical study: Effects of EECT on Acetylcholinesterase activity: While two weeks repeated treatment with EECT (200 and 400 mg/kg) significantly decreased acetylcholinesterase activity in diabetic animals ($p<0.05$ and $p<0.001$ respectively).

References	Name of medical plants	Extract/part	Effective chemical composition	Animal/cell	Outcome
Tang, *et al.*, 2018[26]	*Litchi chinensis* Sonn. (Lychee)	Ethanol extract/Seed	Adenosine, 2, 5-hydroxymethyluridine, 3, 4-p-coumaroylquinic acid, 4, procyanidin B, 5, procyanidin A, 6, 5′-β-D-glucopyranosyloxy jasmonic acid, 7, 4-O-(trans-p-coumaroyl) quinic acid, 8, procyanidin tetramer.	High-fat diet and STZ-induced rat.	Morris water maze test: Hidden platform test: LSE at the doses of 0.7, 1.4 and 2.8 g/kg/day and donepezil at 0.42 mg/kg/day by intragastric administration for 28 consecutive days significantly shortened the escape latency compared to NS treatment (p<0.01) in the T2DM rats. Spatial probe test: LSE (0.7, 1.4 and 2.8 g/kg/day×28 days)significantly increased the residence time, the numbers of those crossing the platform and the percentage of time spent in the target quadrant compared to NS treatment (p<0.01) in the T2DM rats. Effects of LSE on the blood glucose of LSE at the doses of 0.7, 1.4 and 2.8 g/kg/day significantly decreased the blood glucose (14.74±1.50, 13.19±2.57 and 12.33±2.46 mmol/l) in a dose-dependent manner compared to NS treatment in the T2DM rats (p<0.01), although the reductions did not reach the same level in normal rats. Effects of LSE on AChE and Aβ in the blood and hippocampus of T2DM rats: LSE at the doses of 0.7, 1.4 and 2.8 g/kg/day significantly decreased (p<0.01) the concentrations of AChE in the blood (9.19±0.90, 8.57±1.00 and 7.51±0.75 μmol/ml, respectively), while increased (p<0.01) the concentrations of AChE in the hippocampus (1.10±0.24, 1.13±0.43 and 1.22±0.40 U/mg, respectively) compared to NS treatment in the T2DM rats. LSE at the doses of 0.7, 1.4 and 2.8 g/kg/day significantly decreased (p<0.01) the concentrations of Aβ in the blood (4.65±0.60, 3.73±0.45 and 2.54±0.59 pg/ml, respectively) and in the hippocampus (0.25±0.03, 0.22±0.02 and 0.19±0.03 mmol/mg, respectively) compared to NS treatment in T2DM rats.

References	Name of medical plants	Extract/part	Effective chemical composition	Animal/cell	Outcome
Thakur, *et al.*, 2016[27]	*Andrographis paniculata*	Methanolic extract/leaf.	-----	STZ-induced rat	Morris water maze test: Post hoc analysis revealed that on days 7, 8 and 9 of the test, treatment with AP, andrographolide or piracetam significantly decreased escape latencies compared to diabetic control indicating increased memory functions. Blood glucose level: However, in comparison to the vehicle-treated diabetic control group, AP or andrographolide treated ones had significantly (one-way ANOVA analysis) lower blood glucose levels, $p<0.05$. Acetylcholinesterase enzyme activity: In comparison to the corresponding values of the diabetic control group, the mean acetylcholinesterase activities in pre-frontal cortex [$F(8, 45)=68.69$, $p<0.05$] and in hippocampus [$F(8, 45)=65.09$, $p<0.05$], of AP-andrographolide- or piracetam-treated ones, were significantly lower (one-way ANOVA analysis). Observed dose-dependent efficacies of AP in lowering Acetylcholinesterase activities in both the brain regions of diabetic rats were almost identical to those expected from its andrographolide contents.
Venkatesh-warlu *et al.* 2018[21]	*Carica papaya*	Petroleum Ether Extract/ Seed	-----	STZ-induced rat	Morris Water Maze Test: Significant effect in nootropic effect as exemplified by increase in Acetyl cholinesterase (AchE), Malondialdehyde (MDA), Superoxide Dismutase (SOD), Nitric Oxide (NO), Catalase (CAT) and Glutathione (GSH) levels in the brains Significant decrease in AchE ($p<0.001$).

Among the seven reviewed articles, six used a rat model, while one used a mouse model. However, all the articles used Streptozotocin (STZ) to induce a diabetic condition in the animals. Generally, after treatment with LWDHD, FPE, MEPb, EECT, LSE, AP and PEECPS, the mean latency and path length were markedly shortened in the diabetic rats and mice across the respective studies.[21-27] One article noted that this decrease was dose-dependent.[23] Administration of FPE in diabetic mice significantly reduced the prolonged escape latency in a dose dependent manner. The results of swim path analyses showed that all medicinal plant-treated diabetic rats and mice performed well in search accuracy compared to the model rats. In the probe test, platform crossings and the time spent searching for the platform in the target quadrant were significantly enhanced with LWDHD, FPE, MEPb, LSE and AP treatments.[22-24,26,27] Two articles did not perform the probe test.[21,25]

Effect of Medicinal Plants on Acetylcholinesterase Inhibitory Activities

AChE activity was determined by the Ellman colorimetric method to assess cholinergic dysfunction. Its concentration can be measured in the blood, different regions of the brain, or the whole brain. All seven articles reported that medicinal plants can reduce AChE activity in diabetic animals, suggesting an attenuation of memory deficits.[21-27] In addition, one article reported that a medicinal plant can reduce AChE activity in a dose-dependent manner.[27] However, one article demonstrated a decrease in AChE activity in the blood but an increase in AChE activity in the hippocampus.[26] Another article showed that treatment with

donepezil, a cholinesterase inhibitor, significantly decreased AChE activity but did not enhance Choline Acetyltransferase (ChAT) activity. Furthermore, treatment with LWDHD significantly reduced AChE activity and increased ChAT activity in the hippocampus of STZ-treated rats.[22]

Effect of Medicinal Plants on Blood Glucose Level

Blood glucose level was used as a standard measurement for most of the research involving diabetic animals. These animals were fed a High-Fat Diet (HFD) for a certain period and/or given a Streptozotocin (STZ) injection to induce diabetes. Prior to the experiment, their blood glucose levels were measured. Diabetes was successfully induced if the blood glucose level was higher than the glycaemic index of 250 mg/dL (13.3 mmol/L) or 200 mg/dL (11.1 mmol/L), as set accordingly.

Treatment with LWDHD, FPE, LSE, AP and PEECPS significantly reduced blood glucose levels.[21-23,26,27] Additionally, treatment with FPE, LSE and AP dose-dependently decreased blood glucose levels.[23,26,27] Two articles demonstrated that treatment with LWDHD and FPE could elevate the STZ-decreased body weight and normalize body weight in experimental diabetic mice, respectively.[22,23] Nevertheless, one article showed that blood glucose levels remained significantly high in diabetic groups (treated or untreated) compared to the normal control.[24] One remaining article did not perform blood glucose level or body weight monitoring.[25]

DISCUSSION

Although the concise mechanism remains unclear, Type 2 Diabetes Mellitus (T2DM) is known to deteriorate neurodegeneration process. For example, insulin resistance can dysregulate lipid and carbohydrate metabolism, impair cell survival or anti-apoptotic signalling, increase GSK- 3β activation, affect mitochondrial function as well as choline acetyltransferase and expression of neurotrophin gene. These conditions can induce oxidative stress. While insulin resistance occurs in brain can increase the level of Aβ42 and phospho-Tau as well as induce iron accumulation in body which then reduce the glycaemic control ability. Neurodegenerative disorder is widely classified with clinical presentations such as behavioural or cognitive disorder as well as pyramidal and extrapyramidal movement disorders. Therefore, MWM is used as a behavioural parameter to assess hippocampal-dependent learning, spatial and long-term memory ability of diabetic animal models.[28-31]

MWM consists of two parts which are training and probe trials to determine the mean latency, path length, swim pattern, number of platforms crossing and time spent of animal model in target quadrant. The results of this review revealed that diabetic models have increased mean latency and lengthened path length but decreased number of platforms crossing and time spent in target quadrant compared to normal control. When the treatments such as LWDHD, FPE, MEPb, EECT, LSE, AP, andrographolide and PEECPS were given to the diabetic animals, all measurements were improved in dose-dependent manner.[21-27]

LWDHD is the most common used herbal, includes of 6 medicinal plants which are root of *Rehmannia glutinosa*, fruit of *Cornus officinalis*, tubers of *Dioscorea oppositifolia*, rhizomes of *Alisma orientale*, dried sclerotia of *Poria cocos* and root cortex of *Paoenia ostia* in the ratio of 8:4:4:3:3:3. There are approximately 80.3% Chinese and 64.2% European practitioners using this herbal for treatment. LWDHD is a kidney tonifying and Yin nourishing prescription which can maintain and modulate or strengthen and invigorate fundamental system, supporting the process of development, performance and reproduction system. It can be given in the form of decoction (soup), capsules, pills or powder. LWDHD is widely used for the prevention or treatment of diseases affecting digestive, endocrine, immune, nervous, respiratory and urinary system. It was reported to accelerate the information processing speed and enhance cognitive abilities in healthy adult in a placebo-controlled and double-blinded trial. While in diabetic individual, it improved the treatment outcomes such as fasting or post-prandial blood glucose, control and response rates, which is beneficial to relieve the diabetic complications such as microvascular, nephropathy and neuropathy.[32]

These findings were supported and proved by several studies. For example, in SAMP8 mice with cognitive impairment in Alzheimer Disease (AD), treatment of LWDHD for five months was reported to improve spatial memory ability through MWM test. This treatment was also found can enhance retention and memory ability as well as partially improve learning ability when avoidance performance test was assessed. While in rats with non-AD type cognitive impairment induced by *D*-galactose, treatment of LWDHD for six weeks was found to alleviate deficiency in spatial learning and memory performance. However, the medicinal properties of LWDHD and its mechanism of action still require further research and evaluation.[32,33]

The treatment of *Clitorea ternatea* were widely used as brain tonic to promote intelligence and memory function. Similar to that finding a pharmacological study showed that *Clitorea ternatea* treatment can prevent cognitive impairment or treat cognitive deficits induced by STZ in a dose-dependent manner. This is beneficial for the treatment of neurodegenerative disorder by mediating several mechanisms such as reducing the oxidative stress parameters and affecting the levels of CAT, GSH, nitric oxide and SOD. Positive effects of *Clitorea ternatea* on spatial working and reference memory were also reported.[34,35]

While lychee seed is a traditional medicine and it was reported to have neuroprotection effect. LSE comprises of chemical components such as saponins, amino acid, organic acid, fatty acid, flavonoids and volatile oils, which were found able to improve learning and memory activity. Besides that, LSE can

reduce the formation of Aβ and tau proteins as well as AGEs in diabetic animal model and thus relieving the cognitive dysfunction. This statement was supported by several studies. For example, the treatment of LSE in Aβ25-35- induced AD animal models had reported to improve their cognitive ability in MWM test, with shortened escape latency and increased number of platforms crossing, time spent and run percentage in target quadrant. Therefore, lychee seeds can be used as nutritional supplement and drug for prevention or treatment of AD. A recent study also reported that saponin; one of the components extracted and isolated from lychee seeds can improve spatial memory and learning ability in rats with Chronic Cerebral Ischemia (CCI). While polyphenol extracted from lychee seeds was tested in APP/PS1 mice, it was reported to have an ability to inhibit NLRP3 inflammasome, improving cognitive function by showing improved measurement in escape route, escape latency, average speed and time spent in target quadrant and frequency of platforms crossings.[36-39]

The extract of *Andrographis paniculata* which is enriched with andrographolide was reported to improve cognitive function in STZ-induced diabetic rats. This statement was supported by several studies as properties of anti-inflammation and antioxidant have been recognized, which then suggested the neuroprotective benefits of *A. paniculata*. In other researches' findings, the treatment of *A. paniculata* extract ameliorated spatial learning and memory impairments in STZ-treated rats. Besides that, research reported that pre-treatment of *A. paniculata* for 24 hr prior to Lipopolysaccharide (LPS)-induced cognitive impairment had improved behavioural performance of animal model in MWM test, with decreased escape latency and significantly increased the number platforms crossing and time spent in target quadrant. While andrographolide, an active ingredient or diterpenoids present in the aerial part of *Andrographis paniculata*, was reported to improve the cognitive impairment in 12-month-old AβPPswe/PS- 1 mouse by showing lower escape latency in MWM test.[35,40-43]

Since oxidative stress plays an important role to deteriorate and exacerbate neurodegeneration process in diabetes, antioxidant properties of plant may suggest a protective effect against oxidative stress. *Carica papaya* seed was reported to have neuroprotective effect by improving the behavioural measurement in MWM task as shown in Table 1. This statement was supported by other findings. For example, the antioxidant activity of *Carica papaya* seed can protect against Hydrogen Peroxide (H_2O_2)-induced oxidative stress in Detroit 550 fibroblast of human skin. It was also reported that this protective effect is maximal when the extract was given simultaneously with the drug or chemical used to induce disease. Besides that, *Carica papaya* seed was reported to have higher potential to protect brain from oxidative damage compared to vitamin C.[44]

While the treatment with *Flos Puerariae* extract was reported to improve cognitive impairment in STZ-treated animal models by reducing the oxidative stress as well as *Peristrophe bicalyculata* can significantly reduce the escape latency and time spent of diabetic animals in non-target quadrant.[24,35] However, no other study was found to support these statements which may require more research to provide scientific-based evidence. All the medicinal plants reported in the selected articles have shown neuroprotective effect and able to protect animal models from oxidative damage in dose-dependent manner.

AChE is an enzyme which plays a primary role in cholinergic nervous system. It catalyses the cleaving process of Acetylcholine (ACh) into acetate and choline that can then function as neurotransmitter. The cholinergic function is usually exerted in neuromuscular junction and chemical synapses of cerebral cortex to prevent ACh accumulation that may lead to uncontrolled and repeated muscle stimulation. Therefore, AChE is important to terminate synaptic transmission. Besides that, AChE also plays non-cholinergic functions such as cell adhesion, cell growth, cell recognition, cell signalling, dopamine neurons activation, neuritic growth regulation, neuronal network formation, stem cell differentiation and thrombopoiesis. Therefore, the normal function of central and peripheral nervous system must be maintained with continuous presence of ACh and constantly sustained with AChE production or reduced AChE activity.[24,45]

However, the change of AChE function will affect neurotransmitter level, causing the function of nervous system to be lost. For example, AD is a neuronal death related disease caused by amyloidogenic and cholinergic pathways. The abnormal process of Amyloid Precursor Protein (APP) can trigger accumulation of Amyloid-β (Aβ), causing disruption in calcium homeostasis and enhance oxidative stress. These conditions can then activate apoptosis mechanism. As Aβ acts as apoptotic process activator, it stimulates the activation of caspase cascade, leading to tau protein cleavage via intrinsic and extrinsic pathways. Besides that, an increased in AChE may impair brain and cognitive function. Therefore, AChE inhibition is important to prevent apoptotic-induced cell loss in neurodegenerative disorders. Although some AChE inhibitors were used for the treatment of neurodegenerative disorder, but they were mainly used to manage the cognitive manifestation and symptoms or to slow down the disease progression. As a result, AChE inhibitory activity of medicinal plants was evaluated to study their neuroprotective effects.[23, 45]

As shown in the results, the medicinal plants such as LWDHD, FPE, EECT, LSE, AP, andrographolide and PEECPS were reported to reduce or inhibit AChE activity in dose- dependent manner except for MEPb which was found most effective at lower dose, which was 50 mg/kg. AChE inhibition can prevent apoptosis-induced neuronal lost mediated by the cleavage of ACh and thus suggested a neuroprotective effect.[21-27] LWDHD was reported to have AChE inhibitory activity. This has been supported by several studies. For example, in aging mouse induced by *D*-galactose, LWDHD

restored ACh level and enhanced antioxidant activities in brain. This significantly improved the impaired learning and memory ability. While in rat model with dementia induced by aluminium, LWDHD protected brain from oxidative damage by increasing SOD activity and reducing MDA level, suggesting an effect of memory impairment alleviation.[46,47]

Besides that, *Clitorea ternatea* was reported to have AChE inhibitory activity. This statement was supported by a pharmacological review in which *Clitorea ternatea* was found to increase ACh level in hippocampus, representing an improvement in the neurochemical basis of learning and memory abilities. The level of AChE, lipid peroxide and total nitric oxide were decreased upon *Clitorea ternatea* treatment but increased CAT, SOD and GSH levels were shown, suggesting an improvement in cognitive behaviour in diabetic-induced cognitive decline animal model.[33,34,48] While from the findings tabulated in Table 1, *Andrographis paniculata* and andrographolide were shown to improve cholinergic activities in diabetic rats. For example, the major bioactive components of *Andrographis paniculata* such as flavonoids, diterpenoids and polyphenols as well as andrographolide have reported to target AChE and antioxidant activities. It was also reported to decrease hippocampal AChE activity but increase the cholinergic activities in LPS-induced cognitive impairment models.[40]

Moreover, *Carica papaya* seeds, FPE and LSE were reported to have AChE inhibitory activities. For example, the AChE inhibitory activity of *C. papaya* seeds was proven by other studies, which proposed that the alkaloids present in the plants are responsible for AChE activity inhibition.[49,50] While FPE can restore cholinergic activity and improve cognitive impairment by alleviating AChE activities in the cortex of STZ-treated mice as well as LSE increased AChE content but reduced ACh degradation in hippocampus.[35] All the findings reported in Table 1 have showed that medicinal plants have the potential to inhibit AChE activity. Interestingly, *Peristrophe bicalyculata* was reported to have higher potential in inhibiting AChE activity at a lower dose which was 50 mg/kg. However, this statement should be proved by conducting more researches as no study was found to report the similar findings.

Apart from MWM task and AChE inhibitory activity, the potential of medicinal plants to lower blood glucose level was also reviewed. As discussed above, diabetes mellitus can exacerbate the process of neurodegeneration. This association attributes to the production and deposition of AGEs in brain, leading to oxidative stress. The oxidative state of brain induces neuroinflammation, which can then mediate the cholinergic neural pathways to damage neuronal connections. These epidemiological and biological evidences had showed the linkage of diabetes and cognitive impairment. As shown in the method tabulated in Table 1, STZ was almost used by all researchers to induce experimental diabetes. It is a well-known drug and widely used in research to damage and destruct the pancreatic β-cells that are responsible for insulin secretion. Therefore, STZ or high fat glucose diet induced diabetic animal models were used in researches to evaluate the potential of medicinal plants to lower the blood glucose level of diabetic animals. As shown in Table 1, the treatments such as LWDHD, FPE, EECT, LSE, AP, andrographolide and PEECPS can dose-dependently reduce blood glucose level except for MEPb as the blood glucose levels remained significantly high in both treated and untreated diabetic animals.[21-27] These findings were supported by other studies. For example, the treatment of LWDHD was found to have a potential to increase insulin secretion, enhance glucose uptake by muscle or adipose tissue, inhibit glucose production, decrease insulin resistance and enhance insulin sensitivity. This will then lower the blood glucose level.[33] While FPE was also found to lower the increased blood glucose level in C57BL/6J mice with diabetic cardiomyopathy. The isoflavonoid component of FPE or its whole extract was found can significantly reduce blood glucose level especially at a higher dose (200 mg/kg), exerting hypoglycaemic effect and thus retard the disease progression.[51]

Oral treatment of 400 mg/kg of *Clitorea ternatea* leaves extract to Wistar rats for 28 days was reported have significantly reduced the blood glucose level. However, in a clinical trial, the treatment of *Clitorea ternatea* extract alone to healthy individual did not affect the glucose concentration significantly. Therefore, sucrose was given to increase the blood glucose level and *Clitorea ternatea* (1 and 2 g) was ingested simultaneously. *Clitorea ternatea* treatment was found have significantly suppressed the peak postprandial plasma glucose. Besides that, previous findings showed that the action of carbohydrate digestive enzyme such as pancreatic α-amylase and intestinal α-glucosidase can be inhibited by anthocyanins, a phenolic compound extracted from *Clitorea ternatea*.[48,52]

LSE was also reported to reduce blood glucose level of high fat, high sugar and high protein- induced diabetic rats. This was then supported by a study involving rat model with AD as lychee seed can reduce and modulate plasma glucose, improve insulin resistance and insulin sensitivity. Besides that, the treatment of LSE to diabetic patient was found to lower the blood glucose level by reducing insulin resistance. These findings have suggested the anti-diabetic effect of LSE.[36,39]

While the glucose lowering effects of *Andrographis paniculata* and andrographolide were supported by other findings. For example, *Andrographis paniculata* consists of bitter substances such as andrographolide, Kalmeghin and diterpene lactones were reported to have an ability to decrease blood glucose level by inhibiting absorption of glucose in intestine. When *Andrographis paniculata* was prepared in chloroform extract, blood glucose level was significant reduced in both acute and chronic studies. This statement was reported by an international conference which then supported the use of *Andrographis paniculata* to

control diabetes. Research conducted in high-fructose- fat diet induced hyperglycaemic rats also showed that the treatment of purified *Andrographis paniculata* extract and its most active compound andrographolide can significantly reduce blood glucose level. These findings have proved the anti-diabetic activity of *Andrographis paniculata* and andrographolide.[53,54]

Moreover, the glucose lowering effect of *Carica papaya* seed extract was supported by several studies. However, most of the effective findings were shown when the plant prepared in ethyl acetate extract but not petroleum ether. For example, *Carica papaya* prepared in ethyl acetate extract could dose-dependently lower the blood glucose level of STZ-induced diabetic rats. The phytochemical constituents present in ethyl acetate extract such as alkaloids, flavonoids and saponins established the hypoglycaemic potential of *Carica papaya* seed. Besides that, *Carica papaya* seed extract also had an inhibitory effect on α-glucosidase and α-amylase, suggesting that *Carica papaya* seed can delay the digestion of carbohydrate into absorbable form. In addition, the other part of *Carica papaya*, leaf was also reported to significantly reduce blood glucose level of STZ-induced diabetic rats by restoring the function of pancreatic islet cell. These findings were then suggested *Carica papaya* have the potential to reduce blood glucose level of diabetic model.[55-57]

While the treatment of *Peristrophe bicalyculata* in high fat diet-induced diabetic rats have shown a negative result as the blood glucose level of treated and untreated diabetic models remained significantly high. This suggested that *Peristrophe bicalyculata* has no anti-diabetic effect. However, no similar study was found to support this statement which may require more researches on *Peristrophe bicalyculata* to confirm its anti-diabetic effect.[24]

Despite the promising strength of these medicinal plants in anti-diabetic and neuroprotective effects, the dosage used should have low cytotoxicity and be safe for consumption in large doses. An acute toxicity study was carried out according to the Organization for Economic Co-operation and Development (OECD) Guidelines No. 423.[25] No clinical signs of toxicity or mortality were observed in the animals treated with medicinal plants during the toxicity study. This suggests the potential for high protective effects from these medicinal plants that are safe for consumption in large doses.

In a nutshell, the medicinal plants such as LWDHD, FPE, MEPb, EECT, LSE, AP and andrographolide as well as PEECPS were reviewed for their potential to ameliorate neurodegeneration activities in diabetic animals. They were reported to have significant result in MWM test and AChE inhibitory activity, suggesting their ability to improve cognitive impairment and inhibit AChE activity. Besides that, they were also reported to have anti-diabetic effect to lower blood glucose level of diabetic animal models except for *Peristrophe bicalyculata*. From the findings and *p*-value given, 400 mg/kg of EECT showed the most potent effect in improving cognitive function and inhibiting AChE activity. The potential of these medicinal plants was not limited to seed or leaves but also other parts of the plant which had been proved by several studies.

Indisputably, treatment with medicinal plants reduced inducible nitric oxide synthase (iNOS) activity significantly, while increasing the Glutathione (GSH) level remarkably. This may result in diminishing the excess Reactive Oxygen Species (ROS) and reactive nitrogen, thereby ameliorating DNA fragmentation and preventing neuronal injury.[22,58-60] Medicinal plant treatment has also been demonstrated to strengthen Na^+ -K^+-ATPase activity.[22] Additionally, medicinal plants have been shown to reverse the adverse effects of oxidative stress by suppressing the over-expression of caspase-3 and reducing neuronal apoptosis.[22] The mechanisms exhibited by medicinal plants, either directly or indirectly, also lead to the up-regulation of Brain Derived Neurophic Factor (BDNF) and insulin-like growth factor-1 (IGF-1) expressions. Inhibition of β-amyloid deposition may also explain the underlying mechanism of medicinal plants in attenuating hyperglycemic effects and enhancing neuroprotective effects.[22]

However, as mentioned above, different extraction solvent such as ethanol, hydro-methanolic, petroleum ether or purified extract may have different potential in treating and monitoring diseases and the studies used to support the findings of this systematic review may utilize different extraction solvent in preparing the plant extracts. Therefore, more studies should be conducted to determine the most suitable extraction solvent so that the medicinal plants can exert their effects at the highest potential. The toxicity of plants also should be further analysed especially those need higher dosage for effective treatment. This is to ensure the safety use of medicinal plants although positive neuroprotective and glucose lowering effects were reported in this review.

CONCLUSION

Although the dosage and extraction methods differed across these studies, the overarching trend remained consistent, either indicating an increase (up-regulation) or decrease (down-regulation) in the observed findings. Despite the variation in measurement scales or methodologies employed, the fundamental direction of change was reliably observed. This consistency lends robustness to the conclusion that there is indeed a meaningful alteration occurring, regardless of the specific dosage and extraction methods utilized in measurement.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **LWDHD:** Liuwei Dihuang Decoction; **FPE:** *Flos Puerariae* Extract; **MEPb:** Methanolic Leaf Extract of *Peristrophe Bicalyculata*; **EECT:** Ethanol Extract of *Clitorea Ternatea*; **LSE:** Lychee Seed Extract; **AP:** *Andrographis Paniculata* Extract; **PEECPS:** Petroleum Ether Extract of *Carica Papaya* Seeds; **DM:** Diabetic Mellitus; **IDF:** International Diabetes Federation; **WHO:** World Health Organization; **T1DM:** Type 1 Diabetic Mellitus; **T2DM:** Type 2 Diabetic Mellitus; **IDDM:** Insulin Dependent Diabetes Mellitus; **NIDDM:** Non-Insulin Dependent Diabetes Mellitus; **LADA:** Latent Autoimmune Diabetes in Adults; **MeSH:** Medical Subject Headings; **AChE:** Acetylcholinesterase; **MWM:** Morris Water Maze; **RoB:** Risk of Bias; **TL:** Transfer Latency; **STZ:** Streptozotocin; **ChAT:** Choline Acetyltransferase; **HFD:** High-Fat Diet; **GSK-3β:** Glycogen Synthase Kinase-3 Beta; **Aβ42:** Amyloid Beta 42; **AD:** Alzheimer Disease; **CAT:** Catalase; **GSH:** Glutathione; **SOD:** Superoxide Dismutase; **AGEs:** Advanced Glycation End Products; **Aβ25-35:** Amyloid Beta-Peptide (25-35); **CCI:** Chronic Cerebral Ischemia; **NLRP3:** NLR Family Pyrin Domain Containing 3; **LPS:** Lipopolysaccharide; **H_2O_2:** Hydrogen Peroxide; **ACh:** Acetylcholine; **APP:** Amyloid Precursor Protein; **Aβ:** Amyloid-β; **MDA:** Malondialdehyde; **OECD:** Organization for Economic Co-Operation and Development; **iNOS:** Inducible Nitric Oxide Synthase; **ROS:** Reactive Oxygen Species; **DNA:** Deoxyribonucleic Acid; **BDNF:** Brain Derived Neurophic Factor; **IGF-1:** Insulin-Like Growth Factor-1.

REFERENCES

1. Rajamani U. Causes of neurodegeneration in diabetes: possible culprits and therapeutic targets. rain Disord Ther. 2014;03(4):1-6. doi: 10.4172/2168-975X.1000130.
2. Madhusudhanan J, Suresh G, Devanathan V. Neurodegeneration in type 2 diabetes: Alzheimer's as a case study. Brain Behav. 2020;10(5):01577. doi: 10.1002/brb3.1577, PMID 32170854.
3. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol. 2019;11(3):45-63. PMID 31333808.
4. Forouhi NG, Wareham NJ. Epidemiology of diabetes. Medicine. 2019;47(1):22-7. doi: 10.1016/j.mpmed.2018.10.004.
5. Petrov MS. DIAGNOSIS OF ENDOCRINE DISEASE: post-pancreatitis diabetes mellitus: prime time for secondary disease. Eur J Endocrinol. 2021;184(4):137-49. doi: 10.1530/EJE-20-0468, PMID 33460393.
6. World Health Organization. Classification of diabetes mellitus; 2019.
7. Chinnasamy V, Subramaniyan V, Chandiran S, Kayarohanam S, Kanniyan DC, Velaga VS, *et al.* Antiarthritic activity of *Achyranthes aspera* on formaldehyde-Induced arthritis in rats. Open Access Maced J Med Sci. 2019;7(17):2709-14. doi: 10.3889/oamjms.2019.559, PMID 31844425.
8. Paschou SA, Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. On type 1 diabetes mellitus pathogenesis. Endocr Connect. 2018;7(1):38-46. doi: 10.1530/EC-17-0347, PMID 29191919.
9. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383(9911):69-82. doi: 10.1016/S0140-6736(13)60591-7, PMID 23890997.
10. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, *et al.* Treatment of diabetes in older adults: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2019;104(5):1520-74. doi: 10.1210/jc.2019-00198, PMID 30903688.
11. Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, *et al.* Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol (Lausanne). 2017;8:6. doi: 10.3389/fendo.2017.00006, PMID 28167928.
12. Katiri A, Barkaoui M, Msanda F, Boubaker H. Ethnobotanical survey of medicinal plants used for the treatment of diabetes in the Tizi n'test region (Taroudant Province, Morocco). J Pharmacogn Nat Prod. 2017;3(1):2472-0992.
13. Phumthum M, Balslev H. Thai ethnomedicinal plants used for diabetes treatment. OBM Integr Complement Med. 2018;3(3):1-25. doi: 10.21926/obm.icm.1803020.
14. Al-Fatimi M. Ethnobotanical survey of medicinal plants in central Abyan governorate, Yemen. J Ethnopharmacol. 2019;241:111973. doi: 10.1016/j.jep.2019.111973, PMID 31146001.
15. Baddu VD, Ouano NB. Ethnobotanical survey of medicinal plants used by the Y'Apayaos of Sta. Praxedes in the province of Cagayan, Philippines. MJST. 2018;16(1).
16. Kapure N, Vakade K, Nayak BB. Effect of diabecon a multiherbal formulation on serum glucose level in alloxan induced diabetic rats. VIMSHSJ. 2019;6(3):63-5.
17. Adedapo AA, Ogunmiluyi IO. The use of natural products in the management of diabetes: the current trends. J Drug Delivery Ther. 2020;10(1):153-62. doi: 10.22270/jddt.v10i1.3839.
18. Yeung AW, Tzvetkov NT, Durazzo A, Lucarini M, Souto EB, Santini A, *et al.* Natural products in diabetes research: quantitative literature analysis. Nat Prod Res. 2020:1-15.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. BMJ. 2009;339:b2535. doi: 10.1136/bmj.b2535, PMID 19622551.
20. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43. doi: 10.1186/1471-2288-14-43, PMID 24667063.
21. Venkateshwarlu E, Srilatha K, Bhava BS, Umasankar K. Neuroprotective and nootropic activity of Carica papaya seeds on diabetes induced cognitive decline in rats. Iran J Pharm Sci. 2018;14(3):107-16.
22. Liu JP, Feng L, Zhang MH, Ma DY, Wang SY, Gu J, *et al.* Neuroprotective effect of Liuwei Dihuang decoction on cognition deficits of diabetic encephalopathy in streptozotocin-induced diabetic rat. J Ethnopharmacol. 2013;150(1):371-81. doi: 10.1016/j.jep.2013.09.003, PMID 24041458.
23. Liu ZH, Chen HG, Wu PF, Yao Q, Cheng HK, Yu W, et al. *Flos puerariae* Extract Ameliorates Cognitive Impairment in Streptozotocin-Induced Diabetic Mice. Evid Based Complement Alternat Med. 2015; 2015:873243. doi: 10.1155/2015/873243, PMID 26060502.
24. Njan AA, Adenuga FO, Ajayi AM, Sotunde O, Ologe MO, Olaoye SO, *et al.* Neuroprotective and memory-enhancing effects of methanolic leaf extract of *Peristrophe bicalyculata* in rat model of type 2 diabetes mellitus. Heliyon. 2020;6(5):e04011. doi: 10.1016/j.heliyon.2020.e04011, PMID 32490237.
25. Talpate KA, Bhosale UA, Zambare MR, Somani RS. Neuroprotective and nootropic activity of *Clitorea ternatea* Linn.(Fabaceae) leaves on diabetes induced cognitive decline in experimental animals. J Pharm Bioallied Sci. 2014;6(1):48-55. doi: 10.4103/0975-7406.124317, PMID 24459404.
26. Tang Y, Yu C, Wu J, Chen H, Zeng Y, Wang X, *et al.* Lychee seed extract protects against neuronal injury and improves cognitive function in rats with type II diabetes mellitus with cognitive impairment. Int J Mol Med. 2018;41(1):251-63. doi: 10.3892/ijmm.2017.3245, PMID 29138799.
27. Thakur AK, Rai G, Chatterjee SS, Kumar V. Beneficial effects of an *Andrographis paniculata* extract and andrographolide on cognitive functions in streptozotocin-induced diabetic rats. Pharm Biol. 2016;54(9):1528-38. doi: 10.3109/13880209.2015.1107107, PMID 26810454.
28. Bromley-Brits K, Deng Y, Song W. Morris water maze test for learning and memory deficits in Alzheimer's disease model mice. J Vis Exp. 2011;(53). doi: 10.3791/2920, PMID 21808223.
29. de la Monte SM. Insulin resistance and neurodegeneration: progress towards the development of new therapeutics for Alzheimer's disease. Drugs. 2017;77(1):47-65. doi: 10.1007/s40265-016-0674-0, PMID 27988872.
30. Dugger BN, Dickson DW30. Pathology of Neurodegenerative Diseases. Cold Spring Harb Perspect Biol. 2017; 9(7):a028035. doi: 10.1101/cshperspect.a028035, PMID 28062563.
31. Weitzner DS, Engler-Chiurazzi EB, Kotilinek LA, Ashe KH, Reed MN. Morris water maze Test: optimization for mouse strain and testing environment. J Vis Exp. 2015;(100):52706. doi: 10.3791/52706, PMID 26132096.
32. Cheng XR, Qi CH, Wang TX, Zhou WX, Zhang YX. Characteristics of the traditional Liu-Wei-Di-Huang prescription reassessed in modern pharmacology. Chin J Nat Med. 2019;17(2):103-21. doi: 10.1016/S1875-5364(19)30013-5, PMID 30797417.
33. Zhang X, Cui X, Li F, Wang S, Liu X, Hui L, *et al.* Association between diabetes mellitus with metabolic syndrome and diabetic microangiopathy. Exp Ther Med. 2014;8(6):1867-73. doi: 10.3892/etm.2014.1992, PMID 25371746.
34. Al-Snafi A. Pharmacological importance of *Clitoria ternatea*-A review. IOSR J Pharm. 2016;6:68-83.
35. Infante-Garcia C, Garcia-Alloza M. Review of the effect of natural compounds and extracts on neurodegeneration in animal models of diabetes mellitus. Int J Mol Sci. 2019;20(10). doi: 10.3390/ijms20102533, PMID 31126031.
36. Chang CL, Lin Y, Bartolome AP, Chen YC, Chiu SC, Yang WC. Herbal therapies for type 2 diabetes mellitus: chemistry, biology and potential application of selected plants and compounds. Evid Based Complement Alternat Med. 2013; 2013:378657. doi: 10.1155/2013/378657, PMID 23662132.

37. Huang X, Lu G, Li G, Li H, Li B, Yin J, *et al.* Dynamic changes in the renin-angiotensin-aldosterone system and the beneficial effects of renin-angiotensin-aldosterone inhibitors on spatial learning and memory in a rat model of chronic cerebral ischemia. Front Neurosci. 2017;11:359. doi: 10.3389/fnins.2017.00359, PMID 28690496.
38. Qiu WQ, Pan R, Tang Y, Zhou XG, Wu JM, Yu L, *et al.* Lychee seed polyphenol inhibits Aβ-induced activation of NLRP3 inflammasome via the LRP1/AMPK mediated autophagy induction. Biomed Pharmacother. 2020;130:110575. doi: 10.1016/j.biopha.2020.110575, PMID 32768883.
39. Wang X, Wu J, Yu C, Tang Y, Liu J, Chen H, *et al.* Lychee seed saponins improve cognitive function and prevent neuronal injury via inhibiting neuronal apoptosis in a rat model of Alzheimer's disease. Nutrients. 2017;9(2):105. doi: 10.3390/nu9020105, PMID 28165366.
40. Sani D, Khatab NI, Kirby BP, Yong A, Hasan S, Basri H, *et al.* A standardised *Andrographis paniculata* Burm. Nees aqueous extract prevents Lipopolysaccharide-induced cognitive deficits through suppression of inflammatory cytokines and oxidative stress mediators. J Adv Res. 2019;16:87-97. doi: 10.1016/j.jare.2018.11.005, PMID 30899592.
41. Serrano FG, Tapia-Rojas C, Carvajal FJ, Hancke J, Cerpa W, Inestrosa NC. Andrographolide reduces cognitive impairment in young and mature AβPPswe/PS-1 mice. Mol Neurodegener. 2014;9:61. doi: 10.1186/1750-1326-9-61, PMID 25524173.
42. Ng ZX, Myricetin YPH. The resources, biosynthesis, physicochemical, pharmacokinetic, bioavailability, pharmacology and toxicology. In book: handbook of Dietary Flavonoids; 2023. doi: 10.1007/978-3-030-94753-8_19-1.
43. Yong PH, New SY, Azzani M, Wu YS, Chia VV, Ng ZX. Potential of medicinal plants to ameliorate neovascularization activities in diabetes: A systematic review. Endocr Regul. 2023;58(1):26-39. doi: 10.2478/enr-2024-0004, PMID 38345496.
44. Panzarini E, Dwikat M, Mariano S, Vergallo C, Dini L. Administration dependent antioxidant effect of *Carica papaya* seeds water extract. Evid Based Complement Alternat Med. 2014; 2014:281508. doi: 10.1155/2014/281508, PMID 24795765.
45. Lazarevic-Pasti T, Leskovac A, Momic T, Petrovic S, Vasic V. Modulators of acetylcholinesterase activity: from Alzheimer's disease to anti-cancer drugs. Curr Med Chem. 2017;24(30):3283-309. doi: 10.2174/0929867324666170705123509, PMID 28685687.
46. Sangha JS, Sun X, Wally OS, Zhang K, Ji X, Wang Z, *et al.* Liuwei Dihuang (LWDH), a traditional Chinese medicinal formula, protects against β-amyloid toxicity in transgenic Caenorhabditis elegans. PLOS ONE. 2012;7(8):e43990. doi: 10.1371/journal.pone.0043990, PMID 22952840.
47. Thapa R, Goyal A, Gupta G, Bhat AA, Singh SK, Subramaniyan V, *et al.* Recent developments in the role of protocatechuic acid in neurodegenerative disorders. Excli J. 2023;22:595-9. doi: 10.17179/excli2023-5940, PMID 37636028.
48. Oguis GK, Gilding EK, Jackson MA, Craik DJ. Butterfly pea (*Clitoria ternatea*), a cyclotide-bearing plant with applications in agriculture and medicine. Front Plant Sci. 2019;10:645. doi: 10.3389/fpls.2019.00645, PMID 31191573.
49. Ilham R, Lelo A, Harahap U, Widyawati T, Siahaan L. The effectivity of ethanolic extract from papaya leaves (*Carica papaya* L.) as an alternative larvacide to Aedes spp. Open Access Maced J Med Sci. 2019;7(20):3395-9. doi: 10.3889/oamjms.2019.432, PMID 32002060.
50. Malviya R, Raj S, Fuloria S, Subramaniyan V, Sathasivam K, Kumari U, *et al.* Evaluation of antitumor efficacy of chitosan-tamarind gum polysaccharide polyelectrolyte complex stabilized nanoparticles of simvastatin. Int J Nanomedicine. 2021;16:2533-53. doi: 10.2147/IJN.S300991, PMID 33824590.
51. Yu W, Zha W, Guo S, Cheng H, Wu J, Liu C. *Flos puerariae* extract prevents myocardial apoptosis via attenuation oxidative stress in streptozotocin-induced diabetic mice. PLOS ONE. 2014;9(5):98044. doi: 10.1371/journal.pone.0098044, PMID 24865768.
52. Chusak C, Thilavech T, Henry CJ, Adisakwattana S. Acute effect of *Clitoria ternatea* flower beverage on glycemic response and antioxidant capacity in healthy subjects: A randomized crossover trial. BMC Complement Altern Med. 2018;18(1):6. doi: 10.1186/s12906-017-2075-7, PMID 29310631.
53. Nugroho AE, andrie M, Warditiani NK, Siswanto E, Pramono S, Lukitaningsih E. Antidiabetic and anti-hiperlipidemic effect of *Andrographis paniculata* (Burm. f.) Nees and andrographolide in high-fructose-fat-fed rats. Indian J Pharmacol. 2012;44(3):377-81. doi: 10.4103/0253-7613.96343, PMID 22701250.
54. Bhat AA, Thapa R, Goyal A, Subramaniyan V, Kumar D, Gupta S, *et al.* Curcumin-based nanoformulations as an emerging therapeutic strategy for inflammatory lung diseases. Future Med Chem. 2023;15(7):583-6. doi: 10.4155/fmc-2023-0048, PMID 37140132.
55. Adinortey MB, Agbeko R, Boison D, Ekloh W, Kuatsienu LE, Biney EE, *et al.* Phytomedicines used for diabetes mellitus in Ghana: A systematic search and review of preclinical and clinical evidence. eCAM. 2019; 2019:1-23.
56. Agada R, Usman WA, Shehu S, Thagariki D. *In vitro* and *in vivo* inhibitory effects of *Carica papaya* seed on α-amylase and α-glucosidase enzymes. Heliyon. 2020;6(3):03618. doi: 10.1016/j.heliyon.2020.e03618, PMID 32258473.
57. Juárez-Rojop IE, Díaz-Zagoya JC, Ble-Castillo JL, Miranda-Osorio PH, Castell-Rodríguez AE, Tovilla-Zárate CA, *et al.* Hypoglycemic effect of *Carica papaya* leaves in streptozotocin-induced diabetic rats. BMC Complement Altern Med. 2012;12:236. doi: 10.1186/1472-6882-12-236, PMID 23190471.
58. Tuzcu M, Baydas G. Effect of melatonin and vitamin E on diabetes-induced learning and memory impairment in rats. Eur J Pharmacol. 2006;537(1-3):106-10. doi: 10.1016/j.ejphar.2006.03.024, PMID 16626697.
59. Hasanein P, Shahidi S. Effects of combined treatment with vitamins C and E on passive avoidance learning and memory in diabetic rats [journal]. Neurobiol Learn Mem. 2010;93(4):472-8. doi: 10.1016/j.nlm.2010.01.004, PMID 20085822.
60. Ho KL, Ng ZX, Wang CW, Mat Junit S, Huah Lim SH, Ngo CT, *et al.* Comparative analysis of *in vitro* enzyme inhibitory activities and phytochemicals from *Platycladus orientalis* (L.) Franco via solvent partitioning method. Appl Biochem Biotechnol. 2022;194(8):3621-44. doi: 10.1007/s12010-022-03921-9, PMID 35476189.

Cite this article: Yong PH, Yi WX, Azzani M, Guad RM, Ng ZX. Potential of Medicinal Plants to Inhibit Neurodegenerative Activities in Diabetes: A Systematic Review. J Young Pharm. 2024;16(4):620-32.