Berberine for prevention of dementia associated with diabetes and its comorbidities: A systematic review

Shinjyo, N., Parkinson, J., Bell, J.D., Katsuno, T. and Bligh, S.W.A.

Journal Pre-proofs

Systematic Review

Berberine for prevention of dementia associated with diabetes and its comorbidities: A systematic review

Noriko Shinjyo, James Parkinson, Jimmy Bell, Tatsuro Katsuno, Annie Bligh

PII: S2095-4964(20)30005-4
DOI: https://doi.org/10.1016/j.joim.2020.01.004
Reference: JOIM 140

To appear in: *Journal of Integrative Medicine*

Received Date: 23 July 2019
Accepted Date: 4 December 2019

Please cite this article as: N. Shinjyo, J. Parkinson, J. Bell, T. Katsuno, A. Bligh, Berberine for prevention of dementia associated with diabetes and its comorbidities: A systematic review, *Journal of Integrative Medicine* (2020), doi: https://doi.org/10.1016/j.joim.2020.01.004

JIM-07-2019-SR-0243

Systematic Review

Berberine for prevention of dementia associated with diabetes and its comorbidities: A systematic review

Noriko Shinjyo[1], James Parkinson[2], Jimmy Bell[2], Tatsuro Katsuno[3], Annie Bligh[4]
1. Department of Infection and Host Defense, Graduate School of Medicine, Chiba University, Chuo-ku, Chiba 260-8670, Japan
2. Department of Life Sciences, Faculty of Science and Technology at the University of Westminster, London W1W 6UW, United Kingdom
3. Kashiwanoha Clinic of East Asian Medicine, Chiba University Hospital, Kashiwa, Chiba 277-0882, Japan
4. School of Health Sciences, Caritas Institute of Higher Education, Tseung Kwan O, NT 999077, Hong Kong, China

ABSTRACT

Background: A growing number of epidemiological studies indicate that metabolic syndrome (MetS) and its associated features play a key role in the development of certain degenerative brain disorders, including Alzheimer's disease and vascular dementia. Produced by several different medicinal plants, berberine is a bioactive alkaloid with a wide range of pharmacological effects, including antidiabetic effects. However, it is not clear whether berberine could prevent the development of dementia in association with diabetes.
Objective: To give an overview of the therapeutic potential of berberine as a treatment for dementia associated with diabetes.
Search strategy: Database searches A and B were conducted using PubMed and ScienceDirect. In search A, studies on berberine's antidementia activities were identified using "berberine" and "dementia" as search terms. In search B, recent studies on berberine's effects on diabetes were surveyed using "berberine" and "diabetes" as search terms.
Inclusion criteria: Clinical and preclinical studies that investigated berberine's effects associated with MetS and cognitive dysfunction were included.
Data extraction and analysis: Data from studies were extracted by one author, and checked by a second; quality assessments were performed independently by two authors.
Results: In search A, 61 articles were identified, and 22 original research articles were selected. In search B, 458 articles were identified, of which 101 were deemed relevant and selected. Three duplicates were removed, and a total of 120 articles were reviewed for this study. The results demonstrate that berberine exerts beneficial effects directly in the brain: enhancing cholinergic neurotransmission, improving cerebral blood flow, protecting neurons from inflammation, limiting hyperphosphorylation of tau and facilitating β-amyloid peptide clearance. In addition, evidence is growing that berberine is effective against diabetes and associated disorders, such as atherosclerosis, cardiomyopathy, hypertension, hepatic steatosis, diabetic nephropathy, gut dysbiosis, retinopathy and neuropathy, suggesting indirect benefits for the prevention of dementia.
Conclusion: Berberine could impede the development of dementia via multiple mechanisms: preventing brain damages and enhancing cognition directly in the brain, and indirectly through alleviating risk factors such as metabolic dysfunction, and cardiovascular, kidney and liver diseases. This study provided evidence to support the value of berberine in the prevention of dementia associated with MetS.

Please cite this article as: Shinjyo N, Parkinson J, Bell J, Katsuno T, Bligh A. Berberine for prevention of dementia associated with diabetes and its comorbidities: A systematic review. *J Integr Med*. 2019; Epub ahead of print.

Received July 23, 2019; **Accepted** December 4, 2019

Keywords: Berberine; Diabetes; Dementia; Alzheimer's disease; Vascular dementia

Correspondence: Noriko Shinjyo; E-mail address: nshinjyo@chiba-u.jp; Jimmy Bell; E-mail address: J.Bell@westminster.ac.uk; Annie Bligh; E-mail address: abligh@cihe.edu.hk

1. Introduction

Recent World Health Organization data indicate that the global incidence of diabetes is increasing— approximately 422 million adults were living with diabetes in 2014, compared to 108 million in 1980 [1]. Consequently, the incidences of the various comorbidities linked to diabetes are also on the rise, including degenerative and functional brain disorders, such as Alzheimer's disease (AD) and vascular dementia (VaD) [2,3]. VaD is a type of dementia associated with cerebrovascular dysfunctions. Type 2 diabetes mellitus (T2DM) is associated with cardiovascular and cerebrovascular disease, and vascular mechanism may underlie the cognitive decline in VaD [4]. AD is a progressive neurodegenerative disorder and the most common form of dementia. Although the etiology of AD is not fully understood, it is generally characterized by deposition of β-amyloid peptide (Aβ) and hyperphosphorylation of tau protein [4–6]. Aβ reduces both acetylcholine (ACh) uptake and release [7], and deficient cholinergic neurotransmission is likely to be involved in the AD symptomatology [8]. In fact, most currently available dementia medications are acetylcholinesterase (AChE) inhibitors; however, these drugs only provide relief of symptoms [9]. Importantly, T2DM causes insulin resistance in the brain, and dysfunctional insulin signaling is increasingly recognized in the etiology of AD. Studies have suggested a strong association between insulin signaling and Aβ metabolism [10]. Cerebral insulin resistance results in glycogen synthase kinase 3β (GSK3β) activation, which leads to increased Aβ production and tau phosphorylation [11,12], suggesting that dysfunctional insulin signaling or glucose metabolism in the brain could lead to the accumulation of Aβ and hyperphosphorylated tau. Indeed, the term "type 3 diabetes" is often used to characterize AD [13,14], given the close pathophysiological link between cerebral insulin resistance and oxidative stress and the histopathological lesions and cognitive impairment observed in AD [7,8,15,16].

Berberine is an isoquinoline alkaloid produced by several medicinal plant species, such as barberry (*Berberis vulgaris* L.), Indian barberry (*B. aristata* DC.), goldenseal (*Hydrastis canadensis* L.), Oregon grape (*Mahonia aquifolium* (Pursh) Nutt.), Chinese goldthread (*Coptis chinensis* Franch., *C. japonica* Makino., and *C. teeta* Wall.) and Amur cork tree (*Phellodendron amurense* Rupr.). Berberine-containing plants have historically been used to treat gastrointestinal complications such as diarrhea and dysentery [17,18], and berberine's antimicrobial activity has been well-characterized [17,19]. However, in recent years, the focus of berberine research has shifted towards potential therapeutic benefits in treating metabolic dysfunctions, such as T2DM, with data indicating glucose- and lipid-lowering effects [20,21]. Clinical evidence suggests that berberine significantly reduces fasting and postprandial plasma glucose, glycosylated hemoglobin A1c, serum cholesterol, triglycerides and low-density lipoprotein cholesterol (LDL-C) in T2DM patients [22,23]. Therapeutic benefits of berberine in treating T2DM and metabolic syndrome (MetS) have been reviewed previously [20,21,24]. In addition, preclinical evidence suggests that berberine has neuroprotective activities [25,26]. However, there is no comprehensive review to discuss the potential use of berberine as a treatment for dementia associated with metabolic dysfunctions. This

paper reviews the current preclinical and clinical data on the effects of berberine, particularly focusing on cognitive dysfunctions associated with T2DM and its associated comorbidities, and discusses potential benefits and underlying mechanisms at the molecular level.

2. Methods

In order to perform a systematic review of studies reporting the effects of berberine on cognitive dysfunctions and diabetes, two searches (A and B) were conducted using PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and ScienceDirect (https://www.sciencedirect.com/).

2.1. Information sources and Search strategy

2.1.1. Search A: *berberine for dementia prevention*

Studies of berberine's effects on dementia were retrieved using the search terms "(berberine) AND (dementia)" in PubMed's and ScienceDirect's advanced search interfaces, returning articles between January 2000 and May 2019.

2.1.2. Search B: *berberine for diabetes intervention*

To compile the currently available data on the effectiveness of berberine on diabetes and its comorbidities, advanced searches of PubMed and ScienceDirect databases were conducted, matching the search terms "(berberine) AND (diabetes)" in title, abstract and keywords. Articles published between January 2010 and May 2019 were included in the search.

2.2. Study selection and data extraction

Initially, studies were screened for relevance based on the title and abstract. At this point, reviews, unrelated studies and works without available full text were excluded. The full texts of potential studies were assessed following the exclusion and inclusion criteria listed below.

Eligibility criteria: (1) articles published in any non-English language were excluded; (2) case reports were excluded; (3) studies using mixtures of several compounds, conjugates and crude extracts were excluded; (4) original studies *in vivo*, *in vitro* and clinical studies were included. The quality of included articles was evaluated by assessing the intervention methods, materials (including the source of berberine) and the usage of established experimental systems and protocols. The following data were extracted: publishing data, research question(s), study design, outcomes and conclusion. Data were extracted by one author, checked by a second; and quality assessments by two other authors were independently conducted.

2.3 Synthesis of results

Included reports were classified according to the major research questions (i.e., antidementia, antidiabetic, or comorbidities). Results were synthesized, focusing on the association between dementia and MetS. Meta-analysis was not appropriate, due to the highly variable research methodologies and outcome measures.

3. Results

Database searches A and B identified research articles that addressed the therapeutic effects of berberine on dementia and diabetes, respectively. From search A, 65 articles (61 in PubMed and 4 in ScienceDirect) were identified, and 22 articles were deemed appropriate for inclusion according to the selection criteria. Among those, 16 studies used nondiabetic models [27–42] (Table 1) and 6 studies used diabetic models (Table 2). From search B, 458 (372 articles in PubMed and 86 articles in ScienceDirect) were identified and 101 articles met the selection criteria, of which 4 articles were in both A and B. Seven additional studies on diabetes-associated dementia were determined to be relevant. One article [43] was classified into both "studies used diabetic models" (Table 2) and "diabetes-associated dementia" (Tables 3–10); as it was relevant to both sections, a total of 13 articles were finally in Table 2 [43–55] and 91 articles in Tables 3–10 [22,43,56–144]. Tables 3–10 are categorized by eight groups according to the main topics of each study: (1) pancreatic

dysfunction (Table 3), (2) vascular and adipose tissue dysfunction (Table 4), (3) liver dysfunction (Table 5), (4) kidney dysfunction (Table 6), (5) gut dysbiosis and intestinal dysfunction (Table 7), (6) retinopathy (Table 8), (7) neuropathy (Table 9), and (8) others (Table 10). An overview of the search and selection processes is summarized in Fig. 1.

Table 1. Research articles studying the use of berberine to treat dementia in nondiabetic models.

First author (Year)	Dementia type	Study design	Intervention	Effects of berberine	Conclusion	Reference
Aski ML (2018)	VaD	*In vivo*: VaD model induced by chronic CCH in rats	Berberine 50 mg/(kg·d) for 2 months (p.o.)	Attenuated CCH-induced spatial learning and memory deficit; reduced CCH-induced apoptosis in hippocampal CA1 and increased neuronal density.	Berberine protects the hippocampus against CCH, thus may be suggested for VaD.	[27]
Hussien HM (2018)	Heavy metal-induced AD	*In vivo*: heavy metal-induced AD model in rats; *in silico*: Docking	Berberine 50 mg/(kg·d) for 30 d (p.o.)	*In vivo*: protected learning and memory; reduced lipid peroxidation and NO; increased antioxidant levels (GSH, SOD, GST, and GPx); reduced serum and brain AChE and MAO; reduced serum inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-12); reduction of APP and tau in the brain; protected against neurodegeneration in hippocampal CA1. *In silico*: may inhibit AChE, COX-2 and TACE.	Berberine has beneficial effect for AD via anti-inflammatory/antioxidant mechanism.	[28]
He W (2017)	Familial AD	*In vivo*: APP/PS1 AD model mice	Berberine 50 or 100 mg/(kg·d) for 14 d (p.o.)	Mitigated cognitive impairment; inhibited tau phosphorylation in the hippocampus; reduced the expression of NF-κB elements in the hippocampus; enhanced GSH antioxidant; reduced lipid peroxidation; inhibited neuroinflammation (CD45, GFAP, IL-1β, TNF-α).	Berberine attenuated cognitive deficits and limited tau hyperphosphorylation, possibly via NF-κB pathway inhibition, and reduction of oxidative stress and neuroinflammation.	[35]
Kim YJ (2017)	Cholinergic signaling impairment	*In vitro*: AChE inhibition	Berberine 2 μmol/L	80% AChE activity inhibition.	Berberine may enhance cholinergic neurotransmission via enhancement of acetylcholine level.	[36]
Sadeghnia HR (2017)	Glutamine-induced neurotoxicity	*In vitro*: glutamate-induced oxidative stress and apoptosis in PC12 and N2a	Pretreatment with berberine 50 μmol/L for 2 h before glutamate exposure	Inhibited glutamate-induced cell death; reduced glutamate-induced intracellular ROS generation and MDA; increased GSH content and SOD activity; reduced glutamate-induced DNA damage; reduced caspase-3 cleavage and increased Bax/Bcl-2 ratio.	Berberine protects against glutamate-induced neuronal injury by decreasing oxidative stress and inhibiting apoptosis.	[37]
Huang M (2017)	Familial AD	*In vivo*: AD model (3 × Tg-AD) in mice; *in vitro*: 3 × Tg-AD primary hippocampal neurons	Berberine 50 or 100 mg/(kg·d) for 4 months (p.o.)	*In vivo*: attenuated spatial learning deficits; improved short-term and long-term memory; enhanced autophagy in the hippocampus. *In vitro*: enhanced autophagy; reduced APP and BACE1; facilitated Aβ clearance via autophagy.	Berberine alleviates cognitive impairment via promotion of autophagy and facilitation of Aβ clearance.	[38]
Liu X (2014)	Tauopathy	*In vitro*: CA-induced axonal transport impairment and neuronal damage in N2a cells	Berberine 25 μg/mL	Berberine's effects in CA-induced neuronal damages: suppressed reduction of cell viability; reversed PP2A inactivation; attenuated hyperphosphorylation of tau; protected against NF axonal transport impairment and neurite outgrowth impairment; suppressed oxidative stress induction.	Berberine inhibited CA-induced PP2A activity modulation and oxidative stress, and reversed hyperphosphorylation of tau and NFs, and axonal transport impairment.	[39]
Zhan PY (2014)	Cognitive impairment associated with D-galactose-induced brain aging	*In vivo*: D-galactose-induced cognitive deficits and disrupted synaptic communication model in rats	Berberine 100 mg/(kg·d) for 7 weeks (p.o.)	Berberine's effects on D-galactose-induced damage: restored LTP deficits; rescued memory impairment; reversed synaptic plasticity marker activity-regulated cytoskeleton-associated protein (*Arc/Arg3.1*) reduction in the hippocampus.	Berberine rescued D-galactose-induced memory and synaptic impairment, possibly via recovering hippocampal *Arc/Arg3.1* expression, an effector immediate-early gene implicated in memory consolidation.	[40]
Bonesi M (2013)	AChE and BChE inhibition	*In vitro*: AChE and BChE assay	None	Dose-response relationship.	IC_{50} of berberine: AChE, 2.2 μg/mL; BChE, 116.7 μg/mL.	[41]
Jia L (2012)	Inflammation in the brain	*In vitro*: Aβ-induced inflammatory response in microglia (murine primary and BV2)	Berberine 2.5 or 5 μmol/L	Berberine's effects in Aβ-induced microglial inflammation: suppressed IL-6 and monocyte chemotactic protein-1 expression in Aβ-treated microglia; suppressed COX-2 and iNOS induction; inhibited Aβ-induced NF-κB activation, ERK and p38 phosphorylation.	Berberine can suppress Aβ-induced inflammation possibly via inhibition of NF-κB activation.	[42]
Durairajan SS (2012)	AD	*In vivo*: AD model in TgCRND8 mice; *in vitro*: N2a-SweAPP cells	*In vivo*: berberine 25 or 100 mg/kg per day for 4 months (p.o.); *in vitro*: berberine 20 μmol/L	*In vivo*, berberine had actions in AD model: alleviated learning and memory deficits; reduced corticohippocampal Aβ plaque pathology; reduced Aβ peptide level in the brain; reduced microglial and astroglial activation in the brain; suppressed hyperphophorylation of APP, CTF, and tau levels; enhanced GSK3β inactivation (phospho-GSK3β) and Akt phosphorylation. *In vitro*: enhanced Akt and GSK3β phosphorylation; reduced phospho-APP, CTFs and phosphorylated tau, which was inhibited by PI3K inhibitor.	Berberine restored cognitive functions, reduced APP and tau phosphorylation, via PI3K/Akt/GSK3β pathway.	[29]
Ji HF (2012)	Neurotransmission impairment	*In silico*: docking simulation (AChE, BChE, and MAO)	None	None.	Theoretical Kd (μmol/L): AChE: 0.66; BChE: 3.31; MAO-A: 105.2; MAO-B: 66.0.	[30]
Zhu F (2011)	Aβ 40/42, BACE	*In vitro*: HEK293 cells expressing mutant APP (Swedish mutation)	Berberine 1, 5, 10, 20 μmol/L	In mutant APP expressing cells: reduced Aβ 40/42 generation and BACE expression, which were inhibited by U0126 (an antagonist of the ERK1/2 pathway).	Berberine suppresses Aβ40/42 generation by downregulating BACE via ERK1/2 activation.	[31]
Yu CJ (2010)	IDO-1 associated	*In vitro*: recombinant human	Berberine	Inhibition of IDO-1 by berberine. IC_{50}/rhIDO-1: 9.3 μmol/L; IC_{50}/HEK293-hIDO-1: 7 μmol/L; Ki:	Berberine is an uncompetitive, reversible	[32]

	with AD	IDO-1 (rhIDO-1) inhibition assay; HEK293-hIDO-1		8 μmol/L; but the type of inhibition is noncompetitive.	inhibitor of IDO-1, which may be relevant to therapeutic potential for AD.	
Jung HA (2009)	AD	*In vitro*: BACE1, AChE, and BChE inhibition assay; ROS and peroxynitrite inhibition assay	Berberine	Inhibited AChE (IC_{50}: 0.44 μmol/L) and BChE (IC_{50}: 3.44 μmol/L), but did not inhibit BACE1; inhibited peroxynitrite generation (IC_{50}: 23.06 μmol/L), but did not inhibit ROS generation.	Berberine and other berberine alkaloids may have anti-AD effects via inhibition of AChE, BChE and nitrosative stress.	[33]
Zhu F (2006)	AD	*In vivo*: Aβ (1–40)-induced spatial memory deficits in rat	Berberine 50 mg/kg for 14 d (p.o.)	Berberine's effects in Aβ (1–40)-induced spatial memory deficits model: ameliorated Aβ (1–40)-induced spatial memory deficit; enhanced Aβ (1–40)-induced IL-1β and iNOS expression in the hippocampus.	Berberine might be beneficial in AD; however it might exacerbate inflammation.	[34]

Aβ: amyloid β; AChE: acetylcholinesterase; AD: Alzheimer's disease; APP: amyloid precursor protein; BACE: β-site amyloid precursor protein-cleaving enzyme; BChE: butyrylcholinesterase; CA: calyculin A; CCH: cerebral hypoperfusion; COX-2: cyclooxygenase-2; CTF: C-terminal fragment of APP; ERK: extracellular signal-regulated kinase; GFAP: glial fibrillary acidic protein; GPx: glutathione peroxidase; GSH: reduced glutathione; GSK3β: glycogen synthase kinase 3 β; GST: glutathione S-transferase; IC_{50}: half maximal inhibitory concentration; IDO: indoleamine 2, 3-dioxygenase; IL: interleukin; iNOS: inducible nitric oxide synthase; LTP: long-term potentiation; MAO: monoamine oxidase; MDA: malonaldehyde; NF: neurofilament; NF-κB: nuclear factor κB; NO: nitric oxide; PI3K: phosphoinositide 3-kinase; p.o.: per os; PP2A: protein phosphatase 2A; PS1: presenilin-1; ROS: reactive oxygen species; SOD: superoxide dismutase; TACE: tumor necrosis factor-α-converting enzyme; TNF: tumor necrosis factor; VaD: vascular dementia.

Table 2. Research articles studying the use of berberine to treat dementia in diabetic models.

First author (Year)	Dementia type	Study design	Intervention	Effects of berberine	Conclusion	Reference
de Oliveira JS (2019)	Sporadic AD	*In vivo*: ICV-STZ-induced sporadic AD type dementia model in rats	Berberine 50 or 100 mg/(kg·d) for 20 d (p.o.)	Recovered recognition memory; prevented ROS generation and lipid peroxidation in the hippocampus; reduced protein carbonylation in the hippocampus and cerebral cortex; prevented reduction of aminolevulinic acid dehydratase activity (heme synthesis) in the cerebral cortex; prevented the reduction of antioxidants in the hippocampus and cerebral cortex.	Berberine is neuroprotective and preserves recognition memory via reduction of oxidative stress.	[48]
Yin S (2018)	VaD	*In vivo*: STZ-induced VaD model in rats; *in vitro*: cultured endothelial cells treated with HG	*In vivo*: berberine 1.0 g/(kg·d) for 8 weeks (p.o.)	*In vivo*: improved short-term learning and memory and alleviated the impairment of spatial memory; increased posterior cerebral artery blood flow; suppressed hyperglycemia-induced ectopic expression of miR-133a in cerebral middle artery; upregulated GTPCH1 expression and BH4 in cerebral middle artery and serum NO; suppressed serum MDA. *In vitro*: suppressed HG-induced miR-133a expression; recovered BH4 levels and NO generation.	Berberine alleviates cognitive impairment in diabetic mice via improving endothelial NO generation and cerebral blood flow.	[44]
Li HY (2018)	DE-induced dementia	*In vivo*: DE in T2DM model mice (*db/db*)	Berberine 50 mg/(kg·d) for 10 weeks (p.o.)	Reduced cognitive impairment; promoted lipid metabolism (lowered body weight, reduced TAG, TC and LDL-C); decreased fasting glucose (better insulin tolerance); protected hippocampal neurons and synapses; inhibited hippocampal inflammation (NF-κB, TNF-α); reduced ER stress.	Berberine is protective against DE-induced dementia, possibly by reducing inflammation and ER stress.	[49]
Sandeep MS (2017)	Dysfunctional glucose metabolism in the brain associated with diabetes	*In vivo*: STZ-induced diabetic model in rats	Berberine (0.1%)-supplemented diet for 2 months	Restored body weight and improved blood and urine sugar levels; restored brain weight; restored GLUT1 and GLUT3 levels in the brain; restored insulin signaling molecules (IRS, phospho-PI3K and phospho-Akt1) in the brain.	Berberine modulates glucose metabolism in the brain, which may contribute to neuroprotection.	[50]
Chen Q (2017)	Cognitive dysfunction associated with diabetes	*In vivo*: STZ and high-sugar/high-fat diet-induced diabetic model in rats	Berberine 187.5 mg/(kg·d) (p.o.), compared to metformin (Met; 184 mg/[kg·d])	Berberine's effects in medial prefrontal cortex (mPFC) of diabetic model: did not change IR expression; suppressed upregulation of phosho-IRS; inhibited phospho-PI3K, phospho-Akt and phospho-GSK3β; suppressed NF-kB activation, and phospho-JNK, PKC, IL-18, IL-1β and TNF-α induction; upregulated GLUT3 and enhanced glucose-uptake in the brain; suppressed diabetes-induced APP and Aβ formation; suppressed diabetes-induced BACE-1 upregulation; ameliorated fear memory deficit in diabetic rats.	Berberine inhibits inflammation and APP and Aβ formation in mPFC, thereby preventing cognitive dysfunction, possibly via inhibition of PI3K/Akt/GSK3β pathway, JNK, NF-kB and PKC. Berberine is superior in brain protection than Met.	[51]
de Oliveira JS (2016)	Sporadic AD	*In vivo*: ICV-STZ-induced sporadic AD-like dementia model in rats	Berberine 50 or 100 mg/(kg·d) for 21 days (p.o.)	Berberine's effects in ICV-STZ-induced sporadic AD: ameliorated weight loss; inhibited spatial learning and memory deficits; suppressed anxiety; suppressed AChE-induction in the hippocampus and cerebral cortex; suppressed apoptosis induction in the hippocampus and cerebral cortex.	Berberine ameliorated learning/memory deficits and anxiety, possibly via suppression of AChE thereby enhancing cholinergic signaling.	[52]
Moghaddam HK (2014)	Brain damage associated with diabetes	*In vivo*: STZ-induced diabetic model in rats	Berberine 50 or 100 mg/(kg·d) for 8 weeks (p.o.)	Berberine's effects in STZ-induced diabetic model: alleviated weight loss and hyperglycemia; reduced lipid peroxidation and nitrite generation in the hippocampus; restored hippocampal SOD; suppressed astroglial activation in the hippocampus.	Berberine suppressed diabetes-induced reactive gliosis in the hippocampus possibly via suppression of oxidative stress.	[53]
Chatuphonprasert W (2014)	Oxidative stress in the brain	*In vivo*: STZ-induced diabetic model in mice	Berberine 100 mg/(kg·d) for 2 weeks (p.o.)	Reduced oxidative stress (MDA levels) in the brain; improved catalase activity in the brain.	Berberine may alleviate oxidative stress in the brain.	[43]
Moghaddam HK (2013)	Learning and memory impairments	*In vivo*: STZ-induced diabetes in rats	Berberine 50 and 100 mg/(kg·d) for 12 weeks (p.o.)	Berberine improved short-term plasticity in the dentate gyrus of hippocampus.	Berberine prevents diabetes-induced learning and memory defects by improving hippocampal plasticity.	[54]
Kalalian-Moghaddam H (2013)	Learning and memory impairments	*In vivo*: STZ-induced diabetes in rats	Berberine 100 mg/(kg·d) for 11 weeks (p.o.)	Restored hippocampal synaptic plasticity (LTP); ameliorated learning and memory impairment; attenuated apoptosis of hippocampal CA1 neurons.	Berberine prevents diabetes-induced learning and memory defects by improving hippocampal LTP via inhibiting neuronal death.	[55]
Hsu YY (2013)	Glucose-induced neurotoxicity	*In vitro*: HG-induced damage in neuronal cells (SH-SY5Y)	Berberine 1, 3 and 10 μmol/L	Inhibited HG-induced apoptosis of neurons; inhibited HG-induced ROS generation; increased Bcl-2; reduced HG-induced cytochrome c release; induced IGF-1 receptor; induced phosphorylation of Akt and GSK3β; induced nuclear factor erythroid 2 and heme oxygenase-1 expression; restored NGF levels.	Berberine protects neurons from HG-induced oxidative stress and death, possibly via IGF-1/Akt/GSK3β signaling, Nrf2 activation, and NGF induction.	[47]
Bhutada P (2011)	Memory dysfunction associated with diabetes	*In vivo*: STZ-induced diabetic model in rats	Berberine 25-100 mg/kg twice daily (50-200 mg/[kg·d]) for 30 d (p.o.)	Lowered blood glucose; reduced oxidative stress in the hippocampus and cortex; reduced AChE activity in the hippocampus and cortex; improved cognitive performance (spatial memory).	Berberine inhibits diabetes-induced oxidative stress and AChE induction, thereby preventing memory impairment.	[45]
Lu DY (2010)	Neuroinflammation	*In vitro*: microglia (BV-2)	Berberine 1, 3, 10 μmol/L, pretreatment for 30 min	Suppressed LPS-induced and IFN-γ-induced iNOS, COX-2, IL-6, TNF-α, and IL-1β upregulation; suppressed ERK phosphorylation; stimulated phosphorylation of AMPK signaling pathway. AMPK inhibitor (compound C) attenuated the effect of berberine.	Berberine inhibits neuroinflammation by suppressing microglial activation via activation of AMPK signaling.	[46]

Aβ: amyloid β; AChE: acetylcholinesterase; AD: Alzheimer's disease; AMPK: 5'-adenosine monophosphate-activated protein kinase; APP: amyloid precursor protein; BACE: β-site amyloid precursor protein-cleaving enzyme; BH4: tetrahydrobiopterin; *db/db*: leptin receptor-deficient; CA: calyculin A; COX-2: cyclooxygenase-2; DE: diabetic encephalopathy; ER: endoplasmic reticulum; ERK: extracellular signal-regulated kinase; GLUT: glucose transporter; GSK3β: glycogen synthase kinase 3 β; GTPCH1: GTP cyclohydrolase 1; HG: high glucose; ICV-STZ: intracerebroventricular injection of STZ; IFN: interferon; IGF-1: insulin-like growth factor-1; IL: interleukin;

iNOS: inducible nitric oxide synthase; IR: insulin receptor; IRS: insulin receptor substrate; JNK: c-Jun N-terminal kinase; LDL-C: low-density lipoprotein cholesterol; LPS: lipopolysaccharide; LTP: long-term potentiation; MDA: malonaldehyde; NF-κB: nuclear factor κB; NGF: nerve growth factoer; NO: nitric oxide; PI3K: phosphoinositide 3-kinase; PKC: protein kinase C; p.o.: per os; ROS: reactive oxygen species; SOD: superoxide dismutase; STZ: streptozotocin; T2DM: type 2 diabetes mellitus; TAG: triacylglycerol; TC: total cholesterol; TNF: tumor necrosis factor; VaD: vascular dementia.

Table 3. Research articles studying the use of berberine to treat pancreatic dysfunction of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Jiang YY (2017)	Pancreatic dysfunction	*In vivo*: STZ-induced diabetic model in rats; *in vitro*: islet cell line (Rin-5F)	*In vivo*: berberine 250 mg/(kg·d) for 8 weeks (p.o.); *in vitro*: berberine 100 μmol/L	*In vivo*: reduced FBG and GSP; alleviated insulin resistance; restored β-cell functions. *In vitro*: enhanced glucose-stimulated insulin release; did not inhibit fatty acid-induced apoptosis; induced PARP-1 expression.	Berberine is effective against diabetes via restoration of glucose-stimulated insulin release from β-cells.	[56]
Chandirasegaran G (2017)	Pancreatic dysfunction	*In vivo*: STZ-induced diabetic model in rats	Berberine 50 mg/(kg·d) for 45 d (p.o.)	Reduced blood glucose and HbA1c; restored plasma insulin and hemoglobin; suppressed lipid peroxidation and restored antioxidants; reduced pancreatic damage; reduced inflammatory mediators and increased anti-apoptotic and anti-inflammatory factors.	Berberine is anti-hyperglycemic and pancreas-protective possibly via antioxidative and anti-inflammatory activities.	[140]
Chen DL (2017)	Pancreatic dysfunction	*In vivo*: STZ-induced diabetic model in mice; *in vitro*: β cell line (NIT-1) exposed to HG	Berberine 5mg/(kg·d) for 3 weeks (i.p.)	*In vivo*: suppressed serum glucose, TC, TAG and MDA and restored insulin and SOD; suppressed miR-106b and restored SIRT1 in islets. *In vitro*: suppressed HG-induced MDA and restored insulin and SOD; suppressed HG-induced miR-106b and restored SIRT1.	Berberine restores insulin and suppresses hyperglycemia possibly via modulating miR-106b/SIRT1 pathway in pancreatic islets.	[141]
Liu L (2014)	HG-induced oxidative stress in pancreatic islets	*In vitro*: insulinoma cell line (INS-1E) and pancreatic islets isolated from rat and mouse	*In vitro*: berberine 5 μmol/L	Berberine's effects in INS-1E exposed to HG: restored antioxidant (SOD); attenuated nitrosative stress (nitrotyrosine); restored phospho-AMPK; restored UCP2 expression; reduced mitochondrial ROS via AMPK signaling and restoration of UCP2; restored glucose-stimulated insulin secretion via AMPK signaling and restoration of UCP2. Berberine's effects in isolated islets: restored phosho-AMPK in rats and mice; suppressed nitrosative stress via UCP2, and induced SOD in rats and db/db mice; restored insulin secretion via UCP2 in rats and db/db mice.	Berberine inhibited oxidative and nitrosative stress and restored insulin secretion in HG-exposed islets via activation of AMPK and UCP2.	[142]
Shen N (2012)	Pancreatic dysfunction	*In vitro*: mouse β-cell line (NIT-1) exposed to HG; *in vivo*: HFD-induced obesity in mice	*In vitro*: berberine 1 μmol/L; *in vivo*: berberine 50 mg/(kg·d) for 10 weeks (p.o.)	*In vitro*: suppressed HG-induced insulin gene expression in β-cells via AMPK activation. *In vivo*: improved insulin resistance and glucose tolerance; decreased insulin in pancreatic islets.	Berberine may prevent diabetes by inhibiting insulin expression in β-cells via AMPK activation.	[139]
Chueh WH (2012)	Pancreatic dysfunction	*In vitro*: STZ-treated primary pancreatic islet cells from mice	*In vitro*: berberine 1 and 3 μmol/L	Reduced cell death; pre-treatment can reduce the increase in *Bax/Bcl-2* gene expression ratio.	Berberine may protect pancreatic islets via decreasing *Bax/Bcl-2* ratio thereby inhibiting apoptosis.	[138]
Chueh WH (2011)	Pancreatic dysfunction	*In vivo*: nonobese diabetic model in mice	Berberine 50, 150, and 500 mg/(kg·d) for 14 weeks (p.o.)	Restored pancreatic islets and serum insulin levels.	Berberine protects pancreatic islets.	[137]

ADP: adenosine diphosphate; AMPK: 5'-adenosine monophosphate-activated protein kinase; FBG: fasting blood glucose; GSP: glycated serum protein; HbA1c: glycosylated hemoglobin A1c; HFD: high-fat diet; HG: high glucose; i.p.: intraperitoneal injection; MDA: malonaldehyde; PARP-1: ADP-ribose polymerase; p.o.: per os; ROS: reactive oxygen species; SIRT1: sirtuin 1; SOD: superoxide dismutase; STZ: streptozotocin; TAG: triacylglycerol; TC: total cholesterol; UCP: uncoupling protein.

Table 4. Research articles studying the use of berberine to treat vascular and adipose tissue dysfunction of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Hirai T (2019)	Obesity & BAT	*In vitro*: adipocytes (C3H10T1/2), primary white, brown, and beige adipocytes from mice *In vivo*: HFD-induced obesity in mice	*In vitro*: berberine 3 and 10 μmol/L *In vivo*: berberine 10 mg/(kg·d) for 2 weeks (i.p.)	*In vitro*: induced FGF21 expression in brown adipocytes; induced Bmal1 expression in brown and beige adipocytes; enhanced AMPK phosphorylation. *In vivo*: restored *Fgf21* mRNA expression in BAT, which was reduced by HFD; reduced body weight under HFD.	Berberine may induce adipocyte browning by inducing FGF21 via AMPK signaling and modulate Bmal1 (molecular clock), which may contribute to high energy consumption in BAT, thereby suppressing HFD-induced obesity.	[136]
Pei C (2019)	Atherosclerosis	Clinical: patients undergoing PCI for ACS (n45); *in vitro*: ox-LDL-induced macrophage activation	Clinical: berberine-treatment group, berberine 300 mg, 3 times a day, in addition to standard therapy, for 3 months; control group, standard therapy (clopidogrel, aspirin and rosuvastatin); *in vitro*: berberine 25 μmol/L	Clinical: no significant difference between berberine plus standard therapy and standard therapy alone in plasma Gal-3, serum lipids and inflammatory markers. *In vitro*, berberine's effects on ox-LDL-induced responses in macrophages: suppressed Gal-3 expression (overexpression of Gal-3 intervened the inhibitory effect of berberine on macrophage activation), inflammatory cytokines (IL-6, TNF-α and IL-1β), and $CD86^{+}/CD11b^{+}$ cells (%); induced AMPK phosphorylation and inhibited ox-LDL-induced p65 phosphorylation (AMPK inhibitor [compound C] abolished the effects of berberine).	Clinical: berberine has no additional benefit to standard therapy. *In vitro*: berberine alone alleviates ox-LDL-induced inflammatory responses via Gal-3 down-regulation, AMPK activation and NF-κB inhibition in macrophages.	[135]
Paul M (2019)	Platelet hyperreactivity	*In vitro*: human platelets thrombin- and collagen-induced aggregation model, exposed to HG	Berberine 25 and 50 μmol/L	Inhibited HG-potentiated platelet aggregation; inhibited mitochondrial membrane potential depolarization, ROS generation in HG-treated platelets, cardiolipin peroxidation, and restored cell viability; inhibited HG-induced ERK, pI3K, p38 and p53 phosphorylation, cytochrome *c* release, MPTP, and caspase-3 activation; inhibited glutathione reductase, aldose reductase and NOX; inhibited thrombin-induced ATP release.	Berberine attenuates HG-primed platelet aggregation, possibly via attenuation of ROS-mediated p38-p53 activation and platelet apoptosis.	[134]
Hang W (2018)	Cardiomyocyte hypertrophy	*In vitro*: HG-induced hyperglycemia and cardiomyocyte hypertrophy model in H9C2 cell line	Berberine 100 nmol/L	Attenuated HG-induced hypertrophy; protected mitochondria from HG-induced dysfunction (reduced ATP generation and MMP disruption); restored balance of mitochondrial fission/fusion; restored PGC-1α expression, mitogenesis and mitochondrial content; suppressed HG-induced mitophagy and mTOR activity; restored LC3 and Beclin 1 expression and phospho-AMPK.	Berberine ameliorates HG-induced cardiomyocyte injury via restoring AMPK signaling, mitochondrial function and autophagy.	[132]
Hu M (2018)	HFD-induced metabolic dysfunction.	*In vivo*: HFD-induced metabolic dysfunction in mice	Berberine 100, 200, and 300 mg/kg for 8 weeks (p.o.)	Reduced body weight and blood glucose and enhanced glucose tolerance; inhibited adipose tissue fibrosis and ECM secretion in eWAT; suppressed HIF-1α and LOX expression and inhibited adipocyte apoptosis in eWAT.	Berberine alleviates WAT fibrosis via suppression of LOX induction.	[131]
Shi Y (2018)	Atherosclerosis (associated with gut dysbiosis)	*In vivo*: atherosclerosis model mice ($ApoE^{-/-}$ mice fed with high fat diet HFD)	Berberine 50 mg/kg for 12 weeks (p.o.); cohousing with berberine-treated mice	Berberine and cohousing: attenuated HFD-induced atherosclerosis; reduced HFD-induced inflammatory response.	Berberine is anti-atherosclerotic (possibly via altered gut microbiota compositions).	[130]
Li G (2018)	Diabetic cardiac fibrosis	*In vivo*: STZ and HFD-induced type 2 diabetic model in rats; *in vitro*: cardiac fibroblasts exposed to HG	*In vivo*: berberine 200 mg/(kg·d) for 4 weeks (p.o.); *in vitro*: berberine 50 μmol/L	*In vivo*: ameliorated hyperglycemia and hyperlipidemia and improved glucose tolerance; attenuated cardiac fibrosis and dysfunction; reduced cardiac IGF-1 receptor expression, as well as α-SMA, TGF-β, FN and collagen type I expression. *In vitro*: inhibited HG-induced hyperproliferation, expression of α-SMA and collagen type I; reduced expression levels of MMP-2/9/14, and IGF-1R and phospho-ERK1/2 levels.	Long-term berberine treatment ameliorates cardiac fibrosis by downregulating IGF-1R expression, and MMPs, α-SMA and collagen type I in diabetic heart.	[129]
Wang L (2018)	Insulin resistance associated with obesity	*In vivo*: HFD-induced insulin resistance in mice; *in vitro*: SVF	*In vivo*: berberine 75 and 150 mg/(kg·d) for 4 weeks (p.o.); *in vitro*: berberine 10 μmol/L	*In vivo*: reduced serum insulin, FA and fat mass, and alleviated HFD-induced insulin resistance and glucose intolerance; suppressed HFD-induced expression of fibrogenic genes and MMP-9 and TIMP-1 proteins, and alleviated ECM abnormality; recovered phospho-AMPK and phospho-ACC and downregulated TGF-β1 and phospho-Smad3 in adipose tissue; suppressed HFD-induced increase in M1 (inflammatory) macrophages in adipose tissue. *In vitro*: inhibited TGF-β1-induced phospho-Smad3; inhibited TGF-β1-induced expression of fibrogenic genes; inhibited TGF-β1 signaling only partly via phospho-AMPK.	Berberine inhibits aberrant ECM deposition, macrophage infiltration and M1 polarization in adipose tissue, possibly via inducing phospho-AMPK and inhibiting TGF-β1/Smad3 signaling.	[128]

Zhu L (2018)	Atherosclerosis	HFD-induced atherosclerosis model in ApoE$^{-/-}$ mice	Berberine in drinking water (0.5 g/L) for 14 weeks	Alleviated atherosclerosis; suppressed hypercholesterolemia and systemic inflammation; prevented inflammation in the arterial tissues.	Berberine alleviates atherosclerosis via inhibiting inflammation in the arterial tissues.	[74]
Chang W (2017)	Heart diseases	*In vitro*: cardiac myocytes (H9c2)	Berberine 6.25–25 μmol/L	Inhibited oxygen consumption and DNA synthesis; reduced cardiolipin synthesis from oleic acid and increased cardiolipin synthesis from palmitic acid; inhibited PKCδ activation.	Berberine inhibits the growth of cardiomyocytes and oxygen consumption and altered cardiolipin metabolism, possibly via PKCδ inhibition.	[127]
Ma YG (2017)	Hypertension	*In vivo*: STZ-induced diabetic model in rats	Berberine 100 and 200 mg/(kg·d) for 8 weeks (p.o.)	Ameliorated hyperglycemia and hypertension; improved endothelium-dependent/independent relaxation in middle cerebral arteries in diabetes; restored the large-conductance Ca^{2+}-activated K^+ channel activity and β1 subunit expression.	Berberine helps control hyperglycemia and hypertension in diabetes, possibly via restoring ion channel activities	[126]
Li H (2016)	Atherosclerotic plaque instability	*In vivo*: HHCY model, ApoE$^{-/-}$ mice fed with HTL; *ex vivo*: HTL-exposure of organ culture of aortic ring isolated from the descending aorta of mice; *in vitro*: HUVECs exposed to HTL	*In vivo*: berberine 1.0 g/(kg·d) for 4 or 8 weeks (p.o.); *ex vivo*: berberine 10, 50, 100 μmol/L; *in vitro*: berberine 10, 50, 100 μmol/L	*In vivo*: berberine (4 weeks) enhanced the stability of atherosclerotic plaque and berberine (8 weeks) reduced restored NO and suppressed MDA levels in the blood; berberine (8 weeks) restored endothelial function. *Ex vivo*: restored endothelial function (ACh-induced vascular relaxation) via PPARγ; restored SOD activity and suppressed MDA levels via PPARγ. *In vitro*: berberine restored cell viability and reduced ROS, which were dependent on PPARγ.	Berberine enhances atherosclerotic plaque stability in hyperhomocysteinemia, via PPARγ activation and subsequent suppression of oxidative stress and endothelial dysfunction.	[125]
Suman RK (2016)	Diabetic cardiomyopathy	STZ and Isoproterenol-induced diabetes co-existing with myocardial infarction in rats	Berberine (100 mg/[kg·d]) for 30 d (p.o.)	Restored body weight and improved blood glucose, HbA1c, TC, TAG, HDL-C, and LDL-C; protected myocardium, as well as other tissues (pancreas, liver, and kidney).	Berberine produces myocardial salvaging effects in diabetes.	[124]
Ma YG (2016)	Vascular dysfunction	*In vivo*: HFD and STZ-induced diabetic model in rats; *in vitro*: cerebral VSMCs	Berberine 100 mg/(kg·d) for 8 weeks (p.o.)	*In vivo* & *in vitro*: restored body weight, and reduced blood glucose and insulin; inhibited the contractile response of VSMCs; inhibited L-type Ca^{2+} channel current.	Berberine alleviates the cerebral arterial contractility induced by diabetes via regulating intracellular Ca^{2+} levels in smooth muscle cells.	[123]
Geng FH (2016)	Vascular insulin sensitivity associated with diabetes	*In vivo*: STZ and HFD-induced diabetic model in rats; *ex vivo*: mesenteric artery rings isolated from control and diabetic mice; *in vitro*: human artery endothelial cell line (EA.hy926), exposed to HG and palmitate	*In vivo*: berberine 200 mg/(kg·d) for 4 weeks (p.o.); *ex vivo*: berberine 200 mg/(kg·d) for 4 weeks (p.o.) or berberine 10 μmol/L; *in vitro*: berberine 50 μmol/L	*In vivo*: improved glucose tolerance. *Ex vivo*: improved ACh-induced vasodilation, which was inhibited by PI3K/Akt inhibitor (wortmannin). Berberine + insulin directly alleviated vascular dysfunction of mesenteric artery rings isolated from diabetic rats. *In vitro*: increased cell viability and autophagy in HG/HF-treated endothelial cells; upregulated phosphorylation of AMPK, Akt and eNOS, which was blunted in IR knock-down.	Berberine improves vascular functions by protecting endothelial cells from HG/HF-induced stress via AMPK and Akt signaling, which were mediated by IR signaling.	[121]
Chang W (2016a)	Ischemia-reperfusion injury in T2DM	*In vivo*: ischemia-reperfusion in STZ and HFD-induced diabetic model in rat.	Berberine 100 mg/(kg·d) for 7 d before heart perfusion	Berberine pretreatment: reduced TAG, TC and MDA, but did not alter blood glucose and SOD levels; reduced arrhythmias; increased the ratio of AMP/ATP and ADP/ATP; increased AMPK activity, as well as phospho-Akt and phospho-GSK3β.	Berberine is cardioprotective via activation of AMPK and Akt and inactivation of GSK3β.	[120]
Chang W (2016b)	Insulin resistance of cardiomyocytes	*In vitro*: Palmitate-mediated insulin resistance model in cardiomyocytes (H9c2).	Berberine 12.5 μmol/L	Restored glucose uptake and GLUT4 expression in the presence of palmitate; restored the level of phospho-Akt in the presence of palmitate; enhanced TAG accumulation but inhibited palmitate-induced DAG accumulation in the presence of palmitate; enhanced palmitate-induced glucose incorporation into TAG and inhibited palmitate-induced glucose incorporation into DAG and cholesterol.	Berberine attenuates palmitate-induced reduction of glucose uptake, in part via reduction of DAG and accumulation of TAG.	[119]
Zhang J (2015)	Obesity (adipogenesis)	*In vitro*: Adipocyte differentiation model (3T3-L1 cell line)	Berberine 5 μmol/L	Suppressed the expression of adipogenic genes and induced phospho-AMPK; suppressed CREB activation, CCAAT/enhancer-binding protein β (C/EBP-β) expression and CRE activity.	Berberine inhibits adipogenesis via suppressing CRE activity.	[118]
Choi JS (2014)	Obesity (adipogenesis)	*In vitro*: Adipocyte differentiation model (3T3-L1)	Berberine 12.5, 25 and 50 μmol/L	Reduced lipid accumulation; reduced C/EBP-α expression.	Berberine inhibits lipid accumulation in adipocytes possibly via suppressing CRE activity.	[117]
Chen K (2014)	Cardiomyopathy	*In vivo*: myocardial I/R injury in STZ and HFD-induced diabetic model in rats *In vitro*: Primary neonatal rat cardiomyocytes in culture	*In vivo*: berberine 100, 200 and 400 mg/(kg·d) for 4 weeks (p.o.) before I/R *In vitro*: Berberine 50 μmol/L	*In vivo*: enhanced the recovery of cardiac systolic/diastolic function; reduced myocardial apoptosis. *In vitro*: reduced hypoxia/reoxygenation-induced myocardial apoptosis; enhanced AMPK activity, PI3K-Akt activation and eNOS phosphorylation. Pretreatment with PI3K-Akt inhibitor (wortmannin) or AMPK inhibitor (compound C) blunted the anti-apoptotic effect of berberine.	Berberine exerts anti-apoptotic effect and improves cardiac functional recovery after myocardial I/R via AMPK and PI3K-Akt-eNOS signaling.	[116]
Zhang M (2013)	Endothelial dysfunction	*In vitro*: Endothelial cell line (HUVECs) exposed to palmitate	Berberine 5 μmol/L	Suppressed NO and ROS production; restored eNOS levels and suppressed NOX4 induction.	Berberine ameliorates palmitate-induced endothelial dysfunction via upregulation of eNOS and downregulation of NOX4.	[114]
Wang M (2013)	Diabetic cardiomyopathy	*In vitro*: HGI-induced cardiomyocyte hypertrophy.	Berberine 3 μmol/L	Berberine suppressed HGI-induced cardiomyocyte hypertrophy, which was reversed in the presence of PPARα inhibitor; HGI	Berberine can ameliorate HGI-induced cardiomyocyte hypertrophy via PPARα/NO	[115]

	(diabetic cardiac hypertrophy)			inhibited PPARα expression, which was restored by berberine; HGI inhibited NOS activity and NO levels, which was restored by berberine.	signaling.	
Wang LH (2012)	Ischemic arrhythmias	*In vivo*: STZ-induced diabetic model in rats	Berberine 100 mg/(kg·d) (p.o.) for 7 days before ischemia	Suppressed ischemia-induced arrhythmias in diabetic rats; suppressed abnormal prolongation of corrected QT interval; restored transient outward K^+ current and L-type Ca^{2+} current.	Berberine is protective against cardiac arrhythmias via restoring ion currents.	[113]
Li GS (2011)	Diabetic lipotoxicity (visceral WAT insulin resistance)	*In vivo*: HFD and STZ-induced type 2 diabetic model in hamsters	Berberine 150 mg/(kg·d) for 9 weeks (p.o.)	Reduced visceral WAT weight; restored the expression of LXRs and PPARs; suppressed SREBP induction.	Berberine improved visceral white adipose insulin resistance possibly via modulation of SREBPs, LXRs, and PPARs.	[112]
Wang LH (2011)	Diabetic myocardial infarction	*In vivo*: HFD and STZ-induced type 2 diabetic model with/without experimental myocardial infarction in rats	Berberine 180 mg/(kg·d) for 14 d (p.o.)	Suppressed arrhythmia; improved the resting membrane potential and current density; restored Kir2.1 (inward-rectifier K^+ channel) expression in isolated ventricular myocytes.	Berberine suppresses arrhythmia in diabetes via restoration of K^+ channel expression.	[110]

ACC: acetyl-CoA carboxylase; ACh: acetylcholine; ACS: acute coronary syndrome; ADP: adenosine diphosphate; AMP: adenosine monophosphate; AMPK: 5'-adenosine monophosphate-activated protein kinase; ATP: adenosine triphosphate; BAT: brown adipose tissue; CRE: cAMP-response element; CREB: cAMP-response element-binding protein; DAG: diacylglycerol; ECM: extracellular matrix; eNOS: endothelial nitric oxide synthase; ERK: extracellular signal-regulated kinase; eWAT: epididymal white adipose tissue; FA: folic acid; FGF21: fibroblast growth factor 21; FN: fibronectin; GLUT: glucose transporter; GSK3β: glycogen synthase kinase 3 β; HbA1c: glycosylated hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HF: high fat; HFD: high-fat diet; HG: high glucose; HGI: HG and insulin; HHCY: hyperhomocysteinemia; HIF-1α: hypoxia-inducible factor 1α; HTL: homocysteine thiolactone; HUVEC: human umbilical vein endothelial cells; IGF-1: insulin-like growth factor-1; IL: interleukin; i.p.: intraperitoneal injection; I/R: ischemia/reperfusion; IR: insulin receptor; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; LOX: lipoxygenase; LXR: liver X receptor; MDA: malonaldehyde; MMP: matrix metallopeptidase; MPTP: mitochondrial permeable transition pore; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor κB; NO: nitric oxide; NOX: nicotinamide adenine dinucleotide phosphate oxidase; PCI: percutaneous coronary intervention; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-α; PI3K: phosphoinositide 3-kinase; PKCδ: protein kinase Cδ; p.o.: per os; PPAR: peroxisome proliferator-activated receptor; ROS: reactive oxygen species; SMA: smooth muscle actin; SOD: superoxide dismutase; SREBP: sterol regulatory element-binding protein; STZ: streptozotocin; SVF: stromal vascular fraction; T2DM: type 2 diabetes mellitus; TAG: triacylglycerol; TC: total cholesterol; TGF-β: transforming growth factor-β; TIMP: tissue inhibitor of the matrix metalloproteinase; TNF: tumor necrosis factor; VSMC: vascular smooth muscle cells; WAT: white adipose tissue.

Table 5. Research articles studying the use of berberine to treat liver dysfunction of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Zhang B (2018)	T2DM	*In vitro*: primary hepatocytes; *in vivo*: mice	*In vitro*: berberine 5 and 10 μmol/L; *in vivo*: berberine 150 mg/kg for 7 d (p.o.)	*In vitro*: reduced mitochondrial membrane potential; reduced SIRT3 expression; inhibited oxygen consumption rate (complex I activity) in WT cells, but not in $Sirt3^{-/-}$ cells; enhanced glucose uptake and glycolysis and inhibited glucagon-induced gluconeogenesis; increased AMP and decreased cAMP as effectively as nicotinamide (SIRT3 inhibitor) in WT cells, but not in $Sirt3^{-/-}$; suppressed glucagon-induced PKA phosphorylation. *In vivo*: enhanced glucose and pyruvate tolerance; inhibited glucagon-induced glucose generation.	Berberine promotes glucose uptake and inhibits gluconeogenesis via SIRT3 inhibition.	[109]
Liu D (2018)	Fatty liver disease	*In vivo*: HFD-induced obesity model in rats	Berberine 200 mg/(kg·d) for 8 weeks (p.o.)	Reduced FBG, FINS, TAG and LDL-C; reduced lobular inflammation; inhibited HFD-induced liver damage, reduced TLR4 and TNF-α, and induced insulin IR (IRc), and IR substrate (IRS)-1 in the liver.	Berberine may reduce insulin resistance via inhibiting LPS/TLR4/TNF-α signaling in the liver.	[108]
Chandirasegaran G (2018)	Liver dysfunctions associated with diabetes	*In vivo*: STZ-induced diabetic model in rats	Berberine 50 mg/(kg·d) for 45 d (p.o.)	Restored liver glycogen; ameliorated upregulation of hepatic markers; suppressed abnormality in carbohydrate metabolism; reduced lipid peroxidation and restored antioxidant levels; suppressed inflammatory response in the liver and reduced liver damage; restored Bcl2 and suppressed Bax.	Berberine protects the liver from hyperglycemia-induced imbalance in antioxidants and carbohydrate metabolism, inflammation and apoptosis.	[107]
Sun Y (2018)	Hepatic steatosis	*In vivo*: HFHS diet-induced hepatic steatosis in mice	Berberine 5 mg/(kg·d) (i.p.) for 5 weeks	Reduced liver triglyceride; induced autophagy in the liver; induced FGF21; increased oxygen consumption, energy expenditure and the expression of brown-like genes (*UCP1*, *DIO2*, *PRDM16*) in the liver.	Berberine regulates lipid utilization and energy metabolism in the liver via autophagy, FGF21 signaling activation, and brown-like gene induction.	[106]
Wei S (2016)	Hyperglycemia and hyperlipidemia	*In vivo*: STZ and HFD-induced diabetic model in mice; *in vitro*: HepG2 cells exposed to palmitate	*In vivo*: berberine 160 mg/(kg·d) for 4 weeks (p.o.); *in vitro*: berberine 10 μmol/L	*In vivo*: lowered FBG and restored FINS; improved glucose tolerance; reduced TC and TAG; increased HDL-C; reduced alanine aminotransferase and aspartate aminotransferase levels; suppressed liver pathology; suppressed gluconeogenesis and lipogenesis. *In vitro* effects on HepG2: inhibited palmitate-induced HNF-4α expression; inhibited palmitate-induced gluconeogenesis and lipogenesis.	Berberine attenuates hepatic gluconeogenesis and lipogenesis in diabetes via HNF-4α signaling inhibition.	[105]
Li F (2016)	Insulin resistance of hepatocytes	*In vitro*: insulin resistance model in HepG2 cells	Berberine 10 μmol/L	Enhanced glucose up-take; inhibited AChE and restored α7nAChR expression; inhibited NF-κB activation and reduced IL-6 levels.	Berberine enhances glucose uptake and relieves insulin resistance and inflammation in the liver, possibly via inhibition of AChE.	[104]
Zhang Y (2015)	NAFLD	*In vivo*: HFD-induced NAFLD model in rats	Berberine 200 mg/(kg·d) for 16 weeks (p.o.)	Suppressed HFD-induced body weight gain, as well as visceral fat and liver weight increase; restored L-type pyruvate kinase (L-PK) mRNA expression and activity in the liver; suppressed HFD-induced hypermethylation of L-PK promoter, and restored histone acetylation around L-PK.	Berberine may alleviate NAFLD by improving glycolysis in the liver through restoration of L-PK expression.	[103]
Jiang SJ (2015)	Liver dysfunction in diabetes	*In vivo*: STZ and HFD-induced diabetic model in rats	Berberine 156 mg/(kg·d) for 12 weeks (p.o.)	Improved glucose tolerance, decreased plasma hyperlipidemia, and reduced fasting plasma insulin and insulin resistance; restored AMPK and phospho-AMPK levels, and its upstream LKB1 in the liver; upregulated cytoplasmic phospho-TORC2 (inhibition of TORC2 nuclear localization) in the liver; downregulated the expression of gluconeogenic enzymes in the liver.	Berberine inhibits hepatic gluconeogenesis via LKB1-AMPK-TORC2 signaling	[102]
Chatuphonprasert W (2014)	Liver dysfunction in diabetes	*In vivo*: STZ-induced diabetic model in mice	Berberine 100 mg/(kg·d) for 2 weeks (p.o.)	Reduced FBG; restored hepatic CuZn-SOD; reduced oxidative stress (MDA levels) in the liver; improved catalase activity in the liver.	Berberine may alleviate oxidative stress in the liver.	[43]
Teodoro JS (2013)	Hepatic dysfunction in obesity	*In vivo*: HFD-induced obesity model in rats	Berberine 100 mg/(kg·d) for 4 weeks (p.o.)	Reduced HFD-induced weight gain and HFD-induced insulin, and enhanced oral glucose tolerance; increased unsaturated fatty acids in the liver; protected hepatic mitochondria from HFD-induced dysfunctions (membrane potential, oxidative phosphorylation and ATP generation).	Berberine protects liver mitochondria from HFD-induced dysfunctions.	[101]
Lao-ong T (2012)	Oxidative stress in the liver	*In vivo*: STZ-induced diabetic model in mice	Berberine 200 mg/(kg·d) for 2 weeks (p.o.)	Inhibited STZ-induced downregulation of CuZn-SOD and Mn-SOD in the liver; suppressed STZ-induced upregulation of GPx; restored GSH and GSSG contents to normal levels.	Berberine alleviates oxidative stress in the liver.	[99]
Xie X (2011)	Liver glycogen reduction in diabetes	*In vivo*: alloxan-induced diabetic model in mice	Berberine 300 mg/(kg·d) for 12 weeks (p.o.)	Reduced FBG; restored liver glycogen; restored Akt phosphorylation and GSK3β phosphorylation; restored glucokinase activity and IRS phosphorylation in the liver.	Berberine ameliorates hyperglycemia and restores liver glycogen via restoration of glucokinase activity, Akt signaling and GSK3β inactivation.	[98]
Zhou JY (2011)	Liver dysfunction	*In vivo*: STZ-induced diabetic model in rats (hyperlipidemia induced by HFD)	Berberine 150 and 300 mg/(kg·d) for 16 weeks (p.o.)	Restored catalase, SOD, GPx and GSH in the serum and the liver; reduced MDA in the serum and the liver; restored cyclin-dependent kinase 9 and cyclin T1 expression in the liver.	Berberine protects the liver by inducing antioxidants via upregulation of P-TEFb.	[97]
Liu X (2010)	Hepatic insulin	*In vivo*: HFD and STZ-	Berberine 150	Improved oral glucose tolerance; alleviated liver weight increase; reduced blood	Berberine protects the liver via modulating metabolic	[95]

resistance	induced T2DM model in hamster	mg/(kg·d) for 9 weeks (p.o.)	glucose, serum insulin, TC, TAG, FFA, and LDL-C; reduced the expression of SREBPs and target genes and restored the expression of LXRα and PPARα, as well as their target genes in the liver.	regulators such as LXRα, SREBPs, and PPARα in the liver, thereby improving hepatic glucose utilization and lipid metabolism.

AChE: acetylcholinesterase; AChR: acetylcholinesterase receptor; AMPK: 5'-adenosine monophosphate-activated protein kinase; FBG: fasting blood glucose; FFA: free fatty acid; FGF21: fibroblast growth factor 21; FINS: fasting insulin; GPx: glutathione peroxidase; GSH: reduced glutathione; GSK3β: glycogen synthase kinase 3 β; GSSG: oxidized glutathione; HDL-C: high-density lipoprotein cholesterol; HFD: high-fat diet; HFHS: high fat and high sucrose; HNF-4α: hepatocyte nuclear factor 4α; IL: interleukin; i.p.: intraperitoneal injection; IR: insulin receptor; IRS: insulin receptor substrate; LDL-C: low-density lipoprotein cholesterol; LKB1: liver kinase B1; LPS: lipopolysaccharide; LXR: liver X receptor; MDA: malonaldehyde; NAFLD: non-alcoholic fatty liver disease; NF-κB: nuclear factor κB; P-TEFb: positive transcription elongation factor b; PKA: protein kinase A; p.o.: per os; PPAR: peroxisome proliferator-activated receptor; SIRT: sirtuin; SOD: superoxide dismutase; SREBP: sterol regulatory element-binding protein; STZ: streptozotocin; T2DM: type 2 diabetes mellitus; TAG: triacylglycerol; TC: total cholesterol; TLR-4: toll-like receptor 4; TNF-α: tumor necrosis factor-α; TORC2: target of rapamycin complex-2; WT: wildtype.

Table 6. Research articles studying the use of berberine to treat kidney dysfunction of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Zhu L (2018)	Diabetic nephropathy (podocytes damage)	*In vivo*: STZ-induced diabetic nephropathy model in rats; *in vitro*: HG-induced diabetic nephropathy model in podocytes	*In vivo*: berberine 100, or 200 mg/(kg·d) (p.o.); *in vitro*: Berberine 30 or 90 μmol/L	*In vivo*, berberine's effects in DN model: ameliorated renal injury in the DN model; ameliorated inflammation in the blood and renal cortex; inhibited TLR4/NF-κB pathway. *In vitro*: berberine's effects in HG-induced DN model: suppressed podocyte apoptosis; suppressed inflammation in podocytes; reduced HG-induced upregulation of TLR4 and inhibited NF-κB signaling.	Berberine ameliorates DN, relieving STZ-induced renal injury, inflammatory response and HG-induced podocyte apoptosis, partly via TLR4/NK-κB inhibition.	[96]
Wang YY (2018)	Diabetic nephropathy (GMC-induced podocytes damage)	*In vitro*: HG-induced injury model in rat GMCs and podocytes	Berberine treatment (50 and 100 μmol/L) of GMCs	Suppressed HG-induced proliferation of GMCs; suppressed GMC-derived exosome-induced injury in podocytes; suppressed GMC-derived exosome-induced PI3K activation, Akt phosphorylation, p65 phosphorylation, and TGFβR induction (TGF-β1/PI3K-Akt pathway).	Berberine protects the function of podocytes via inhibition of TGF-β signaling from GMCs.	[94]
Li Z (2017)	Diabetic nephropathy (glomerular hypertrophy)	*In vivo*: STZ-induced diabetic nephropathy model in rats	Berberine 400 mg/(kg·d) for 12 weeks.	Alleviated glomerular hypertrophy and mesangial matrix expansion; suppressed TGF-β, α-SMA, vimentin and NF-κB in the kidneys.	Berberine inhibits renal fibrosis associated with diabetes via suppression of TGF-β and NF-κB signaling.	[93]
Jin Y (2017)	Diabetic nephropathy (podocytes damage)	*In vitro*: HG-induced podocyte (MPC5) injury model	*In vitro*: berberine 2.5 and 5 μmol/L	Enhanced podocyte survival under HG; protected podocytes from HG-induced apoptosis via autophagy induction; induced AMPK activation; enhanced autophagy in podocytes under HG via AMPK.	Berberine enhances autophagy and protects podocytes from HG-induced injury via AMPK activation.	[92]
Zhang X (2016)	Renal fibrosis	*In vivo*: renal fibrosis in STZ-induced diabetic model in mice; *in vitro*: HG-induced EMT	*In vivo*: berberine 200 mg/(kg·d) for 12 weeks. (p.o.); *in vitro*: normal rat kidney tubular epithelial cells (NRK 52E) exposed to HG	*In vivo*: reduced FBG, kidney weight/body weight ratio, SCr, BUN and albuminuria; suppressed fibrosis by inhibiting EMT (α-SMA and collagen-1 expression); enhanced Nrf2/HO-1 signaling. *In vitro*: suppressed HG-induced EMT; enhanced HO-1 and NQO1 expression via Nrf2 signaling; suppressed HG-induced TGF-β/Smad signaling.	Berberine inhibits diabetic kidney fibrosis via inhibition of EMT through enhancement of Nrf2 signaling and inhibition of TGF-β/Smad signaling.	[91]
Ni WJ (2016)	Diabetic nephropathy	*In vivo*: STZ and HF/HG diet-induced diabetic model in rats; *in vitro*: GMCs exposed to HG	Berberine 100 mg/(kg·d) for 8 weeks (p.o.)	*In vivo*, berberine's effects in diabetic model: reduced blood glucose, kidney/body weight ratio, urine total protein and creatinine ratio (UTP/C), BUN, SCr; ameliorated renal pathology; reduced PGE2 and EP1 expression. *In vitro*, berberine's effects in HG-exposed GMCs: reduced PGE2-EP1 signaling; suppressed GMCs proliferation.	Berberine is renoprotective, possibly via inhibition of PGE2-EP1-Ca^{2+} signaling in GMCs.	[90]
Tang LQ (2016)	Diabetic nephropathy (ECM accumulation)	*In vivo*: STZ and HF/HG diet-induced diabetic nephropathy model in rats	Berberine 100 and 200 mg/(kg·d) for 8 weeks (p.o.)	Berberine ameliorated renal pathology; berberine restored β-arrestin 1 and β-arrestin 2 and suppressed ICAM-1 and VCAM-1 in diabetic kidneys.	Berberine inhibits ECM accumulation in the kidneys, possibly via restoration of β-arrestin levels.	[88]
Ni WJ (2015)	Diabetic nephropathy (kidney fibrosis)	*In vivo*: STZ-induced diabetic nephropathy model in rats	Berberine 100 and 200 mg/(kg·d) for 8 weeks (p.o.)	Berberine's effects in diabetic nephropathy: lowered FBG, BUN and SCr, and suppressed albuminuria and kidney weight increase; suppressed type IV collagen and FN expression in the kidney; restored the expression of MMP-2 and attenuated the induction of MMP-9, TIMP-2 and TMIP-9 in the kidney; suppressed TGF-β expression in the kidney.	Berberine protects the kidney, possibly via suppressing MMP/TIMP system-induced kidney fibrosis.	[87]
Sun SF (2015)	Diabetic nephropathy (renal inflammation)	*In vivo*: STZ and HFD-induced diabetic model in rats	Berberine 25 mg/(kg·d) for 20 weeks (p.o.)	Reduced blood glucose and lipids (TC, TAG and LDL-C) and albuminuria; attenuated kidney injury; inactivated NF-κB signaling and inhibited renal inflammation; inactivated TGF-β/Smad3 signaling and suppressed renal fibrosis.	Berberine inhibits kidney dysfunction via suppression of renal inflammation and fibrosis via inactivation of NF-κB and TGF-β signaling in the kidneys.	[86]
Yang Y (2014)	Diabetic nephropathy	*In vivo*: HG/HF diet and STZ-induced diabetic model in rats	Berberine 100 and 200 mg/(kg·d) for 8 weeks (p.o.)	Suppressed increase in kidney weight/body weight ratio; suppressed increase in albuminuria, BUN and SCr; restored production of EP4 and G protein Gs α subunit (Gαs) and cAMP levels in renal cortex; ameliorated renal injury and delayed glomerular fibrosis.	Berberine restores renal functional parameters in diabetes possibly via restoring EP4-Gαs-cAMP signaling pathway.	[85]
Lan T (2014)	Mesangial cell proliferation and hypertrophy	*In vitro*: hypertrophy and HF-induced proliferation and hypertrophy of mesangial cells from rat kidneys	Berberine 30 μmol/L	Attenuated HG-induced mesangial cell proliferation and hypertrophy; inhibited HF-induced cell cycle progression (S phase); restored HG-induced suppression of cyclin-dependent kinase inhibitors p21 and p27; suppressed HG-induced TGF-β1 and FN expression; suppressed HG-induced NF-κB and AP-1 activation and c-jun phosphorylation.	Berberine attenuates HG-induced TGF-β expression, cell cycle progression, mesangial cell proliferation and hypertrophy possibly via inhibition of HG-induced NF-κB and AP-1 activation.	[84]

Tang LQ (2014)	Diabetic nephropathy	*In vivo*: HFD and STZ-induced diabetic model in rats	Berberine 100 and 200 mg/(kg·d) for 8 weeks (p.o.)	Attenuated renal damage, hyperglycemia and hyperlipidemia; reduced IL-6 and PGE_2 levels in renal cortex; restored the expression levels of prostaglandin receptors (EP1, EP3, and EP4) in renal cortex.	Berberine alleviates kidney dysfunction via modulation of prostaglandin signaling.	[83]
Xie X (2013)	Renal inflammation and fibrosis	*In vitro*: GMCs isolated from rats, exposed to HG; *in vivo*: STZ-induced diabetes in rats	*In vitro*: berberine 30 and 90 μmol/L; *in vivo*: berberine 200 mg/(kg·d) for 12 weeks	*In vitro*: inhibited HG-induced NF-κB and Ras homolog gene family, member A (RhoA)/Rho-associated protein kinase (ROCK) activation; reduced induction of FN, ICAM-1 and TGF-β. *In vivo*: reduced STZ-induced glomerular injury; reduced FN accumulation in the kidneys; reduced NF-κB and RhoA/ROCK activation; inhibited ICAM-1 and TGF-β induction.	Berberine ameliorates diabetes-induced renal inflammation and fibronectin accumulation, by inhibiting NF-κB activation and RhoA/ROCK signaling.	[144]
Wang FL (2013)	Renal hypertrophy and inflammation	*In vivo*: HFD and STZ-induced diabetic model in rats	Berberine 100 and 200 mg/(kg·d) for 8 weeks (p.o.)	Reduced FBG, triglyceride, TC and LDL-C levels in diabetic rats; ameliorated kidney hypertrophy and inflammation; reduced type IV collagen and TGF-β expression in the kidneys; improved renal functions (reduced BUN, SCr, urine microalbumin/creatinine, and urine protein/creatinine); restored G protein-coupled receptor kinase (GRK) expression patterns and cAMP levels in renal cortex.	Berberine exerts renoprotection in diabetes possibly via modulating G protein-adenylate cyclase-cAMP signaling pathway.	[82]
Lan T (2012)	Mesangial hypertrophy	*In vitro*: GMCs isolated from rats, exposed to HG	Berberine 30 and 90 μmol/L	Inhibited HG-induced mesangial hypertrophy and α-SMA formation; suppressed HG-induced TGF-β and FN expression; inhibited HG-induced SphK1 activation; suppressed HG-induced AP-1 activation.	Berberine protects against mesangial hypertrophy by suppressing TGF-β and SphK1/AP-1 pathways.	[80]
Huang K (2012)	Renal fibrosis	*In vitro*: GMCs isolated from rats, exposed to HG; *in vivo*: STZ-induced diabetes in rats	*In vitro*: berberine 10 30, and 90 μmol/L; *in vivo*: berberine 200 mg/(kg·d) for 12 weeks (p.o.)	*In vitro*: reduced HG-induced SphK1-sphingosine 1-phosphate (S1P2) receptor expression in GMCs; suppressed S1P2 receptor-mediated FN expression under HG; inhibited HG-induced NF-κB activation.*In vivo*: reduced diabetes-induced S1P2 receptor expression in the kidneys; reduced FN expression in the kidneys.	Berberine suppresses diabetic renal fibrosis via inhibiting NF-κB activation and downregulating S1P2 receptor expression.	[81]
Wu D (2012)	Diabetic nephropathy	HFD and STZ-induced diabetic model in rats	*In vivo*: berberine 100 and 200 mg/(kg·d) for 8 weeks	Alleviated weight loss and reduced blood glucose, HbA1c, urine volume and urine protein; restored kidney weight and Ccr and reduced SCr and BUN; reduced MDA and increased SOD in the kidneys; restored nephrin and podocin expression.	Berberine exerts renoprotective effects via inhibiting oxidative stress and restoring podocytes survival.	[79]
Lan T (2010)	Renal hypertrophy	Alloxan-induced diabetic model in mice	*In vivo*: berberine 300 mg/(kg·d) for 12 weeks (p.o.)	Reduced FBG, kidney/body weight ratio, BUN, SCr and 24 h albuminuria; prevented renal hypertrophy, TGF-β upregulation, and FN and collagen IV accumulation; downregulated SphK and S1P expression.	Berberine prevents renal hypertrophy via inhibiting SphK-S1P signaling.	[77]
Liu W (2010)	Renal fibrosis	Alloxan-induced diabetic model in mice	Berberine 300 mg/(kg·d) for 12 weeks (p.o.)	Improved blood glucose, BUN and SCr levels; reduced NF-κB nuclear localization and expression in the kidney; restored IκB-α expression in the kidney; suppressed ICAM-1, TGF-β1 and FN induction in the kidney	Berberine prevents renal fibrosis via suppressing matrix accumulation by inhibiting NF-κB activation.	[76]

AMPK: 5'-adenosine monophosphate-activated protein kinase; AP-1: activator protein 1; BUN: blood urea nitrogen; cAMP: cyclic adenosine monophosphate; Ccr: creatinine clearance; DN: diabetic nephropathy; ECM: extracellular matrix; EMT: epithelial-mesenchymal transition; EP: prostaglandin E2 receptor; FBG: fasting blood glucose; FN: fibronectin; GMC: glomerular mesangial cell; HbA1c: glycosylated hemoglobin A1c; HF: high fat; HFD: high-fat diet; HG: high glucose; HO-1: heme oxygenase-1; ICAM-1: intercellular adhesion molecule-1; LDL-C: low-density lipoprotein cholesterol; MDA: malonaldehyde; MMP: matrix metallopeptidase; NF-κB: nuclear factor κB; NQO-1: NADPH quinone oxidoreductase-1; PGE2: prostaglandin E2; PI3K: phosphoinositide 3-kinase; p.o.: per os; S1P: sphingosine 1-phosphate; SCr: serum creatinine; SMA: myofibroblast differentiation marker; SOD: superoxide dismutase; SphK: sphingosine kinase; STZ: streptozotocin; TAG: triacylglycerol; TC: total cholesterol; TGF-β: transforming growth factor-β; TGF-βR: transforming growth factor-β receptor; TIMP: tissue inhibitor of the matrix metalloproteinase; TLR-4: toll-like receptor 4; VCAM-1: vascular cell adhesion molecule-1.

Table 7. Research articles studying the use of berberine to treat gut dysbiosis, intestinal dysfunction and systemic inflammation of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Shi Y (2018)	Gut microbiota dysfunction associated with atherosclerosis	*In vivo*: atherosclerosis model mice ($ApoE^{-/-}$ mice fed with HFD)	Berberine 50 mg/kg for 12 weeks (p.o.); cohousing with berberine-treated mice	Berberine and cohousing: increased *Verrucomicrobia* and inhibited HFD-induced suppression of *Firmicutes*; suppressed trimethylamine-N-oxide and flavin-containing monooxygenase 3 induction by HFD; reduced HFD-induced inflammatory response (berberine attenuated HFD-induced atherosclerosis).	The anti-atherosclerotic effect of berberine is related to altered gut microbiota compositions.	[130]
Sun Y (2018)	Gut dysbiosis associated with obesity	*In vivo*: HFD-induced obesity model in mice; *in vitro*: palmitate-induced mitochondrial stress model in intestinal epithelial cells (NCl-H716)	Berberine 100 mg/(kg·d) dietary supplementation for 8 weeks	*In vivo*: reduced body weight, tissue weight of perirenal fat and epididymal fat pads, TC, TAG and LDL-C, increased HDL-C, improved insulin sensitivity and glucose tolerance and reduced gluconeogenesis; enhanced GLP-1 and G protein-coupled receptor 43 expression; restored mucosal and mitochondrial structure in colon; restored mitochondrial function; suppressed HFD-induced activation of complex I, and inactivation of complexes II and IV; partly restored SCFAs reduced by HFD and had significant impact on gut microflora (reduced *Firmicutes*, recovered *Bacteroidetes*, increased *Clostridiales*, *Oscillospira*, *Parabacteroides* and *Mogibacteriaceae*). *In vitro*: inhibited palmitate-induced ATP elevation, MMP disruption, respiration inhibition and apoptosis.	Berberine prevents metabolic dysfunctions possibly via restoring gut microbiota, GLP-1 expression, and SCFAs, as well as protecting intestinal epithelial cells from fatty acid-induced damages.	[75]
Zhu L (2018)	Intestinal epithelial barrier dysfunction associated with atherosclerosis	HFD-induced atherosclerosis model in $ApoE^{-/-}$ mice	Berberine in drinking water (0.5 g/L) for 14 weeks	Prevented inflammation in the intestine; promoted intestinal epithelial barrier integrity; increased *Verrucomicrobia*, particularly *Akkermansia* and *Bacterooides*; increased the number of intestinal goblet cells and restored the thickness of mucus layer.	Berberine modulates gut microbiota, specifically increases the abundance of *Akkermansia*, which may contribute to metabolic protection.	[74]
Liu D (2018)	Gut dysbiosis associated with FLD	*In vivo*: HFD-induced obesity model in rats	Berberine 200 mg/(kg·d) for 8 weeks (p.o.)	Reduced *Escherichia coli* and increased *Lactobacillus* in the gut microbiota; reduced plasma endotoxin.	Berberine modulates the gut microbiota, thereby reducing inflammation.	[108]
Zhang X (2015)	Gut dysbiosis associated with obesity and MetS	*In vivo*: HFD-induced gut microbial dysbiosis model in rats	Berberine 100 or 200 mg/(kg·d) for 18 weeks (p.o.)	Reduced body weight and obesity index; reverted HFD-induced population shift in gut microbiota; increased SCFA-producing bacteria, including *Allobaculum*, *Bacteriodes*, *Blautia*, *Butyricoccus* and *Phascolarctobacterium*.	Berberine restores balance in gut microbiota.	[73]
Zhang Q (2014)	Intestinal glucose and lipid metabolism	*In vivo*: STZ and HFD-induced diabetic model in rats	Berberine 120 and 240 mg/(kg·d) for 6 weeks (p.o.)	Reduced FBG and FINS and restored oral glucose tolerance; restored postprandial GLP-1 levels; upregulated GLP-1 receptor and downregulated GnRH and GnRH receptor expression in the ileum.	Berberine improves blood glucose levels, possibly via GnRH-GLP-1 pathway in the ileum.	[72]
Shan CY (2013)	Intestinal barrier dysfunctions	*In vivo*: HFD and STZ-induced diabetes in rats	Berberine 100 mg/kg for 2 weeks (p.o.)	Improved insulin resistance; restored intestinal mucosa structure and reduced plasma LPS; restored glutamine-induced GLP-2 secretion from ileum.	Berberine treatment augments GLP2 secretion and restores intestinal functions in T2DM.	[71]
Zhang X (2012)	Gut microbial dysbiosis associated with obesity and metabolic disorders	*In vivo*: HFD-induced obesity and insulin resistance in rats	Berberine 100 mg/(kg·d) for 18 weeks (p.o.)	Prevented obesity and improved insulin sensitivity; prevented systemic inflammation; reduced the bacterial diversity of the gut microbiota; reduced total bacterial population under HFD; enriched *Allobaculum* and *Blautia* (SCFA producers); increased fecal SCFA levels.	Berberine prevents HFD-induced obesity and insulin resistance at least partly via enriching SCFA-producing gut microbiota.	[70]
Li ZQ (2012)	Intestinal glucose uptake	*In vivo*: postmaltose (in rats and dogs) and postglucose blood glucose (in rats); insulin sensitivity test in rats. *In vitro*: maltose digestion and glucose transport by enterocytes (Caco-2); α-glycosidase inhibition assay	*In vivo*: rats, berberine 500 mg/kg (p.o.); dogs, 80 mg/kg, 1 h before tests.*In vitro*: Berberine 250 mg/L	*In vivo*: delayed postmaltose blood glucose in rats and dogs; did not affect postglucose blood glucose in rats; had no effect on insulin levels. *In vitro*: inhibited maltose digestion by Caco-2 cells; inhibited α-glycosidase activity.	Berberine acutely inhibits digestion of maltose in the intestine.	[69]
Liu L (2010)	Intestinal disaccharide metabolism	*In vivo*: STZ-induced diabetic model in rats; *in vitro*: intestinal epithelial cells (Caco-2)	*In vivo*: berberine 100 and 200 mg/(kg·d) for 5 weeks (p.o.); *in vitro*: berberine 10 and 50 μmol/L	*In vivo*: reduced food intake and blood glucose and restored serum insulin level; decreased sucrase and maltase activity and SI complex expression in the small intestine; reduced blood glucose after oral sucrose or maltose administration. *In vitro*: inhibited sucrase and maltase activity, which was suppressed by H-89 (PKA inhibitor); inhibited SI complex mRNA expression.	Berberine suppresses disaccharidase activity and SI complex mRNA expression, which has beneficial metabolic effects. The effect involves PKA-dependent pathway.	[68]

ATP: adenosine triphosphate; FBG: fasting blood glucose; FINS: fasting insulin; FLD: fatty liver disease; GLP: glucagon-like peptide; GnRH: gonadotropin-releasing hormone; HDL-C: high-density lipoprotein cholesterol; HFD: high-fat diet; LDL-C: low-density lipoprotein cholesterol; LPS: lipopolysaccharide; MetS: metabolic syndrome; MMP: matrix metallopeptidase; PKA: protein kinase A; p.o.: per os; SCFA: short-chain fatty acid; SI complex: sucrase-isomaltase complex; STZ: streptozotocin; T2DM: type 2 diabetes mellitus; TAG: triacylglycerol; TC: total cholesterol.

Table 8. Research articles studying the use of berberine to treat retinopathy of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Chen H (2018)	Diabetic retinopathy	*In vitro*: HG-induced primary Müller cell apoptosis (diabetic retinopathy) model	Berberine 10 and 20 μmol/L	Improved viability of Müller cells under HG; restored phospho-AMPK levels and suppressed phospho-mTOR levels against HG; induced autophagy (Beclin1 and LC3I/II expression); inhibited HG-induced apoptosis (Bcl2 and Bax).	Berberine may protect Müller cells from HG-induced apoptosis via activation of AMPK signaling, suppression of mTOR and induction of autophagy.	[66]
Fu D (2016)	Diabetic retinopathy	*In vitro*: human Müller cell exposed to HOG-LDL vs native-LDL	Berberine 5 μmol/L pretreatment	Berberine pretreatment attenuated negative effects of HOG-LDL on Müller cells: improved cell viability; enhanced Nrf2 and GPx-1; suppressed Nox4 and ROS generation; suppressed autophagy and apoptosis; inhibited angiogenesis, glial activation and inflammation; activated AMPK signaling.	Berberine inhibits oxidative stress and HOG-LDL-induced Müller cell injury possibly via AMPK.	[65]
Tian P (2013)	Retinal endothelial damage	*In vitro*: leukocyte-mediated death of retinal endothelial cells (human retinal endothelial cells cocultured with leukocyte isolated from diabetic patients)	*In vitro*: berberine 5, 25 and 50 μmol/L; *ex vivo*: berberine 0.5 g, twice/day for 1 month	Berberine inhibited leukocyte-mediated retinal endothelial cell apoptosis; inhibited leukocyte adhesion to retinal endothelial cells; inhibited HG-induced NF-κB activation in retinal endothelial cells; inhibited HG-induced oxidative stress via SOD, catalase and GPx induction. Leukocytes from diabetic patients after berberine treatment were less damaging to retinal endothelial cells.	Berberine may prevent diabetic retinopathy via protection of retinal endothelial cells and inhibiting HG-induced leukocyte activation.	[64]

AMPK: 5'-adenosine monophosphate-activated protein kinase; GPx: glutathione peroxidase; HG: high glucose; HOG: highly oxidized; glycated; LDL: low-density lipoprotein; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor κB; ROS: reactive oxygen species; SOD: superoxide dismutase.

Table 9. Research articles studying the use of berberine to treat neuropathy of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Yerra VG (2018)	Motor and sensory dysfunctions associated with diabetic neuropathy	*In vivo*: STZ-induced diabetic model in rats; *in vitro*: HG-exposed in N2a cells	*In vivo*: berberine 50 and 100 mg/(kg·d) for 2 weeks (p.o.); *in vitro*: berberine 5 and 10 μmol/L	*In vivo*: reduced plasma glucose and MDA, and increased GSH; ameliorated motor and sensory dysfunctions; reduced DNA fragmentation in sciatic nerve; restored phospho-AMPK and ATP levels; reduced IL-6 and TNF-α in sciatic nerves; restored the levels of antioxidative stress proteins and mitochondrial biogenesis-related proteins. *In vitro,* berberine's effects in HG-exposed neurons: induced mitochondrial biogenesis and restored membrane potential; restored phospho-AMPK and Nrf2 levels.	Berberine activates AMPK. Berberine alleviates neurotoxicity in diabetes, possibly via protecting mitochondria and restoring Nrf2-mediated endogenous antioxidant system.	[63]
Zhou J (2016)	Diabetic neuropathy	*In vivo*: STZ and high sugar/high fat-induced diabetic model in rats	Berberine 100 mg/(kg·d) for 24 weeks (p.o.)	Reduced FBG, HbA1c, TAG and TC; restored somatosensory transmission; protected hippocampal CA1 neurons; restored neuritin expression; downregulated phosphorylation of p38 and JNK, but not ERK in the hippocampus.	Berberine has a beneficial effect against diabetic neuropathy possibly via neuritin expression and inhibition of p38 and JNK pathways.	[62]
Kim SO (2013)	Diabetic neuropathy	*In vivo*: STZ-induced diabetes in rats	Berberine 10 and 20 mg/kg for 1 or 2 weeks (i.p.)	Single and two-week administration of berberine exhibited anti-allodynic effects.	Berberine could be anti-allodynic possibly via anti-inflammatory or antidepressant capacity.	[61]

AMPK: 5'-adenosine monophosphate-activated protein kinase; ATP: adenosine triphosphate; CA: calyculin A; ERK: extracellular signal-regulated kinase; FBG: fasting blood glucose; GSH: reduced glutathione; HbA1c: glycosylated hemoglobin A1c; HG: high glucose; IL: interleukin; i.p.: intraperitoneal injection; JNK: c-Jun N-terminal kinase; MDA: malonaldehyde; p.o.: per os; STZ: streptozotocin; TAG: triacylglycerol; TC: total cholesterol; TNF: tumor necrosis factor.

Table 10. Research articles studying the use of berberine to treat other associated disorders of diabetes.

First author (Year)	Target	Study design	Intervention	Effects of berberine	Conclusion	Reference
Memon MA (2018)	T2DM	Clinical: case-control with population as newly diagnosed type 2 diabetic patients (n = 200)	Group 1: metformin 200 mg (three times per day) for 3 months; Group 2: berberine 500 mg (three times per day) for 3 months	Berberine reduced blood glucose, cholesterol, TAG, LDL-C, HbA1c, insulin resistance and methylglyoxal.	Berberine is effective in treating T2DM. Berberine is more effective than metformin.	[60]
Dong Y (2016)	Metabolic dysfunctions associated with T2DM	*In vivo*: T2DM model using Zucker diabetic fatty rats (fa/fa) fed with HFD	Berberine 300mg/(kg·d) for 12 weeks (p.o.)	*In vivo*: reduced serum HbA1C, insulin, TC and TAG; restored the glyoxylate and dicarboxylate metabolism, pentose and glucuronate interconversions and sphingolipid metabolism.	Berberine is antidiabetic via restoration of glycometabolism and lipometabolism.	[58]
Liu C (2015)	Hyperglycemia and hyperlipidemia	STZ and HG/HFD-induced diabetic model in hamsters	Berberine 100 mg/(kg·d) for 6 weeks (p.o.)	Reduced body and liver weight gain, FBG, insulin, and serum lipid (TC, TAG, and LDL-C) levels; reduced oxidative stress (reduced plasma MDA and increased plasma SOD); reduced apolipoprotein B and increased apolipoprotein A1 levels; induced GLUT4 in the skeletal muscle and LDL receptor in the liver.	Berberine is effective against hyperglycemia and hyperlipidemia and reduces oxidative stress, possibly via enhancing glucose consumption in the muscle and lipid metabolism in the liver.	[59]
Xu M (2014)	Hyperglycemia	*In vitro*: hepatocytes (HepG2) and myoblasts (C2C12)	Berberine 20 µmol/L	Inhibited mitochondrial complex I and reduced ATP synthesis in myoblasts; increased glucose consumption and lactate release in both hepatocytes and myoblasts; enhanced AMPK and acetyl coenzyme A synthetase phosphorylation, and AMPK inhibition.	Berberine enhances glucose consumption possibly via shifting cellular metabolism from mitochondrial oxidative phosphorylation to glycolysis, independently of AMPK signaling.	[57]
Yang TC (2014)	Glucose uptake by skeletal muscles	*In vitro*: myotubes (differentiated C2C12 cells)	Berberine 6.25 and 12.5µg/mL for 24 h	Berberine enhanced glucose uptake.	Berberine may help alleviate hyperglycemia by promoting glucose uptake by skeletal muscles.	[143]
Chen Y (2011)	Glucose homeostasis	*In vivo*: STZ-induced diabetic model in rats; *in vitro*: DPP-4 and PTP1B assay	Berberine 100 mg/(kg·d) for 7 weeks (p.o.)	Reduced FBG; improved oral glucose tolerance; reduced plasma lipids (TC, HDL-C, LDL-C, and TAG) and FFA; inhibited DPP-4 and PTP1B.	Berberine improves glucose homeostasis via inhibition of DPP-4 and PTP1B, thereby restoring GLP-1 and modulating insulin signaling.	[133]
Chueh WH (2012)	Hyperglycemia	*In vivo*: spontaneous type 1 diabetes model in mice	Berberine 50, 150, 500 mg/(kg·d) for 14 weeks (p.o.)	Serum berberine concentration was negatively associated with serum glucose levels.	Berberine improves hyperglycemia in type 1 diabetes.	[122]
Cok A (2011)	Cellular glucose uptake	*In vitro*: fibroblast (L929)	Berberine 10–100 µmol/L	Enhanced glucose uptake	Berberine activates cellular glucose uptake via p38 MAP kinase and ERK signaling pathways.	[111]
Wang Y (2011)	Hyperglycemia	*In vivo*: HFD and STZ-induced diabetic model in rats	Berberine 50, 100, and 150 mg/(kg·d) for 6 weeks (p.o.)	Reduced blood glucose and improved OGTT; reduced food intake; did not change plasma insulin levels; did not change SOD, MDA or GSH in the liver.	Berberine is hypoglycemic via unknown mechanism.	[78]
Chen C (2010)	Glucose uptake	*In vitro*: adipocytes (3T3-L1) and myocytes (L6); *in vivo*: HFD-induced obesity and leptin receptor deficient (*db/db*) mice	*In vitro*: berberine 1.25–20 µmol/L; *in vivo*: berberine 100 mg/(kg·d) for 2 weeks (p.o.)	*In vitro*: promoted glucose uptake by 3T3-L1 and L6 cells; inhibited PTP1B and increased IR phosphorylation; increased insulin signaling (phospho-IRS, phosphor-Akt). *In vivo*: reduced blood glucose; did not increase plasma insulin level and insulin synthesis in pancreas; activated insulin signaling.	Berberine mimics insulin action via inhibition of PTP1B activity.	[100]
Ma X (2010)	Glucose transport in skeletal muscles	*In vitro*: skeletal muscles isolated from rats	Berberine 0.3 mmol/L	Induced AMPKα phosphorylation and increased AMPK activity; stimulated glucose transport in the absence of insulin; increased AS160 phosphorylation (downstream of AMPK); decreased PCr content.	Berberine reduces the intracellular energy status and acutely stimulates AMPK and insulin-independent glucose transport in skeletal muscle.	[89]
Gu Y (2010)	Metabolic dysfunction in T2DM and dyslipidemia	Clinical: T2DM patients (n = 60); metabolomics	Berberine 1.0 g/d for 3 months	Reduced fasting and postload plasma glucose, HbA1c, TAG, TC and LDL-C; reduced FFAs including C16:0 and C18:0.	Berberine is effective in treating T2DM through downregulation of FFAs.	[67]
Zhang H (2010)	Hyperglycemia	Clinical: T2DM patients; *in vitro*: human cell lines (CEM, HCT-116, SW1990, HT1080, 293T and human liver cells)	Clinical: berberine 1.0 g/d for 2 months; *in vitro*: berberine 2.5–15 µmol/L	Clinical: increased IR expression; lowered blood glucose and HbA1c. *In vitro*: upregulated IR; sensitized IR and Akt phosphorylation to low-dose insulin.	Berberine lowers blood glucose in T2DM through upregulation of IR.	[22]

AMPK: 5'-adenosine monophosphate-activated protein kinase; ATP: adenosine triphosphate; DPP-4: dipeptidyl peptidase-4; ERK: extracellular signal-regulated kinase; FBG: fasting blood glucose; FFA: free fatty acid; GLP: glucagon-like peptide; GLUT: glucose transporter; GSH: reduced glutathione; HbA1c: glycosylated hemoglobin A1c; HFD: high-fat diet; HG: high glucose; IR: insulin receptor; IRS: insulin receptor substrate; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; MAP: mitogen-activated protein; MDA: malonaldehyde; OGTT: oral glucose tolerance test; PCr: phosphocreatine; PTP1B: protein tyrosine phosphatase 1B; SOD: superoxide dismutase; STZ: streptozotocin; T2DM: type 2 diabetes mellitus; TAG: triacylglycerol; TC: total cholesterol.

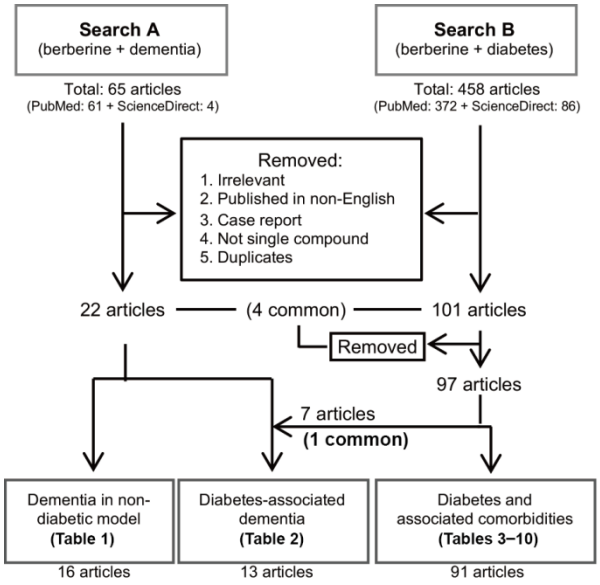

Fig. 1. Flowchart of search strategy used in the systematic review. The relevant number of papers at each step is given.

3.1. Antidementia

Tables 1 and 2 shows 25 studies that suggested direct neuroprotective and cognition-enhancing effects of berberine. Potential benefits were demonstrated in 16 nondiabetic studies (Table 1) and in 9 studies using diabetic models (Table 2). In nondiabetic models, berberine protected learning and memory in heavy metal-induced AD [28], Aβ-induced memory deficits model [34], familial AD models [29,35,38] and D-galactose-induced brain damage [40,145]. In the rat VaD model induced by chronic cerebral hypoperfusion, berberine protected hippocampal calyculin A1 (CA1) neurons and prevented memory deficit [27]. Mechanistically, berberine reduced oxidative stress in the brain by increasing the levels of antioxidants, including glutathione, glutathione peroxidase and superoxide dismutase (SOD) [28,35,37], reduced AChE expression levels [28] and AChE activity at as low as 0.44–6 μmol/L half maximal inhibitory concentration [30,33,36,41] and uncompetitively inhibited indoleamine 2,3-dioxygenase [32], the first rate-limiting enzyme of kynurenine pathway, thereby potentially reducing the accumulation of neurotoxic metabolites involved in AD pathogenesis [146–148]. Berberine reduced Aβ generation in Swedish mutant amyloid precursor (APP)-expressing cells [31] and suppressed the Aβ-induced inflammatory response in microglia [42]. In addition, berberine reduced hyperphosphorylation of tau and APP [29,39], possibly through inactivation of GSK3β via Akt signaling [29].

On the other hand, growing evidence suggests that berberine prevents dementia associated with diabetes [43–55,61–63] (Table 2). Berberine inhibited apoptosis in the hippocampus and cerebral cortex, suppressed anxiety and restored recognition memory in the sporadic AD model induced by intracerebroventricular injection of streptozotocin (STZ), possibly via reduction of AChE activity [44,51]. It also suppressed hippocampal inflammation, protected neurons and synapses and ameliorated cognitive impairment through improved lipid metabolism in leptin receptor-deficient (*db*/*db*) diabetic mice [49]. In STZ-induced diabetic model, berberine alleviated cognitive dysfunctions [44,45,49,53,55,62] by protecting hippocampal CA1 neurons [55,62] and restoring hippocampal short-term and long-term plasticity [54,55], reducing oxidative stress [55], inhibiting brain inflammation [51,53], suppressing Aβ generation via inhibition of the phosphoinositide 3-kinase (PI3K)/Akt/GSK3β pathway [51] and reducing diabetes-associated AChE induction in the hippocampus and cortex [45]. In the STZ-induced VaD model in rats, berberine enhanced nitric oxide (NO) generation and blood flow in the cerebral artery, reduced oxidative stress and alleviated memory impairment, possibly via suppression of hyperglycemia-induced ectopic expression of miR-133a [44]. Of note, berberine supplementation restored glucose transporter levels and insulin

signaling in the brain [50], suggesting that modulation of glucose metabolism in the brain may underlie the neuroprotective effect of berberine. Moreover, berberine activated 5'-adenosine monophosphate-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis, restored mitochondrial membrane potential in neurons under high glucose (HG) stress [63] and protected neurons from glucose-induced oxidative stress *in vitro* [37,47], suggesting that berberine could alleviate neuronal damages under hyperglycemia.

3.2. Prevention of MetS

3.2.1. Pancreatic dysfunction

Both clinical and preclinical studies (Table 3) have shown that berberine could alleviate insulin resistance and reduce blood glucose [60,72,75,124,139,140], which is likely due to the protection of pancreatic β-cells [56,137,140] and restoration of insulin secretion [56,139,142]. Molecular mechanisms underlying berberine's pancreatic protection include modulation of anti-apoptotic Bax and pro-apoptotic Bcl-2 expression levels [138], activation of AMPK [139,142], restoration of sirtuin 1 (SIRT1) [141] and induction of uncoupling protein 2 (UCP2) [142]. SIRT1 is a nicotinamide adenine dinucleotide^{+}-dependent histone deacetylase that plays crucial roles in the protection of pancreatic β-cells against inflammation and oxidative stress [149]; UCP2 regulates redox homeostasis and insulin expression in β-cells. Thus, it is likely that berberine promotes the survival of β-cells through several molecular pathways.

3.2.2. Vascular dysfunction

In STZ-induced diabetic models (Table 4), berberine reduced total cholesterol, triglyceride and LDL-C, while increasing high-density lipoprotein cholesterol (HDL-C) [58,59,62,75,105,108,120,129,141]. In ApoE$^{-/-}$ mice fed with high-fat diet (HFD), a model for Western diet-induced atherosclerosis, berberine significantly attenuated the development of severe cardiovascular symptoms [130]. Berberine has also been shown to reduce total cholesterol and LDL-C in clinical trials [23,60]. In studies *in vitro*, berberine alleviated palmitate-induced endothelial dysfunction via upregulation of endothelial nitric oxide synthase (eNOS) and downregulation of nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4) [114], an enzyme involved in age-associated cardiovascular dysfunction via oxidative stress and inflammation [150]; it also inhibited HG-potentiated platelet aggregation [134], suppressed HG-induced endothelial dysfunction and restored NO generation possibly via suppressing ectopic miR-133a expression and restoring peroxisome proliferator-activated receptor (PPAR) γ and AMPK signaling [44,121,123,125,126]. In another study, it reduced oxidized LDL-induced inflammatory responses in macrophages via AMPK activation and nuclear factor (NF)-κB inhibition [135]. In addition, berberine protected cardiomyocytes from HG-induced damage and ischemia-reperfusion via enhancement of AMPK [116,120,124,132], PPARα [115] and PI3K-Akt-eNOS anti-apoptotic signaling pathways [116]. Berberine also attenuated cardiac fibrosis, possibly by reducing insulin-like growth factor (IGF)-1 receptor expression in cardiac fibroblasts [129], and enhanced lipid metabolism in cardiomyocytes, possibly via protein kinase C inhibition [119,127]; it also suppressed cardiac arrhythmia by modulating K^{+} and Ca^{2+} [110,113]. Furthermore, berberine may alleviate vascular dysfunction in diabetes by acting on adipose tissues. Berberine reduced body weight in HFD-fed mice [131,136], and induced fibroblast growth factor 21 (FGF21) and brain and muscle aryl hydrocarbon receptor nuclear translocator protein (Arnt)-like 1 expression in brown adipocytes *in vivo* and *in vitro* [136], suggesting that berberine could modulate lipid metabolism in adipose tissues. Berberine also blocked adipogenesis *in vitro* [117,118], suppressed inflammatory (M1) macrophage polarization and aberrant extracellular matrix (ECM) deposition in adipose tissue of HFD-induced insulin-resistance model mice [128,131]. In another study, it alleviated visceral white adipose tissue insulin resistance, possibly via sterol regulatory element-binding proteins (SREBPs) and PPARs [112]. Thus, berberine could alleviate diabetes-associated vascular dysfunctions via multiple pathways.

3.2.3. Liver dysfunction

As shown in Table 5, berberine alleviated liver damage in STZ- and HFD-induced diabetic models [43,95,97,105,107,108], as well as in alloxan-induced diabetic model [98]. Treatment with berberine improved carbohydrate metabolism, and reduced oxidative stress, lipid peroxidation, inflammation and apoptotic cell death in the liver in STZ-induced diabetic model [43,99,107]. Similarly, in HFD-induced obesity models, insulin receptor and insulin receptor substrate (IRS)-1 induction, reduced inflammation [108] and hepatic mitochondrial protection were observed [101]. There may be several mechanisms that support these outcomes: berberine could improve glucose metabolism in the liver by stimulating glucose uptake [109], enhance glycolysis by restoring the expression and activity of the rate-limiting glycolytic enzyme [103], while suppressing gluconeogenic enzymes [102,109], enhance lipid metabolism in the liver by modulating metabolic regulators such as human liver X receptor α (LXRα), SREBPs and PPARα [95], and induce brown-like gene expression and high energy expenditure via FGF21 and SIRT1 signaling activation [106]. Furthermore, berberine could relieve hepatic inflammation possibly via AChE inhibition and restoration of ACh receptor-mediated anti-inflammatory signaling [104]. Thus, berberine has treatment effects that should combat diabetes-associated liver dysfunction and non-alcoholic fatty liver disease (NAFLD).

3.2.4. Kidney dysfunction

As shown in Table 6, berberine ameliorated renal inflammation and injury in diabetic models [79,83,85,86,90,96]. Underlying mechanisms include inhibition of kidney fibrosis via tumor growth factor (TGF)-β signaling suppression and Nrf2 activity enhancement [76,77,80,82,86,91,93,144], suppression of HG-induced mesangial cell proliferation and hypertrophy via suppression of NF-κB and AP-1 [81,84,90], and attenuation of ECM accumulation [87], possibly by restoring β-arrestin [88] and E prostanoid receptor 4 (EP4)-Gαs-cAMP signaling pathway [83,85]. In addition, berberine directly protected podocytes from HG-induced injury *in vitro* [23,94], possibly by inhibiting podocyte apoptosis via AMPK-dependent autophagy induction [92].

3.2.5. Intestinal metabolism, gut dysbiosis and systemic inflammation

As shown in Table 7, berberine significantly affected intestinal microbiota and metabolism. Not only did berberine modulate intestinal glucose uptake by directly inhibiting digestion of disaccharides [68,69], but modulation of the gut microbiome may underlie these beneficial effects. For example, berberine increased *Verrucomicrobia*, which was associated with attenuation of atherosclerosis [130], increased *Akkermansia* and restored intestinal barrier integrity [71,74], and restored short-chain fatty acid-producing *Bacteroidetes* in obese rodents [75]. It is postulated that berberine-mediated changes of gut microbiota, particularly the increase of short-chain fatty acid-producing bacteria [73,75], may contribute to the alleviation of inflammation, insulin resistance and obesity [70,74]. Berberine also reduced the levels of plasma endotoxin and systemic inflammation in HFD-induced obesity model, possibly by reducing *Escherichia coli* and increasing *Lactobacillus* [108].

3.2.6. Diabetic retinopathy

As shown in Table 8, berberine protected retinal Müller cells from HG- and LDL-induced damage via enhancing AMPK signaling [65,66] and prevented retinal endothelial injuries induced by HG-activated leukocytes [64].

3.2.7. Diabetic neuropathy

Berberine ameliorated diabetic neuropathy [61–63] (Table 9), indicating the protection of the peripheral nervous system.

3.2.8. Additional evidence

As shown in Table 10, both clinical and preclinical studies demonstrated that berberine can effectively restore normal glucose and lipid levels in the blood [22,58–60,67,78,122,133]. Suggested underlying mechanisms include enhanced glucose uptake [100,111,143], mitochondrial complex I inhibition [57] and AMPK signaling enhancement [57,89].

4. Discussion

4.1. Direct evidence supporting berberine's antidementia effects

AD is a metabolic disease with diabetes-associated molecular and biochemical features; dysfunctional insulin signaling in the brain may account for the structural and functional abnormalities in AD [151]. The expression levels of IGFs are significantly reduced in the AD brain, which was associated with reduced levels of IRS, IRS-associated PI3K and downstream serine/threonine-specific protein kinase Akt, as well as increased GSK3β activity [16]. As a master regulator of cellular energy metabolism, GSK3β is highly expressed in the adult hippocampus, particularly with age [152]. Its multiple functions include regulation of neural plasticity via neurogenesis, migration, axonal growth and synaptic plasticity [153]. The PI3K/Akt/GSK3β pathway plays crucial roles in neuroprotection and synaptic plasticity under various physiological and pathological circumstances [154,155]. However, abnormally active GSK3β contributes to brain disorders including impairments in mood regulation, cognitive task performance [156] and hippocampal neurogenesis [157]. Importantly, tau protein is one of the targets of GSK3β [158], and the PI3K/Akt/GSK3β pathway may play a key role in AD pathogenesis via enhanced phosphorylation of tau [158]. These data suggest that dysfunctional glucose metabolism may underlie AD development [16]. In fact, experimental diabetes induced by STZ causes cholinergic dysfunction and memory impairment [159]. Furthermore, intracerebral administration of STZ led to features characteristic of AD, including cognitive impairment and ACh homeostasis disturbances [160], which could be alleviated by insulin sensitizers [15,161].

Our literature survey indicated that berberine directly protects the brain cells against damages associated with dementia [27,29,32,34,39], possibly via antioxidative and anti-inflammatory effects [28,35,37,42], and also by reducing Aβ levels [31,38]. Berberine was able to promote cognitive functions [38,40], through enhancing cholinergic neurotransmission [30,33,36,41]. In addition, berberine alleviated diabetes-associated cognitive impairment [44,45,48,49,51–55], possibly via the restoration of insulin signaling [50,51] and reduction of oxidative stress and inflammation [43,46,47] in the brain. Although bioavailability of berberine is relatively low, it crosses the blood brain barrier and stably distributes in the brain tissue, compared to other organs [162], suggesting that berberine could prevent dementia through direct actions in the brain. As a whole, berberine could protect brain functions via a number of mechanisms: neuroprotection [55,62], reducing oxidative stress [28,35,37,43], suppressing brain inflammation [51,53], reducing the generation of Aβ, hyperphosphorylated tau and APP [29,31,39,146], enhancing ACh signaling [28,30,33,36,41,45], and possibly reducing the accumulation of neurotoxic metabolites [32], suggesting that berberine is an effective therapy against dementia including AD and VaD.

4.2. Antidementia effects of berberine via prevention of diabetes and comorbidities: an indirect mechanism

Evidence suggests strong associations between dementia and diabetes [7,8,15,16], which indicates that the risk of developing dementia could be reduced by a successful diabetes intervention. Berberine is a promising antidiabetic agent, as reported in previous review articles [20,21,24,163]. In the present work, we have updated how berberine acts against diabetes and its associated complications; we also discuss the potential of berberine as a treatment for diabetes-associated dementia.

4.2.1. Protection of pancreas

T2DM is characterized by hyperglycemia, associated with insulin resistance and insufficient insulin secretion due to pancreatic β-cell dysfunction. Our literature survey revealed that berberine protects pancreatic cells and restores insulin secretion by β-cells [56,137–142]. Brain insulin resistance is a key feature of AD and related dementias, and evidence suggesting the link between systemic and brain insulin resistance is growing [164,165]. Thus, berberine may prevent dementia development by restoring pancreas functions and systemic insulin signaling.

4.2.2. Vascular protection

VaD is the second common form of dementia [166]. Although there are controversies surrounding the etiology of VaD, cerebral small vessel disease, associated with the breakdown of blood-brain barrier and perivascular inflammation, is likely the most common cause [166,167]. The risk factors include dyslipidemia, hypertension and cardiovascular dysfunction [166]. High levels of LDL-C and low levels of HDL-C increase the risk for carotid atherosclerosis and coronary artery disease, which may result in cerebral hypoperfusion or embolism, leading to cognitive dysfunctions [166,168]. In addition, cardiovascular disease-associated oxidative stress and lipid peroxidation, due to low levels of antioxidants, are thought to cause damage to brain cells [166,169,170]. Dyslipidemia and hypertension, associated with obesity and insulin resistance, are often present in the prediabetic period of T2DM, which may account for the comorbidity of cardiovascular disease and diabetes [171,172]. T2DM dyslipidemia is characterized by increased triglycerides and LDL-C and reduced HDL-C levels [173,174]. Evidence suggests that cholesterol-lowering therapy reduces cardiovascular risk in diabetic patients [174,175]; however, low HDL-C likely contributes to diabetes as well as cardiovascular disease [173]. Thus, lowering total cholesterol while restoring HDL-C would be most beneficial for treating diabetes-associated cardiovascular diseases and VaD. On the other hand, studies have suggested that impaired endothelial dysfunctions and platelet hyperaggregation, causing microvasculature injuries, are the main causes of increased morbidity and mortality of T2DM [176]. Impaired eNOS activity and hypercoagulable states associated with atherosclerosis and vascular dysfunction are observed in the vascular system of diabetes and associated MetS [177,178]. In addition, altered glucose metabolism and glucose overload in cardiomyocytes promote oxidative stress and accumulation of advanced glycation end-products, subsequently causing apoptosis and cardiac dysfunction [179,180]. Furthermore, pro- and anti-inflammatory mediators released from perivascular adipose tissue are involved in the development of atherosclerosis [181], suggesting that adipocytes may play a key role in diabetes-associated cardiovascular dysfunctions.

The results demonstrated that berberine could protect cardiovascular functions by reducing the risk of hypertension [123,126] and coagulation [134], attenuating cardiac hypertrophy [115,129,132] and cardiac arrhythmias [110,113], and inhibiting potential cardiovascular damages associated with dyslipidemia [74,114,116,119–121,124,125,130,135,136]. In addition, berberine reduced obesity and cardiovascular risk at least in part via modulating adipocyte populations and inflammatory state in the adipose tissues [112,117,118,128,131]. Taken together, berberine could promote vascular functions, thereby preventing the development of VaD.

4.2.3. Liver protection

The liver plays a vital role in energy metabolism. Hepatic insulin signaling is essential for the maintenance of carbohydrate and lipid homeostasis, and the liver plays a major role in the development of insulin resistance and T2DM [182]. NAFLD and T2DM are common conditions associated with insulin resistance and vascular dysfunctions, and NAFLD prevalence is high in prediabetic and obese populations [182–184]. Evidence suggests the link between T2DM or NAFLD and insulin resistance in the brain [185,186], and that hepatic ceramide, a neurotoxin that causes insulin resistance, may mediate brain insulin resistance and neurodegeneration in T2DM and NAFLD [187]. In fact, NAFLD induces signs of AD in wild-type mice and accelerates pathological signs of dementia in an AD model [188]. Thus, the liver could be an important target in the prevention of AD and MetS-associated dementia.

The results indicated that berberine protects liver functions [102,103,105,108] through restoring glucose and lipid metabolism [95,101,104–106,109] and suppressing inflammation and oxidative stress [43,97,98,104,107]. Collectively, berberine could prevent dementia through the restoration of liver functions.

4.2.4. Kidney protection

Diabetic nephropathy is a major complication and a common cause for chronic kidney disease (CKD) [189], which is significantly associated with cognitive impairment [190,191]. Between 16% and 38% of dialysis patients have cognitive impairment, which is approximately threefold higher than age-matched controls [192]; VaD seems more prominent in CKD than other types of dementias, such as AD [193]. Dialysis patients tend to have reduced total brain and subcortical volumes and perform poorly in attention/information processing speed and executive function [194]. Glomerular mesangial cell hypertrophy and podocyte loss are the major pathological changes of diabetic nephropathy [195], and injuries to podocytes associated with dysregulation of AMPK play a key role in diabetic nephropathy [195]. Indeed, deficient autophagy caused by AMPK dysregulation can induce podocyte loss and glomerulosclerosis [196], pointing to the importance of AMPK signaling in treating diabetic nephropathy and associated cognitive impairment.

This study revealed that berberine prevents diabetic nephropathy [79,83,85,86,90,96]. Potential mechanisms include podocyte protection [92,94] via AMPK activation [92], and inhibition of renal fibrosis and inflammation [76,77,80–82,84,86,91,93,144] via TGF-β signaling suppression [80,82,84,86,91,93,144]. Considering that TGF-β promotes kidney cell injury via inhibition of AMPK [197], it is probable that berberine ameliorated kidney fibrosis by counteracting TGF-β signaling by restoring AMPK activity. Collectively, berberine could prevent diabetic nephropathy via suppression of hypertrophy and podocyte protection, thereby alleviating cognitive impairment associated with kidney dysfunction.

4.2.5. Restoration of gut microbiota and intestinal metabolism

Among 100 trillion micro-organisms residing in human body, the vast majority are in the intestinal tract [198]. Growing evidence indicates that a critical role of the gut microbiota is as a host metabolism regulator [199], and the imbalance of gut microbiota (gut dysbiosis) has been linked to various metabolic disorders including diabetes [200,201]. Changes in the intestinal ecosystem could alter intestinal permeability, cause inflammation and modulate bile acid metabolism, short-chain fatty acids and other metabolites, contributing to insulin resistance [202] and progression of diabetes-associated conditions [203,204]. In fact, links between the gut microbiota and NAFLD [205], cardiovascular disease [206] or CKD have been suggested [207]. Furthermore, the intestinal microbiota likely takes part in bidirectional communication between the gut and the brain [208]. Thus, gut microbiota provides a promising therapeutic target to alleviate diabetes-associated dementia.

Our literature review indicated that berberine influences body metabolism and suppresses systemic inflammation via modulation of gut microbiota [70,74,75,108,130]. Of note, berberine-containing plants, such as Coptis and Phellodendron spp., have been used traditionally to treat diarrhea, as well as to promote intestinal health [209], and berberine's antimicrobial activity against various pathogenic bacteria is well known [210]. Due to poor absorption of berberine, it is reasonable to speculate that antidiabetic action of berberine is at least in part mediated via effects on the gut microbiota [210].

4.2.6. Retinal protection

Evidence suggests that the status of retinal neuronal structure and vasculature can reflect that of the cerebral nervous system [211]. Our literature survey revealed that berberine could prevent diabetic retinopathy [64–66]. Although the mechanistic link between retinal injuries and cognitive dysfunction is not clear, these data support that berberine could prevent diabetes-associated damages to the neuronal network in the central nervous system, including retina.

4.2.7. Enhancing glucose and lipid metabolism

In addition to preventing diabetes-associated tissue damages, berberine may reduce the risk of MetS development by enhancing glucose and lipid metabolism. However, despite berberine's well-established antihyperglycemic and antihyperlipidemic activities, the underlying molecular mechanisms are less clear. One suggested mechanism is that berberine lowers blood glucose by enhancing AMPK activity in peripheral tissues [89, 212]. AMPK is a serine/threonine kinase that is

activated in response to adenosine triphosphate (ATP) depletion; its action is to restore cellular ATP levels and energy supply, acting as an energy sensor and a metabolic master regulator [213]. Enhanced AMPK activity, upon berberine-treatment, has been observed in several studies using diabetic animal models [63,65,102,128] as well as *in vitro* models [57,65,66,114,128,132,135]. However, it is not clear whether the glucose-lowering effect is indeed mediated by AMPK activation [57]. Recent studies suggest that berberine's glucose-lowering effects could operate through a variety of mechanisms, including: enhanced cellular glucose uptake and consumption [57,59,100,111,143] via p38 MAP kinase and ERK signaling [111]; protein-tyrosine phosphatase 1B (PTP1B) inhibition, thereby mimicking insulin signaling [100,133]; and insulin receptor sensitization to low-dose insulin [22]. However, this mechanism is likely independent of AMPK [57,111]. In addition, berberine is a potent mitochondrial complex I inhibitor and can affect glucose consumption through reduction of ATP generation from mitochondrial oxidative phosphorylation and consequent enhancement of glycolytic activity [57]. Thus, berberine might act as antihyperglycemic, through multiple targets including mitochondrial complex I, while AMPK activation might benefit different aspects of diabetic complications, such as suppression of inflammation [135] and hepatic gluconeogenesis [102]. On the other hand, the antihyperlipidemic activity of berberine could be explained by induction of brown adipocytes via FGF21 signaling [106,136,214], possibly through AMPK [136].

4.3. Limitations and future perspectives

In summary, evidence from numerous studies supports the effectiveness of berberine as a dementia intervention via direct neuroprotection in the brain as well as indirect mechanisms through the prevention of diabetes-associated comorbidities (Fig. 2). Growing evidence suggests that both AD and VaD are associated with diabetes [7,8,15,16,215,216], and the risk of dementia development could be reduced by successful intervention of diabetes and its comorbidities [13,215,217]. As summarized in previous review articles, berberine is a promising antidiabetic agent [20,21,24,163], and preclinical evidence suggests that berberine has neuroprotective effects [25,218–221]. Here, we collectively evaluated the effectiveness of berberine as a treatment for diabetes-associated dementia by two database searches (Fig. 1). The advantage of this study is that it clarified direct and indirect evidence by categorizing the publications into three groups: antidementia effects that has no obvious association with diabetes (Table 1), effects on diabetes-associated dementia (Table 2) and antidiabetic effects (Tables 3 to 10). The limitations of the study include the fact that most of the articles reviewed in this report are preclinical studies using *in vivo* and/or *in vitro* models, thus future research must focus on clinical significance. In addition, it is unknown whether berberine, as a constituent of traditional medicine, rather than as an isolate, could exert the same effectiveness. Berberine is a natural alkaloid found in various medicinal plant species [36,222–229] (Table 11). These medicinal plants could be useful in the prevention of dementia associated with metabolic disorders. Using locally available plants may have advantages over isolates, reducing the cost and possibly providing additional therapeutic and nutritional benefits derived from the plants. In fact, some of those plants, including *B. vulgaris*, Coptis spp. and *P. amurense* have been used in traditional medicines to treat cardiovascular diseases, diabetes and dementia [230–233]. However, those plants contain berberine at different levels, and the variability of berberine contents within the same species, depending on the geographical origins and plant parts used, is nonnegligible [222,228]. Furthermore, those plants and their extracts contain numerous other constituents, which might produce synergistic effects, either enhancing or reducing the efficacy of berberine. Further research is needed to assess the effectiveness and safety of berberine-containing medicinal plants in the prevention of dementia associated with metabolic dysfunctions.

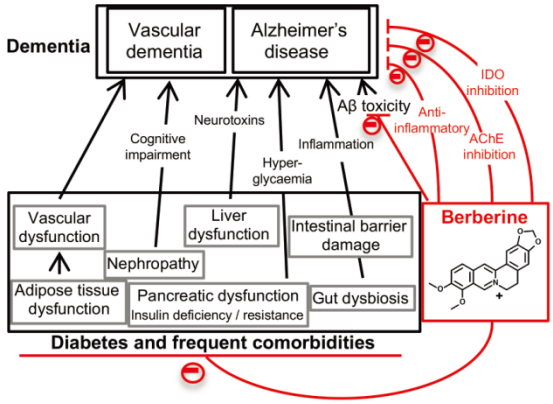

Fig. 2. Potential mechanisms underlying therapeutic effects of berberine to treat and prevent dementia. Berberine enhances cognition via direct actions in the brain, as well as indirectly via alleviating diabetes and associated complications. Notable berberine actions are indicated in red. AChE: acetylcholinesterase; IDO: indoleamine 2, 3-dioxygenase.

Table 11. Berberine contents in medicinal plants.

Species	Part	Content (mg/g)	Extraction method	Reference
Berberis aristata DC.	Root	121.8	EtOH/ultrasonic	[222]
	Stem	102.3	EtOH/ultrasonic	
Berberis asiatica Roxb. ex DC.	Root	78.1	EtOH/ultrasonic	[222]
	Stem	29.9	EtOH/ultrasonic	
Berberis chitria Buch-Ham. ex Lindl.	Root	106	EtOH/ultrasonic	[222]
	Stem	2	EtOH/ultrasonic	
Berberis jaeschkeana C.K.Schneid.	Root	11.2	EtOH/ultrasonic	[222]
	Stem	6.4	EtOH/ultrasonic	
Berberis koehneana C.K.Schneid.	Root	144.9	EtOH/ultrasonic	[222]
	Stem	29.5	EtOH/ultrasonic	
Berberis lycium Royle	Root	172.8	EtOH/ultrasonic	[222]
	Stem	18.2	EtOH/ultrasonic	
Berberis petiolaris Wall. ex G.Don	Root	24.1	EtOH/ultrasonic	[222]
	Stem	5.2	EtOH/ultrasonic	
Berberis pseudumbellata R.Parker	Root	43.8	EtOH/ultrasonic	[222]
	Stem	14.6	EtOH/ultrasonic	
Berberis thunbergii DC.	NA	6.36	MeOH	[223]
Berberis vulgaris L.	Root	7.14–13.8	MeOH	[224]
Coptis chinensis Franch.	Rhizome	65.2	1% HCl in MeOH/ultrasonic	[225]
Coptis deltoidea C.Y. Cheng & P.K. Hsiao	Rhizome	47.2	1% HCl in MeOH/ultrasonic	[225]
Coptis omeiensis (C. Chen) C.Y. Cheng	Rhizome	62.2	1% HCl in MeOH/ultrasonic	[225]
Coptis teeta Wall.	Rhizome	92.6	1% HCl in MeOH/ultrasonic	[225]
Chelidonium majus L.		5.37	MeOH	[225]
Hydrastis canadensis L.	Root	24.4	Acetonitrile:water:phosphoric acid (70:30:0.1, v:v:v)	[226]
	Root	37.8	MeOH/reflux	[227]
	Rhizome	46.2	MeOH/reflux	[227]
Mahonia aquifolium (Pursh) Nutt.		3.34	MeOH	[223]
Mahonia leschenaultii (Wall. ex Wight & Arn.) Takeda	Root	62.2	EtOH/ultrasonic	[228]
Mahonia napaulensis DC.	Root	86.6	EtOH/ultrasonic	[227]
Phellodendron amurense Rupr.	Stem	17.8–47.0	75% EtOH/ultrasonic	[229]
Phellodendron chinense C.K. Schneid.	Bark	269.7	70% EtOH/reflux	[36]

EtOH: ethanol; MeOH: methanol; NA: no information available.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Authors' contribution

NS, JB, and AB contributed to the initial project conception. NS designed the study and wrote the initial draft of the manuscript. NS, JP, and TK contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. NS contributed to data collection. All authors contributed to interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. World Health Organization. Global report on diabetes. (2016) [2019-5-31]. https://www.who.int/diabetes/publications/grd-2016/en/.
2. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. Lancet 2012;379(9833):2291–9.
3. Bello-Chavolla OY, Antonio-Villa NE, Vargas-Vázquez A, Ávila-Funes JA, Aguilar-Salinas CA. Pathophysiological mechanisms linking type 2 diabetes and dementia: review of evidence from clinical, translational and epidemiological research. Curr Diabetes Rev 2019; Epub ahead of print.
4. Chornenkyy Y, Wang WX, Wei A, Nelson PT. Alzheimer's disease and type 2 diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction upstream of observed cognitive decline. Brain Pathol 2019;29(1):3–17.
5. Salas IH, De Strooper B. Diabetes and Alzheimer's disease: a link not as simple as it seems. Neurochem Res 2019;44(6):1271–8.
6. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol 2018;14(10):591–604.
7. Kar S, Issa AM, Seto D, Auld DS, Collier B, Quirion R. Amyloid β-peptide inhibits high-affinity choline uptake and acetylcholine release in rat hippocampal slices. J Neurochem 1998;70(5):2179–87.
8. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry 1999;66(2):137–47.
9. McHardy SF, Wang HL, McCowen SV, Valdez MC. Recent advances in acetylcholinesterase inhibitors and reactivators: an update on the patent literature (2012–2015). Expert Opin Ther Pat 2017;27(4):455–76.
10. Ng RC, Cheng OY, Jian M, Kwan JS, Ho PW, Cheng KK, et al. Chronic adiponectin deficiency leads to Alzheimer's disease-like cognitive impairments and pathologies through AMPK inactivation and cerebral insulin resistance in aged mice. Mol Neurodegener 2016;11(1):71.
11. De Felice FG. Alzheimer's disease and insulin resistance: translating basic science into clinical applications. J Clin Invest 2013;123(2):531–9.
12. Avrahami L, Farfara D, Shaham-Kol M, Vassar R, Frenkel D, Eldar-Finkelman H. Inhibition of glycogen synthase kinase-3 ameliorates β-amyloid pathology and restores lysosomal acidification and mammalian target of rapamycin activity in the Alzheimer disease mouse model: *in vivo* and *in vitro* studies. J Biol Chem 2013;288(2):1295–306.
13. de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes—evidence reviewed. J Diabetes Sci Technol 2008;2(6):1101–13.
14. de la Monte SM. Type 3 diabetes is sporadic Alzheime's disease: mini-review. Eur Neuropsychopharmacol 2014;24(12):1954–60.
15. de la Monte SM, Tong M, Lester-Coll N, Plater MJ, Wands JR. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. J Alzheimers Dis 2006;10(1):89–109.
16. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease—is this type 3 diabetes? J Alzheimers Dis 2005;7(1):63–80.
17. Menees S, Saad R, Chey WD. Agents that act luminally to treat diarrhea and constipation. Nat Rev Gastroenterol Hepatol 2012;9(11):661–74.

18. Tang J, Feng Y, Tsao S, Wang N, Curtain R, Wang Y. Berberine and *Coptidis rhizoma* as novel antineoplastic agents: a review of traditional use and biomedical investigations. J Ethnopharmacol 2009;126(1):5–7.
19. Castle T, Barton BH. The British flora medica, or, history of the medicinal plants of Great Britain. London: Chatto Wind; 1877.
20. Liang Y, Xu X, Yin M, Zhang Y, Huang L, Chen R, et al. Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: a systematic literature review and a meta-analysis. Endocr J 2019;66(1):51–63.
21. Ju J, Li J, Lin Q, Xu H. Efficacy and safety of berberine for dyslipidaemias: a systematic review and meta-analysis of randomized clinical trials. Phytomedicine 2018;50:25–34.
22. Zhang H, Wei J, Xue R, Wu J, Zhao W, Wang Z, et al. Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism 2010;59(2):285–92.
23. Zhang Y, Li X, Zou D, Liu W, Yang J, Zhu N, et al. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocrinol Metab 2008;93(7):2559–65.
24. Ma X, Chen Z, Wang L, Wang G, Wang Z, Dong X, et al. The pathogenesis of diabetes mellitus by oxidative stress and inflammation: its inhibition by berberine. Front Pharmacol 2018;9:782.
25. Lin X, Zhang N. Berberine: pathways to protect neurons. Phytother Res 2018;32(8):1501–10.
26. Ye M, Fu S, Pi R, He F. Neuropharmacological and pharmacokinetic properties of berberine: a review of recent research. J Pharm Pharmacol 2009;61(7):831–7.
27. Aski ML, Rezvani ME, Khaksari M, Hafizi Z, Pirmoradi Z, Niknazar S, et al. Neuroprotective effect of berberine chloride on cognitive impairment and hippocampal damage in experimental model of vascular dementia. Iran J Basic Med Sci 2018;21(1):53–8.
28. Hussien HM, Abd-Elmegied A, Ghareeb DA, Hafez HS, Ahmed HEA, El-Moneam NA. Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. Food Chem Toxicol 2018;111:432–44.
29. Durairajan SS, Liu LF, Lu JH, Chen LL, Yuan Q, Chung SK, et al. Berberine ameliorates β-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease transgenic mouse model. Neurobiol Aging 2012;33(12):2903–19.
30. Ji HF, Shen L. Molecular basis of inhibitory activities of berberine against pathogenic enzymes in Alzheimer's disease. ScientificWorldJournal 2012;2012:823201.
31. Zhu F, Wu F, Ma Y, Liu G, Li Z, Sun Y, et al. Decrease in the production of β-amyloid by berberine inhibition of the expression of β-secretase in HEK293 cells. BMC Neurosci 2011;12:125.
32. Yu CJ, Zheng MF, Kuang CX, Huang WD, Yang Q. Oren-gedoku-to and its constituents with therapeutic potential in Alzheimer's disease inhibit indoleamine 2,3-dioxygenase activity *in vitro*. J Alzheimers Dis 2010;22(1):257–66.
33. Jung HA, Min BS, Yokozawa T, Lee JH, Kim YS, Choi JS. Anti-Alzheimer and antioxidant activities of *Coptidis Rhizoma* alkaloids. Biol Pharm Bull 2009;32(8):1433–8.
34. Zhu F, Qian C. Berberine chloride can ameliorate the spatial memory impairment and increase the expression of interleukin-1β and inducible nitric oxide synthase in the rat model of Alzheimer's disease. BMC Neurosci 2006;7:78.
35. He W, Wang C, Chen Y, He Y, Cai Z. Berberine attenuates cognitive impairment and ameliorates tau hyperphosphorylation by limiting the self-perpetuating pathogenic cycle between NF-κB signaling, oxidative stress and neuroinflammation. Pharmacol Rep 2017;69(6):1341–8.
36. Kim YJ, Lim HS, Kim Y, Lee J, Kim BY, Jeong SJ. Phytochemical quantification and the *in vitro* acetylcholinesterase inhibitory activity of *Phellodendron chinense* and its components. Molecules 2017;22(6):E925.

37. Sadeghnia HR, Kolangikhah M, Asadpour E, Forouzanfar F, Hosseinzadeh H. Berberine protects against glutamate-induced oxidative stress and apoptosis in PC12 and N2a cells. Iran J Basic Med Sci 2017;20(6):594–603.
38. Huang M, Jiang X, Liang Y, Liu Q, Chen S, Guo Y. Berberine improves cognitive impairment by promoting autophagic clearance and inhibiting production of β-amyloid in APP/tau/PS1 mouse model of Alzheimer's disease. Exp Gerontol 2017;91:25–33.
39. Liu X, Zhou J, Abid MD, Yan H, Huang H, Wan L, et al. Berberine attenuates axonal transport impairment and axonopathy induced by calyculin A in N2a cells. PLoS One 2014;9(4):e93974.
40. Zhan PY, Peng CX, Zhang LH. Berberine rescues D-galactose-induced synaptic/memory impairment by regulating the levels of Arc. Pharmacol Biochem Behav 2014;117:47–51.
41. Bonesi M, Loizzo MR, Conforti F, Passalacqua NG, Saab A, Menichini F, et al. *Berberis aetnensis* and *B. libanotica*: a comparative study on the chemical composition, inhibitory effect on key enzymes linked to Alzheimer's disease and antioxidant activity. J Pharm Pharmacol 2013;65(12):1726–35.
42. Jia L, Liu J, Song Z, Pan X, Chen L, Cui X, et al. Berberine suppresses amyloid-β-induced inflammatory response in microglia by inhibiting nuclear factor-κB and mitogen-activated protein kinase signaling pathways. J Pharm Pharmacol 2012;64(10):1510–21.
43. Chatuphonprasert W, Lao-Ong T, Jarukamjorn K. Improvement of superoxide dismutase and catalase in streptozotocin-nicotinamide-induced type 2-diabetes in mice by berberine and glibenclamide. Pharm Biol 2014;52(4):419–27.
44. Yin S, Bai W, Li P, Jian X, Shan T, Tang Z, et al. Berberine suppresses the ectopic expression of miR-133a in endothelial cells to improve vascular dementia in diabetic rats. Clin Exp Hypertens 2018; Epub ahead of print.
45. Bhutada P, Mundhada Y, Bansod K, Tawari S, Patil S, Dixit P, et al. Protection of cholinergic and antioxidant system contributes to the effect of berberine ameliorating memory dysfunction in rat model of streptozotocin-induced diabetes. Behav Brain Res 2011;220(1):30–41.
46. Lu DY, Tang CH, Chen YH, Wei IH. Berberine suppresses neuroinflammatory responses through AMP-activated protein kinase activation in BV-2 microglia. J Cell Biochem 2010;110(3):697–705.
47. Hsu YY, Tseng YT, Lo YC. Berberine, a natural antidiabetes drug, attenuates glucose neurotoxicity and promotes Nrf2-related neurite outgrowth. Toxicol Appl Pharmacol 2013;272(3):787–96.
48. de Oliveira JS, Abdalla FH, Dornelles GL, Palma TV, Signor C, da Silva Bernardi J, et al. Neuroprotective effects of berberine on recognition memory impairment, oxidative stress, and damage to the purinergic system in rats submitted to intracerebroventricular injection of streptozotocin. Psychopharmacology (Berl) 2019;236(2):641–55.
49. Li HY, Wang XC, Xu YM, Luo NC, Luo S, Hao XY, et al. Berberine improves diabetic encephalopathy through the SIRT1/ER stress pathway in *db/db* mice. Rejuvenation Res 2018;21(3):200–9.
50. Sandeep MS, Nandini CD. Influence of quercetin, naringenin and berberine on glucose transporters and insulin signaling molecules in brain of streptozotocin-induced diabetic rats. Biomed Pharmacother 2017;94:605–11.
51. Chen Q, Mo R, Wu N, Zou X, Shi C, Gong J, et al. Berberine ameliorates diabetes-associated cognitive decline through modulation of aberrant inflammation response and insulin signaling pathway in DM rats. Front Pharmacol 2017;8:334.
52. de Oliveira JS, Abdalla FH, Dornelles GL, Adefegha SA, Palma TV, Signor C, et al. Berberine protects against memory impairment and anxiogenic-like behavior in rats submitted to sporadic Alzheimer's-like dementia: involvement of acetylcholinesterase and cell death. Neurotoxicology 2016;57:241–50.

53. Moghaddam HK, Baluchnejadmojarad T, Roghani M, Khaksari M, Norouzi P, Ahooie M, et al. Berberine ameliorate oxidative stress and astrogliosis in the hippocampus of STZ-induced diabetic rats. Mol Neurobiol 2014;49(2):820–6.
54. Moghaddam HK, Baluchnejadmojarad T, Roghani M, Goshadrou F, Ronaghi A. Berberine chloride improved synaptic plasticity in STZ induced diabetic rats. Metab Brain Dis 2013;28(3):421–8.
55. Kalalian-Moghaddam H, Baluchnejadmojarad T, Roghani M, Goshadrou F, Ronaghi A. Hippocampal synaptic plasticity restoration and anti-apoptotic effect underlie berberine improvement of learning and memory in streptozotocin-diabetic rats. Eur J Pharmacol 2013;698(1–3):259–66.
56. Jiang YY, Cui HM, Wang JL, Liu H, Dang MM, Zhang QY, et al. Protective role of berberine and *Coptis chinensis* extract on T2MD rats and associated islet Rin-5f cells. Mol Med Rep 2017;16(5):6981–91.
57. Xu M, Xiao Y, Yin J, Hou W, Yu X, Shen L, et al. Berberine promotes glucose consumption independently of AMP-activated protein kinase activation. PLoS One 2014;9(7):e103702.
58. Dong Y, Chen YT, Yang YX, Zhou XJ, Dai SJ, Tong JF, et al. Metabolomics study of type 2 diabetes mellitus and the antidiabetic effect of berberine in Zucker diabetic fatty rats using uplc-ESI-hdms. Phytother Res 2016;30(5):823–8.
59. Liu C, Wang Z, Song Y, Wu D, Zheng X, Li P, et al. Effects of berberine on amelioration of hyperglycemia and oxidative stress in high glucose and high fat diet-induced diabetic hamsters *in vivo*. Biomed Res Int 2015;2015:313808.
60. Memon MA, Khan RN, Riaz S, Ain QU, Ahmed M, Kumar N. Methylglyoxal and insulin resistance in berberine-treated type 2 diabetic patients. J Res Med Sci 2018;23:110.
61. Kim SO, Kim HJ. Berberine ameliorates cold and mechanical allodynia in a rat model of diabetic neuropathy. J Med Food 2013;16(6):511–7.
62. Zhou J, Du X, Long M, Zhang Z, Zhou S, Zhou J, et al. Neuroprotective effect of berberine is mediated by MAPK signaling pathway in experimental diabetic neuropathy in rats. Eur J Pharmacol 2016;774:87–94.
63. Yerra VG, Kalvala AK, Sherkhane B, Areti A, Kumar A. Adenosine monophosphate-activated protein kinase modulation by berberine attenuates mitochondrial deficits and redox imbalance in experimental diabetic neuropathy. Neuropharmacology 2018;131:256–70.
64. Tian P, Ge H, Liu H, Kern TS, Du L, Guan L, et al. Leukocytes from diabetic patients kill retinal endothelial cells: effects of berberine. Mol Vis 2013;19:2092–105.
65. Fu D, Yu JY, Connell AR, Yang S, Hookham MB, McLeese R, et al. Beneficial effects of berberine on oxidized LDL-induced cytotoxicity to human retinal Müller cells. Invest Ophthalmol Vis Sci 2016;57(7):3369–79.
66. Chen H, Ji Y, Yan X, Su G, Chen L, Xiao J. Berberine attenuates apoptosis in rat retinal Müller cells stimulated with high glucose via enhancing autophagy and the AMPK/mTOR signaling. Biomed Pharmacother 2018;108:1201–7.
67. Gu Y, Zhang Y, Shi X, Li X, Hong J, Chen J, et al. Effect of traditional Chinese medicine berberine on type 2 diabetes based on comprehensive metabonomics. Talanta 2010;81(3):766–72.
68. Liu L, Yu Y, Yang JS, Li Y, Liu YW, Liang Y, et al. Berberine suppresses intestinal disaccharidases with beneficial metabolic effects in diabetic states, evidences from *in vivo* and *in vitro* study. Naunyn Schmiedebergs Arch Pharmacol 2010;381(4):371–81.
69. Li ZQ, Zuo DY, Qie XD, Qi H, Zhao MQ, Wu YL. Berberine acutely inhibits the digestion of maltose in the intestine. J Ethnopharmacol 2012;142(2):474–80.
70. Zhang X, Zhao Y, Zhang M, Pang X, Xu J, Kang C, et al. Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats. PLoS One 2012;7(8):e42529.

71. Shan CY, Yang JH, Kong Y, Wang XY, Zheng MY, Xu YG, et al. Alteration of the intestinal barrier and GLP2 secretion in berberine-treated type 2 diabetic rats. J Endocrinol 2013;218(3):255–62.
72. Zhang Q, Xiao X, Li M, Li W, Yu M, Zhang H, et al. Berberine moderates glucose metabolism through the GnRH-GLP-1 and MAPK pathways in the intestine. BMC Complement Altern Med 2014;14:188.
73. Zhang X, Zhao Y, Xu J, Xue Z, Zhang M, Pang X, et al. Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats. Sci Rep 2015;5:14405.
74. Zhu L, Zhang D, Zhu H, Zhu J, Weng S, Dong L, et al. Berberine treatment increases *Akkermansia* in the gut and improves high-fat diet-induced atherosclerosis in *Apoe*$^{-/-}$ mice. Atherosclerosis 2018;268:117–26.
75. Sun Y, Jin C, Zhang X, Jia W, Le J, Ye J. Restoration of GLP-1 secretion by berberine is associated with protection of colon enterocytes from mitochondrial overheating in diet-induced obese mice. Nutr Diabetes 2018;8(1):53.
76. Liu W, Zhang X, Liu P, Shen X, Lan T, Li W, et al. Effects of berberine on matrix accumulation and NF-κB signal pathway in alloxan-induced diabetic mice with renal injury. Eur J Pharmacol 2010;638(1–3):150–5.
77. Lan T, Shen X, Liu P, Liu W, Xu S, Xie X, et al. Berberine ameliorates renal injury in diabetic C57BL/6 mice: involvement of suppression of SphK-S1P signaling pathway. Arch Biochem Biophys 2010;502(2):112–20.
78. Wang Y, Campbell T, Perry B, Beaurepaire C, Qin L. Hypoglycemic and insulin-sensitizing effects of berberine in high-fat diet- and streptozotocin-induced diabetic rats. Metabolism 2011;60(2):298–305.
79. Wu D, Wen W, Qi CL, Zhao RX, Lü JH, Zhong CY, et al. Ameliorative effect of berberine on renal damage in rats with diabetes induced by high-fat diet and streptozotocin. Phytomedicine 2012;19(8–9):712–8.
80. Lan T, Liu W, Xie X, Huang K, Peng J, Huang J, et al. Berberine suppresses high glucose-induced TGF-β1 and fibronectin synthesis in mesangial cells through inhibition of sphingosine kinase 1/AP-1 pathway. Eur J Pharmacol 2012;697(1–3):165–72.
81. Huang K, Liu W, Lan T, Xie X, Peng J, Huang J, et al. Berberine reduces fibronectin expression by suppressing the S1P-S1P2 receptor pathway in experimental diabetic nephropathy models. PLoS One 2012;7(8):e43874.
82. Wang FL, Tang LQ, Yang F, Zhu LN, Cai M, Wei W. Renoprotective effects of berberine and its possible molecular mechanisms in combination of high-fat diet and low-dose streptozotocin-induced diabetic rats. Mol Biol Rep 2013;40(3):2405–18.
83. Tang LQ, Liu S, Zhang ST, Zhu LN, Wang FL. Berberine regulates the expression of E-prostanoid receptors in diabetic rats with nephropathy. Mol Biol Rep 2014;41(5):3339–47.
84. Lan T, Wu T, Chen C, Chen X, Hao J, Huang J, et al. Berberine attenuates high glucose-induced proliferation and extracellular matrix accumulation in mesangial cells: involvement of suppression of cell cycle progression and NF-κB/AP-1 pathways. Mol Cell Endocrinol 2014;384(1–2):109–16.
85. Yang Y, Ni W, Cai M, Tang L, Wei W. The renoprotective effects of berberine via the EP4-Gαs-cAMP signaling pathway in different stages of diabetes in rats. J Recept Signal Transduct Res 2014;34(6):445–55.
86. Sun SF, Zhao TT, Zhang HJ, Huang XR, Zhang WK, Zhang L, et al. Renoprotective effect of berberine on type 2 diabetic nephropathy in rats. Clin Exp Pharmacol Physiol 2015;42(6):662–70.
87. Ni WJ, Ding HH, Zhou H, Qiu YY, Tang LQ. Renoprotective effects of berberine through regulation of the MMPs/TIMPs system in streptozocin-induced diabetic nephropathy in rats. Eur J Pharmacol 2015;764:448–56.

88. Tang LQ, Ni WJ, Cai M, Ding HH, Liu S, Zhang ST. Renoprotective effects of berberine and its potential effect on the expression of β-arrestins and intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in streptozocin-diabetic nephropathy rats. J Diabetes 2016;8(5):693–700.
89. Ma X, Egawa T, Kimura H, Karaike K, Masuda S, Iwanaka N, et al. Berberine-induced activation of 5'-adenosine monophosphate-activated protein kinase and glucose transport in rat skeletal muscles. Metabolism 2010;59(11):1619–27.
90. Ni WJ, Tang LQ, Zhou H, Ding HH, Qiu YY. Renoprotective effect of berberine via regulating the PGE2-EP1-Gαq-Ca^{2+} signaling pathway in glomerular mesangial cells of diabetic rats. J Cell Mol Med 2016;20(8):1491–502.
91. Zhang X, He H, Liang D, Jiang Y, Liang W, Chi ZH, et al. Protective effects of berberine on renal injury in streptozotocin (STZ)-induced diabetic mice. Int J Mol Sci 2016;17(8):E1327.
92. Jin Y, Liu S, Ma Q, Xiao D, Chen L. Berberine enhances the AMPK activation and autophagy and mitigates high glucose-induced apoptosis of mouse podocytes. Eur J Pharmacol 2017;794:106–14.
93. Li Z, Zhang W. Protective effect of berberine on renal fibrosis caused by diabetic nephropathy. Mol Med Rep 2017;16(2):1055–62.
94. Wang YY, Tang LQ, Wei W. Berberine attenuates podocytes injury caused by exosomes derived from high glucose-induced mesangial cells through TGFβ1-PI3K/AKT pathway. Eur J Pharmacol 2018;824:185–92.
95. Liu X, Li G, Zhu H, Huang L, Liu Y, Ma C, et al. Beneficial effect of berberine on hepatic insulin resistance in diabetic hamsters possibly involves in SREBPs, LXRα and PPARα transcriptional programs. Endocr J 2010;57(10):881–93.
96. Zhu L, Han J, Yuan R, Xue L, Pang W. Berberine ameliorates diabetic nephropathy by inhibiting TLR4/NF-κB pathway. Biol Res 2018;51(1):9.
97. Zhou JY, Zhou SW. Protective effect of berberine on antioxidant enzymes and positive transcription elongation factor b expression in diabetic rat liver. Fitoterapia 2011;82(2):184–9.
98. Xie X, Li W, Lan T, Liu W, Peng J, Huang K, et al. Berberine ameliorates hyperglycemia in alloxan-induced diabetic C57BL/6 mice through activation of Akt signaling pathway. Endocr J 2011;58(9):761–8.
99. Lao-ong T, Chatuphonprasert W, Nemoto N, Jarukamjorn K. Alteration of hepatic glutathione peroxidase and superoxide dismutase expression in streptozotocin-induced diabetic mice by berberine. Pharm Biol 2012;50(8):1007–12.
100. Chen C, Zhang Y, Huang C. Berberine inhibits PTP1B activity and mimics insulin action. Biochem Biophys Res Commun 2010;397(3):543–7.
101. Teodoro JS, Duarte FV, Gomes AP, Varela AT, Peixoto FM, Rolo AP, et al. Berberine reverts hepatic mitochondrial dysfunction in high-fat fed rats: a possible role for SirT3 activation. Mitochondrion 2013;13(6):637–46.
102. Jiang SJ, Dong H, Li JB, Xu LJ, Zou X, Wang KF, et al. Berberine inhibits hepatic gluconeogenesis via the LKB1-AMPK-TORC2 signaling pathway in streptozotocin-induced diabetic rats. World J Gastroenterol 2015;21(25):7777–85.
103. Zhang Y, Chang X, Song X, Chen C, Chen H, Lu Z, et al. Berberine reverses abnormal expression of L-type pyruvate kinase by DNA demethylation and histone acetylation in the livers of the non-alcoholic fatty disease rat. Int J Clin Exp Med 2015;8(5):7535–43.
104. Li F, Zhao YB, Wang DK, Zou X, Fang K, Wang KF. Berberine relieves insulin resistance via the cholinergic anti-inflammatory pathway in HepG2 cells. J Huazhong Univ Sci Technol Med Sci 2016;36(1):64–9.
105. Wei S, Zhang M, Yu Y, Lan X, Yao F, Yan X, et al. Berberine attenuates development of the hepatic gluconeogenesis and lipid metabolism disorder in type 2 diabetic mice and in palmitate-incubated HepG2 cells through suppression of the HNF-4α miR122 pathway. PLoS One 2016;11(3):e0152097.

106. Sun Y, Xia M, Yan H, Han Y, Zhang F, Hu Z, et al. Berberine attenuates hepatic steatosis and enhances energy expenditure in mice by inducing autophagy and fibroblast growth factor 21. Br J Pharmacol 2018;175(2):374–87.
107. Chandirasegaran G, Elanchezhiyan C, Ghosh K. Effects of berberine chloride on the liver of streptozotocin-induced diabetes in albino Wistar rats. Biomed Pharmacother 2018;99:227–36.
108. Liu D, Zhang Y, Liu Y, Hou L, Li S, Tian H, et al. Berberine modulates gut microbiota and reduces insulin resistance via the TLR4 signaling pathway. Exp Clin Endocrinol Diabetes 2018;126(8):513–20.
109. Zhang B, Pan Y, Xu L, Tang D, Dorfman RG, Zhou Q, et al. Berberine promotes glucose uptake and inhibits gluconeogenesis by inhibiting deacetylase SIRT3. Endocrine 2018;62(3):576–87.
110. Wang LH, Yu CH, Fu Y, Li Q, Sun YQ. Berberine elicits anti-arrhythmic effects via IK1/Kir2.1 in the rat type 2 diabetic myocardial infarction model. Phytother Res 2011;25(1):33–7.
111. Cok A, Plaisier C, Salie MJ, Oram DS, Chenge J, Louters LL. Berberine acutely activates the glucose transport activity of GLUT1. Biochimie 2011;93(7):1187–92.
112. Li GS, Liu XH, Zhu H, Huang L, Liu Y, Ma CM, et al. Berberine-improved visceral white adipose tissue insulin resistance associated with altered sterol regulatory element-binding proteins, liver x receptors, and peroxisome proliferator-activated receptors transcriptional programs in diabetic hamsters. Biol Pharm Bull 2011;34(5):644–54.
113. Wang LH, Li XL, Li Q, Fu Y, Yu HJ, Sun YQ, et al. Berberine alleviates ischemic arrhythmias via recovering depressed I_{to} and I_{Ca} currents in diabetic rats. Phytomedicine 2012;19(3–4):206–10.
114. Zhang M, Wang CM, Li J, Meng ZJ, Wei SN, Li J, et al. Berberine protects against palmitate-induced endothelial dysfunction: involvements of upregulation of AMPK and eNOS and downregulation of NOX4. Mediat Inflamm 2013;2013:260464.
115. Wang M, Wang J, Tan R, Wu Q, Qiu H, Yang J, et al. Effect of berberine on PPARα/NO activation in high glucose- and insulin-induced cardiomyocyte hypertrophy. Evid Based Complement Altern Med 2013;2013:285489.
116. Chen K, Li G, Geng F, Zhang Z, Li J, Yang M, et al. Berberine reduces ischemia/reperfusion-induced myocardial apoptosis via activating AMPK and PI3K-Akt signaling in diabetic rats. Apoptosis 2014;19(6):946–57.
117. Choi JS, Kim JH, Ali MY, Min BS, Kim GD, Jung HA. *Coptis chinensis* alkaloids exert anti-adipogenic activity on 3T3-L1 adipocytes by downregulating C/EBP-α and PPAR-γ. Fitoterapia 2014;98:199–208.
118. Zhang J, Tang H, Deng R, Wang N, Zhang Y, Wang Y, et al. Berberine suppresses adipocyte differentiation via decreasing CREB transcriptional activity. PLoS One 2015;10(4):e0125667.
119. Chang W, Chen L, Hatch GM. Berberine treatment attenuates the palmitate-mediated inhibition of glucose uptake and consumption through increased 1,2,3-triacyl-sn-glycerol synthesis and accumulation in H9c2 cardiomyocytes. Biochim Biophys Acta 2016;1861(4):352–62.
120. Chang W, Li K, Guan F, Yao F, Yu Y, Zhang M, et al. Berberine pretreatment confers cardioprotection against ischemia-reperfusion injury in a rat model of type 2 diabetes. J Cardiovasc Pharmacol Ther 2016;21(5):486–94.
121. Geng FH, Li GH, Zhang X, Zhang P, Dong MQ, Zhao ZJ, et al. Berberine improves mesenteric artery insulin sensitivity through up-regulating insulin receptor-mediated signaling in diabetic rats. Br J Pharmacol 2016;173(10):1569–79.
122. Chueh WH, Lin JY. Protective effect of berberine on serum glucose levels in non-obese diabetic mice. Int Immunopharmacol 2012;12(3):534–8.
123. Ma YG, Zhang YB, Bai YG, Dai ZJ, Liang L, Liu M, et al. Berberine alleviates the cerebrovascular contractility in streptozotocin-induced diabetic rats through modulation of intracellular Ca^{2+} handling in smooth muscle cells. Cardiovasc Diabetol 2016;15:63.

124. Suman RK, Borde MK, Mohanty IR, Maheshwari U, Deshmukh YA. Myocardial salvaging effects of berberine in experimental diabetes co-existing with myocardial infarction. J Clin Diagn Res 2016;10(3):FF13–8.
125. Li H, He C, Wang J, Li X, Yang Z, Sun X, et al. Berberine activates peroxisome proliferator-activated receptor γ to increase atherosclerotic plaque stability in *Apoe*$^{-/-}$ mice with hyperhomocysteinemia. J Diabetes Investig 2016;7(6):824–32.
126. Ma YG, Liang L, Zhang YB, Wang BF, Bai YG, Dai ZJ, et al. Berberine reduced blood pressure and improved vasodilation in diabetic rats. J Mol Endocrinol 2017;59(3):191–204.
127. Chang W, Zhang M, Chen L, Hatch GM. Berberine inhibits oxygen consumption rate independent of alteration in cardiolipin levels in H9c2 cells. Lipids 2017;52(11):961–7.
128. Wang L, Ye X, Hua Y, Song Y. Berberine alleviates adipose tissue fibrosis by inducing AMP-activated kinase signaling in high-fat diet-induced obese mice. Biomed Pharmacother 2018;105:121–9.
129. Li G, Xing W, Zhang M, Geng F, Yang H, Zhang H, et al. Antifibrotic cardioprotection of berberine via downregulating myocardial IGF-1 receptor-regulated MMP-2/MMP-9 expression in diabetic rats. Am J Physiol Hear Circ Physiol 2018;315(4):H802–13.
130. Shi Y, Hu J, Geng J, Hu T, Wang B, Yan W, et al. Berberine treatment reduces atherosclerosis by mediating gut microbiota in *apoE*$^{-/-}$ mice. Biomed Pharmacother 2018;107:1556–63.
131. Hu M, Wu F, Luo J, Gong J, Fang K, Yang X, et al. The role of berberine in the prevention of HIF-1α activation to alleviate adipose tissue fibrosis in high-fat-diet-induced obese mice. Evid Based Complement Altern Med 2018;2018:4395137.
132. Hang W, He B, Chen J, Xia L, Wen B, Liang T, et al. Berberine ameliorates high glucose-induced cardiomyocyte injury via AMPK signaling activation to stimulate mitochondrial biogenesis and restore autophagic flux. Front Pharmacol 2018;9:1121.
133. Chen Y, Wang Y, Zhang J, Sun C, Lopez A. Berberine improves glucose homeostasis in streptozotocin-induced diabetic rats in association with multiple factors of insulin resistance. ISRN Endocrinol 2011;2011:519371.
134. Paul M, Hemshekhar M, Kemparaju K, Girish KS. Berberine mitigates high glucose-potentiated platelet aggregation and apoptosis by modulating aldose reductase and NADPH oxidase activity. Free Radic Biol Med 2019;130:196–205.
135. Pei C, Zhang Y, Wang P, Zhang B, Fang L, Liu B, et al. Berberine alleviates oxidized low-density lipoprotein-induced macrophage activation by downregulating galectin-3 via the NF-κB and AMPK signaling pathways. Phytother Res 2019;33(2):294–308.
136. Hirai T, Mitani Y, Kurumisawa K, Nomura K, Wang W, Nakashima KI, et al. Berberine stimulates fibroblast growth factor 21 by modulating the molecular clock component brain and muscle Arnt-like 1 in brown adipose tissue. Biochem Pharmacol 2019;164:165–76.
137. Chueh WH, Lin JY. Berberine, an isoquinoline alkaloid in herbal plants, protects pancreatic islets and serum lipids in nonobese diabetic mice. J Agric Food Chem 2011;59(14):8021–7.
138. Chueh WH, Lin JY. Berberine, an isoquinoline alkaloid, inhibits streptozotocin-induced apoptosis in mouse pancreatic islets through down-regulating *Bax*/*Bcl-2* gene expression ratio. Food Chem 2012;132(1):252–60.
139. Shen N, Huan Y, Shen ZF. Berberine inhibits mouse insulin gene promoter through activation of AMP activated protein kinase and may exert beneficial effect on pancreatic β-cell. Eur J Pharmacol 2012;694(1–3):120–6.
140. Chandirasegaran G, Elanchezhiyan C, Ghosh K, Sethupathy S. Berberine chloride ameliorates oxidative stress, inflammation and apoptosis in the pancreas of streptozotocin induced diabetic rats. Biomed Pharmacother 2017;95:175–85.
141. Chen DL, Yang KY. Berberine alleviates oxidative stress in islets of diabetic mice by inhibiting miR-106b expression and up-regulating SIRT1. J Cell Biochem 2017;118(12):4349–57.

142. Liu L, Liu J, Gao Y, Yu X, Xu G, Huang Y. Uncoupling protein-2 mediates the protective action of berberine against oxidative stress in rat insulinoma INS-1E cells and in diabetic mouse islets. Br J Pharmacol 2014;171(13):3246–54.
143. Yang TC, Chao HF, Shi LS, Chang TC, Lin HC, Chang WL. Alkaloids from *Coptis chinensis* root promote glucose uptake in C2C12 myotubes. Fitoterapia 2014;93:239–44.
144. Xie X, Chang X, Chen L, Huang K, Huang J, Wang S, et al. Berberine ameliorates experimental diabetes-induced renal inflammation and fibronectin by inhibiting the activation of RhoA/ROCK signaling. Mol Cell Endocrinol 2013;381(1–2):56–65.
145. Shwe T, Pratchayasakul W, Chattipakorn N, Chattipakorn SC. Role of D-galactose-induced brain aging and its potential used for therapeutic interventions. Exp Gerontol 2018;101:13–36.
146. Yu D, Tao BB, Yang YY, Du LS, Yang SS, He XJ, et al. The IDO inhibitor coptisine ameliorates cognitive impairment in a mouse model of Alzheimer's disease. J Alzheimers Dis 2015;43(1):291–302.
147. Sharma R, Razdan K, Bansal Y, Kuhad A. Rollercoaster ride of kynurenines: steering the wheel towards neuroprotection in Alzheimer's disease. Expert Opin Ther Targets 2018;22(10):849–67.
148. Jacobs KR, Lim CK, Blennow K, Zetterberg H, Chatterjee P, Martins RN, et al. Correlation between plasma and CSF concentrations of kynurenine pathway metabolites in Alzheimer's disease and relationship to amyloid-β and tau. Neurobiol Aging 2019;80:11–20.
149. Kitada M, Ogura Y, Monno I, Koya D. Sirtuins and type 2 diabetes: role in inflammation, oxidative stress, and mitochondrial function. Front Endocrinol 2019;10:187.
150. Vendrov AE, Vendrov KC, Smith A, Yuan J, Sumida A, Robidoux J, et al. NOX4 NADPH oxidase-dependent mitochondrial oxidative stress in aging-associated cardiovascular disease. Antioxid Redox Signal 2015;23(18):1389–409.
151. de la Monte SM, Tong M. Brain metabolic dysfunction at the core of Alzheimer's disease. Biochem Pharmacol 2014;88(4):548–59.
152. Lee SJ, Chung YH, Joo KM, Lim HC, Jeon GS, Kim D, et al. Age-related changes in glycogen synthase kinase 3β (GSK3β) immunoreactivity in the central nervous system of rats. Neurosci Lett 2006;409(2):134–9.
153. Zhou FQ, Snider WD. Cell biology. GSK3β and microtubule assembly in axons. Science 2005;308(5719):211–4.
154. Wu H, Lu D, Jiang H, Xiong Y, Qu C, Li B, et al. Simvastatin-mediated upregulation of VEGF and BDNF, activation of the PI3K/Akt pathway, and increase of neurogenesis are associated with therapeutic improvement after traumatic brain injury. J Neurotrauma 2008;25(2):130–9.
155. Hu YS, Long N, Pigino G, Brady ST, Lazarov O. Molecular mechanisms of environmental enrichment: impairments in Akt/GSK3β, neurotrophin-3 and CREB signaling. PLoS One 2013;8(5):e64460.
156. Pardo M, Abrial E, Jope RS, Beurel E. GSK3β isoform-selective regulation of depression, memory and hippocampal cell proliferation. Genes Brain Behav 2016;15(3):348–55.
157. Eom TY, Jope RS. Blocked inhibitory serine-phosphorylation of glycogen synthase kinase-3α/β impairs *in vivo* neural precursor cell proliferation. Biol Psychiatry 2009;66(5):494–502.
158. Kitagishi Y, Nakanishi A, Ogura Y, Matsuda S. Dietary regulation of PI3K/AKT/GSK3β pathway in Alzheimer's disease. Alzheimers Res Ther 2014;6(3):35.
159. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev 2007;56(2):384–402.
160. Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, de la Monte SM. Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. J Alzheimers Dis 2006;9(1):13–33.
161. Haan MN. Therapy insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. Nat Clin Pr Neurol 2006;2(3):159–66.

162. Tan XS, Ma JY, Feng R, Ma C, Chen WJ, Sun YP, et al. Tissue distribution of berberine and its metabolites after oral administration in rats. PLoS One 2013;8(10):e77969.
163. Chang W, Chen L, Hatch GM. Berberine as a therapy for type 2 diabetes and its complications: from mechanism of action to clinical studies. Biochem Cell Biol 2015;93(5):479–86.
164. Xourgia E, Papazafiropoulou A, Melidonis A. Antidiabetic treatment on memory and spatial learning: from the pancreas to the neuron. World J Diabetes 2019;10(3):169–80.
165. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol 2018;14(3):168–81.
166. Appleton J, Scutt P, Sprigg N, Bath P. Hypercholesterolaemia and vascular dementia. Clin Sci (Lond) 2017;131(14):1561–78.
167. O'Brien JT, Thomas A. Vascular dementia. Lancet 2015;386(10004):698–706.
168. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. BMJ 1994;308(6944):1604–8.
169. Polidori MC, Mattioli P, Aldred S, Cecchetti R, Stahl W, Griffiths H, et al. Plasma antioxidant status, immunoglobulin g oxidation and lipid peroxidation in demented patients: relevance to Alzheimer disease and vascular dementia. Dement Geriatr Cogn Disord 2004;18(3–4):265–70.
170. Dantoine TF, Debord J, Merle L, Lacroix-Ramiandrisoa H, Bourzeix L, Charmes JP. Paraoxonase 1 activity: a new vascular marker of dementia? Ann N Y Acad Sci 2002;977:96–101.
171. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes dyslipidemia. Diabetes Ther 2016;7(2):203–219.
172. Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375(9733):2215–22.
173. Abbasi A, Corpeleijn E, Gansevoort RT, Gans RO, Hillege HL, Stolk RP, et al. Role of HDL cholesterol and estimates of HDL particle composition in future development of type 2 diabetes in the general population: the PREVEND study. J Clin Endocrinol Metab 2013;98(8):E1352–9.
174. Patti AM, Giglio RV, Papanas N, Rizzo M, Rizvi AA. Future perspectives of the pharmacological management of diabetic dyslipidemia. Expert Rev Clin Pharmacol 2019;12(2):129–43.
175. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364(9435):685–96.
176. Carrizzo A, Izzo C, Oliveti M, Alfano A, Virtuoso N, Capunzo M, et al. The main determinants of diabetes mellitus vascular complications: endothelial dysfunction and platelet hyperaggregation. Int J Mol Sci 2018;19(10):E2968.
177. Tousoulis D, Kampoli AM, Stefanadis C. Diabetes mellitus and vascular endothelial dysfunction: current perspectives. Curr Vasc Pharmacol 2012;10(1):19–32.
178. Sobel BE, Schneider DJ. Platelet function, coagulopathy, and impaired fibrinolysis in diabetes. Cardiol Clin 2004;22(4):511–26.
179. Joubert M, Manrique A, Cariou B, Prieur X. Diabetes-related cardiomyopathy: the sweet story of glucose overload from epidemiology to cellular pathways. Diabetes Metab 2019;45(3):238–47.
180. Kenny HC, Abel ED. Heart failure in type 2 diabetes mellitus. Circ Res 2019;124(1):121–41.
181. Hildebrand S, Stümer J, Pfeifer A. PVAT and its relation to brown, beige, and white adipose tissue in development and function. Front Physiol 2018;9:70.
182. Buckley AJ, Thomas EL, Lessan N, Trovato FM, Trovato GM, Taylor-Robinson SD. Non-alcoholic fatty liver disease: relationship with cardiovascular risk markers and clinical endpoints. Diabetes Res Clin Pr 2018;144:144–52.

183. Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int 2009;29(1):113–9.
184. Chen CH, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of Taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. J Clin Gastroenterol 2006;40(8):745–52.
185. de la Monte SM, Longato L, Tong M, Wands JR. Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. Curr Opin Investig Drugs 2009;10(10):1049–60.
186. Tong M, de la Monte SM. Mechanisms of ceramide-mediated neurodegeneration. J Alzheimers Dis 2009;16(4):705–14.
187. Lyn-Cook LE Jr, Lawton M, Tong M, Silbermann E, Longato L, Jiao P, et al. Hepatic ceramide may mediate brain insulin resistance and neurodegeneration in type 2 diabetes and non-alcoholic steatohepatitis. J Alzheimers Dis 2009;16(4):715–29.
188. Kim DG, Krenz A, Toussaint LE, Maurer KJ, Robinson SA, Yan A, et al. Non-alcoholic fatty liver disease induces signs of Alzheimer's disease (AD) in wild-type mice and accelerates pathological signs of AD in an AD model. J Neuroinflammation 2016;13:1.
189. Deckers K, Camerino I, van Boxtel MP, Verhey FR, Irving K, Brayne C, et al. Dementia risk in renal dysfunction: a systematic review and meta-analysis of prospective studies. Neurology 2017;88(2):198–208.
190. Elias MF, Dore GA, Davey A. Kidney disease and cognitive function. Contrib Nephrol 2013;179:42–57.
191. Hobson P, Lewis A, Nair H, Wong S, Kumwenda M. How common are neurocognitive disorders in patients with chronic kidney disease and diabetes? Results from a cross-sectional study in a community cohort of patients in North Wales, UK. BMJ Open 2018;8(12):e023520.
192. Kurella Tamura M, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. Kidney Int 2011;79(1):14–22.
193. Zammit AR, Katz MJ, Bitzer M, Lipton RB. Cognitive impairment and dementia in older adults with chronic kidney disease: a review. Alzheimer Dis Assoc Disord 2016;30(4):357–66.
194. Chiu YL, Tsai HH, Lai YJ, Tseng HY, Wu YW, Peng YS, et al. Cognitive impairment in patients with end-stage renal disease: Accelerated brain aging? J Formos Med Assoc 2019;118(5):867–75.
195. Szrejder M, Piwkowska A. AMPK signaling: implications for podocyte biology in diabetic nephropathy. Biol Cell 2019;111(5):109–20.
196. Lin TA, Wu VC, Wang CY. Autophagy in chronic kidney diseases. Cells 2019;8(1):E61.
197. Thakur S, Viswanadhapalli S, Kopp JB, Shi Q, Barnes JL, Block K, et al. Activation of AMP-activated protein kinase prevents TGF-β1-induced epithelial-mesenchymal transition and myofibroblast activation. Am J Pathol 2015;185(8):2168–80.
198. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 2016;164(3):337–40.
199. Gérard C, Vidal H. Impact of gut microbiota on host glycemic control. Front Endocrinol 2019;10:29.
200. Aydin Ö, Nieuwdorp M, Gerdes V. The gut microbiome as a target for the treatment of type 2 diabetes. Curr Diab Rep 2018;18(8):55.
201. Harsch IA, Konturek PC. The role of gut microbiota in obesity and type 2 and type 1 diabetes mellitus: new insights into "Old" diseases. Med Sci 2018;6(2):E32.
202. Sircana A, Framarin L, Leone N, Berrutti M, Castellino F, Parente R, et al. Altered gut microbiota in type 2 diabetes: just a coincidence? Curr Diab Rep 2018;18(10):98.
203. Sharma S, Tripathi P. Gut microbiome and type 2 diabetes: where we are and where to go? J Nutr Biochem 2019;63:101–8.

204. Belizário JE, Faintuch J, Garay-Malpartida M. Gut microbiome dysbiosis and immunometabolism: new frontiers for treatment of metabolic diseases. Mediat Inflamm 2018;2018:2037838.
205. Safari Z, Gérard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cell Mol Life Sci 2019;76(8):1541–58.
206. García-Ríos A, Camargo Garcia A, Perez-Jimenez F, Perez-Martinez P. Gut microbiota: a new protagonist in the risk of cardiovascular disease? Clin Investig Arter 2019;31(4):178–185
207. Jazani NH, Savoj J, Lustgarten M, Lau WL, Vaziri ND. Impact of gut dysbiosis on neurohormonal pathways in chronic kidney disease. Diseases 2019;7(1):E21.
208. Sochocka M, Donskow-Łysoniewska K, Diniz BS, Kurpas D, Brzozowska E, Leszek J. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease—a critical review. Mol Neurobiol 2019;56(3):1841–51.
209. Chen T, Xiong S, Jiang S, Wang M, Wu Q, Wei H. Effects of traditional Chinese medicine on intestinal bacteria: a review. Indian J Trad Knowl 2012;11(3):401–7.
210. Han J, Lin H, Huang W. Modulating gut microbiota as an anti-diabetic mechanism of berberine. Med Sci Monit 2011;17(7):RA164–7.
211. Cheung CY, Chan VTT, Mok VC, Chen C, Wong TY. Potential retinal biomarkers for dementia: what is new? Curr Opin Neurol 2019;32(1):82–91.
212. Turner N, Li JY, Gosby A, To SW, Cheng Z, Miyoshi H, et al. Berberine and its more biologically available derivative, dihydroberberine, inhibit mitochondrial respiratory complex I: a mechanism for the action of berberine to activate AMP-activated protein kinase and improve insulin action. Diabetes 2008;57(5):1414–8.
213. Lyons CL, Roche HM. Nutritional modulation of AMPK-impact upon metabolic-inflammation. Int J Mol Sci 2018;19(10):E3092.
214. Hu X, Zhang Y, Xue Y, Zhang Z, Wang J. Berberine is a potential therapeutic agent for metabolic syndrome via brown adipose tissue activation and metabolism regulation. Am J Transl Res 2018;10(11):3322–9.
215. Ninomiya T. Diabetes mellitus and dementia. Curr Diab Rep 2014;14(5):487.
216. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5(1):64–74.
217. Moran C, Callisaya ML, Srikanth V, Arvanitakis Z. Diabetes therapies for dementia. Curr Neurol Neurosci Rep 2019;19(8):58.
218. Yuan NN, Cai CZ, Wu MY, Su HX, Li M, Lu JH. Neuroprotective effects of berberine in animal models of Alzheimer's disease: a systematic review of pre-clinical studies. BMC Complement Altern Med 2019;19(1):109.
219. Jiang W, Li S, Li X. Therapeutic potential of berberine against neurodegenerative diseases. Sci China Life Sci 2015;58(6):564–9.
220. Ji H, Shen L. Berberine: a potential multipotent natural product to combat Alzheimer's disease. Molecules 2011;16(8):6732–40.
221. Kulkarni SK, Dhir A. Berberine: a plant alkaloid with therapeutic potential for central nervous system disorders. Phytother Res 2010;24(3):317–24.
222. Singh A, Bajpai V, Kumar S, Arya KR, Sharma KR, Kumar B. Quantitative determination of isoquinoline alkaloids and chlorogenic acid in *Berberis* species using ultra high performance liquid chromatography with hybrid triple quadrupole linear ion trap mass spectrometry. J Sep Sci 2015;38(12):2007–13.
223. Singh A, Bajpai V, Kumar S, Singh Rawat AK, Kumar B. Analysis of isoquinoline alkaloids from mahonia leschenaultia and mahonia napaulensis roots using UHPLC-Orbitrap-MSn and UHPLC-QqQLIT-MS/MS. J Pharm Anal 2017;7(2):77–86.

224. Och A, Szewczyk K, Pecio Ł, Stochmal A, Załuski D, Bogucka-Kocka A. UPLC-MS/MS profile of alkaloids with cytotoxic properties of selected medicinal plants of the *Berberidaceae* and *Papaveraceae* families. Oxid Med Cell Longev 2017;2017:9369872.
225. Qi L, Ma Y, Zhong F, Shen C. Comprehensive quality assessment for Rhizoma Coptidis based on quantitative and qualitative metabolic profiles using high performance liquid chromatography, Fourier transform near-infrared and Fourier transform mid-infrared combined with multivariate statistical analysis. J Pharm Biomed Anal 2018;161:436–43.
226. Dawes ML, Brettell T. Analysis of goldenseal, *Hydrastis canadensis* L., and related alkaloids in urine using HPLC with UV detection. J Chromatogr B Anal Technol Biomed Life Sci 2012;880(1):114–8.
227. McNamara CE, Perry NB, Follett JM, Parmenter GA, Douglas JA. A new glucosyl feruloyl quinic acid as a potential marker for roots and rhizomes of goldenseal, *Hydrastis canadensis*. J Nat Prod 2004;67(11):1818–22.
228. Xian X, Sun B, Ye X, Zhang G, Hou P, Gao H. Identification and analysis of alkaloids in cortex *Phellodendron amurense* by high-performance liquid chromatography with electrospray ionization mass spectrometry coupled with photodiode array detection. J Sep Sci 2014;37(13):1533–45.
229. Končić MZ, Kremer D, Schühly W, Brantner A, Karlović K, Kalođera Z. Chemical differentiation of *Berberis croatica* and *B. vulgaris* using HPLC fingerprinting. Croat Chem Acta 2010;83(4):451–6.
230. Li JC, Shen XF, Shao JA, Tao MM, Gu J, Li J, et al. The total alkaloids from *Coptis chinensis* Franch improve cognitive deficits in type 2 diabetic rats. Drug Des Devel Ther 2018;12:2695–706.
231. Steinmann D, Baumgartner RR, Heiss EH, Bartenstein S, Atanasov AG, Dirsch VM, et al. Bioguided isolation of (9Z)-octadec-9-enoic acid from *Phellodendron amurense* Rupr. and identification of fatty acids as PTP1B inhibitors. Planta Med 2012;78(3):219–24.
232. Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of *Berberis vulgaris* and its active constituent, berberine. Phytother Res 2008;22(8):999–1012.
233. Tabeshpour J, Imenshahidi M, Hosseinzadeh H. A review of the effects of *Berberis vulgaris* and its major component, berberine, in metabolic syndrome. Iran J Basic Med Sci 2017;20(5):557–68.