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Review Article

Natural Products and Therapy of Diabetes-Associated Cognitive Decline

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1. Abstract

Cognitive impairment caused by diabetes is increasingly concerned and investigated. Both type 1 and type 2 diabetes mellitus have been proved to be related to the declined performance on numerous domains of cognitive function. The pathogenesis of cognitive impairments in diabetes is complex and multiple. Natural products have low or few incidences of drug adverse reactions when they are used for a long time, so it is very beneficial for the therapy of chronic diseases. This review sorted natural products against diabetes-associated cognitive deficiency at the aspect of compounds, the extracts, and prescriptions. Moreover, the action mechanisms of these natural products were analyzed and summarized. These researches laid a certain foundation for the deep study of diabetes-associated cognitive impairments. Diabetes Mellitus (DM), characterized by long-term hyper glycemia, is one of the most important and prevalent chronic diseases, and has a cumulative impact on almost every country, age group, and economy across the world. Data from the International Diabetes Federation show that approximately415 million people were suffering from diabetes worldwide in 2015, and this number is expected to exceed 640million by the year 2040. It is estimated that half of patients with diabetes are unaware of their disease and are thus more prone to developing diabetic complications [1]. Complications of diabetes are common among patients with type 1 or type 2 DM (T1DM or T2DM), and are responsible for significant morbidity and mortality, especially the chronic complications. The chronic diabetic complications are generally divided into micro vascular and macro vascular complications, while the former have much higher prevalence than the latter [2].Micro vascular complications of DM mainly include neuropathy, nephropathy, and retinopathy. Diabetic Encephalopathy (DE) is an emerging diabetic complication, which is an important diabetic complication and affects at least 40% of diabetics [3,4]. Diabetes-Associated Cognitive Decline (DACD) is the core component of DE. DE is one of the severe micro vascular complications of diabetes, characterized by impaired cognitive functions, and electrophysiological, neuro chemical and structural abnormalities. The pathogenesis of DE is complex and no golden standard for its diagnosis. Nevertheless, most researches reach a consensus that chronic metabolic alterations, vascular changes, and neuronal apoptosis may play pivotal roles in neuronal loss and cognitive dysfunction. In the last decade, lots of natural products, including the Traditional Chinese Herbs, are reported to be effective on diabetes-associated cognitive deficits in animals. In this review, we will introduce some natural products that were reported to have beneficial effects on DACD inrodents in the past decade, mainly focusing on the classification of these compounds according to chemical structure and their possible mechanism of action.

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2. Compounds Sorting by Chemical Structure

2.1 Flavonoids

Dietary intakes of flavonols are positively correlated with the protected cognitive function in middle-aged adults over time [5]. Twelve compounds of flavonoids are reported to attenuate cognitive deficits of diabetic rodents, which are listed as following: Curcumin, Quercetin, Luteolin, Naringin, Epigallocatechin-3-gallate, Chrysin, Puerarin, Vitexin, Calycosin, Glabridin, Pelargonidin, and Crocin. Curcumin is a poly phenolic flavonoid found in turmeric and several traditional herbal medicines; chronic treatment with Curcumin attenuates diabetic encephalopathy in rats [6].Quercetin[3,3',4',5,7-pentahydroxyflavone], widely distributed in the plant kingdom, has ameliorative effect on memory dysfunction in streptozotocin-induced diabetic rats [7].Luteolin (3',4',5,7-tetrahydroxyflavone), attenuates diabetes-associated cognitive decline in rats [8,9].Naringin, a natural di hydro flavonoid widely distributed in grapefruit and other citrus fruits, ameliorates cognitive deficits of rats in T1DM or T2DM [10,11].Epigallocatechin-3-gallate is a poly phenolic bioflavonoid derived from a variety of plants, especially from green tea;epigallocatechin-3-gallate ameliorates learning and memory deficits in diabetic rats [12]. Chrysin, a natural plant flavonoid extracted from many plants, honey and propolis, ameliorates diabetes-associated cognitive deficits in Wistar rats [13]. Puerarin, an iso flavonoid extracted from Kudzu roots, ameliorates cognitive deficits in streptozotocin-induced diabetic rats [14]. Vitexin, an apigenin flavone glucoside, improves spatial learning and memory ability of diabetic rats [15]. Calycosin, an O-methylated iso flavone isolated from AstragalusmembranaceusBge. Var. mongholicus and Trifoliumpratense L., can ameliorate diabetic encephalopathy in rats [16]. Glabridin, a major active iso flavane from Glycyrrhizaglabra (licorice),improves learning and memory abilities in non-diabetic rats, while it reverses learning and memory deficits in diabetic rats [17].Single-dose oral pelargonidin, a kind of anthocyanins, may attenuate spatial memory in the Y-shaped maze paradigm and multiple-dose chronic pelargonidin could improve retention and recall capability in the passive avoidance test in T1DM rats [18]. Crocin is the major yellow pigment of saffron and gardenia yellow, which are extracts of Crocus sativusstigmas and Gardenia jasminoides fruits, respectively. And Crocin improves learning and memory impairments in streptozotocin diabetic rats [19].

2.2. Alkaloids

Berberine is an iso quinoline alkaloid, which is mainly found in Coptischinensis; chronic treatment with Berberine improves the cognitive dysfunction caused by T1DM or T2DM in rodents [20-22]. Huperzine A is a novel Lycopodium alkaloid extracted from the Chinese folk medicine Huperzia serrate, and huperzine A ameliorates cognitive deficits instreptozotocin-Induced diabetic rats [23].Caffeine consumption prevents diabetes-Induced memory impairment of T2DMmice [24]. Oxymatrine, a major quinolizidine alkaloid from the root of Sophoraflavescens Alt, attenuates diabetes-associated cognitive deficits in rats [25].

2.3. Phenols

Sesamol (5-hydroxy-1,3-benzodioxoleor 3,4-methylenedioxyphenol), a major constituent of sesame seed oil, attenuates diabetes-associated cognitive decline in rats [26]. Resveratrol (3,5,4-trihydroxy-trans-stilbene), found mainly in grapes and red wine, prevents memory deficits instreptozotocin-induced diabetic rats [27]. Tocotrienol, a member of the vitamin E family, can prevent diabetes-associated cognitive deficits in rats [28].

2.4. Terpenoids

Catalpol, an iridoid glycoside, shows treatment and/or prevention on diabetic encephalopathy in rats [29].Aucubin, aniridoid mono terpene, is found in the Traditional Chinese Herbs, such as Plantagoasiatica, Eucommiaulmoides, and Plantagolanceolata L, and aucubin can exert neuro protection against primary diabetic encephalopathy in rats [30-32].Carvacrol (2-methyl-5-isopropylphenol), a phenolic mono terpene, is the major compound of essential oils produced by numerous aromatic plants and spices of the family Lamiaceae, including the genera Origanum and Thymus. Carvacrol attenuates diabetes-associated cognitive deficits in rats [33]. An drographolide, a lab danediterpenoid, is the main bioactive component of the medicinal plant and rographispaniculata, and An drographolide indicates beneficial effects on cognitive functions in streptozotocin-induced diabetic rats [34].

2.5. Organic Acids

Danshensu [3-(3, 4-dihydroxyphenyl)-2-hydroxy-propanoic acid], a hydrophilic phenolic compound from Salviamiltiorrhiza Bunge, ameliorates the cognitive decline in streptozotocin-induced diabetic mice [35]. Cinnamic acid, mainly found in cinnamon (Cinnamomum cassia), improves memory of diabetic mice [36]. Rosmarinic acid, a principal constituent from Salvia officinalis L., shows preventive effects against learning and memory deficit induced by diabetes in rats [37].

2.6. Saponins

Ginseng extracts and the isolated ginsenosides show relevant to cognition in humans [38]. Ginsenoside Re, a triterpenoidsaponin compound derived from Panax ginseng C. A. Mey., remarkably attenuates cognitive deficits caused by diabetes in rats [39]. Ginsenoside Rg5 improves cognitive dysfunction in streptozotocin-

induced memory impaired rats [40].

2.7. Xanthone

Mangifer in [2-C-β-Dgluco-pyranosyl-1,3,6,7-tetrahydroxyxanthone],a C-glucosideofxanthone, can markedly ameliorate diabetes-associated cognitive decline in rats [41]. Mangifer in mainly exists in Mangiferaindica L., also in Chinese Herbal Medicines Rhizoma Anemarrhenae and Rhizoma Belamcandae.

2.8. Carotene and carotenoid

Lycopene, a carotenoidn mostly found in tomatoes and tomato products, improves the cognitive function of diabetic rats [42].

2.9. Resins

Gugulipid, an ethyl acetate extract of the resin of plant Commiphorawhighitii, has protective effects against streptozotocin-induced memory deficits in mice [43]. Moreover, gugulipidacts as a potential anti-dementia drug (Central Drug Research Institute, Lucknow has obtained US patent No. 6896901 for use of gugulipid as cognitive enhancer).

2.10. Butylphthalide

L-3-n-Butylphthalide, extracted as a pure component from the seed of Chinese celery, ameliorates the cognitive dysfunction in streptozotocin-induced diabetic rats [44].

3. Extracts and Prescriptions from Natural Products against DACD

3.1. Extracts

Chronic treatment with total Saponins from Rhizoma Anemarrhenae significantly augments the learning ability of the diabetic rats in the Morris water maze test, which is related to the reduction of Aβ accumulation and suppression of inflammation in brain [45]. Chronic supplementation with the extracts of with aniasomnifera and Aloevera improves memory impairment and motor dysfunction of diabetic mice, accompanied by the lowered blood glucose level and reduced oxidative damage [46].Saffron aqueous extract shows ameliorative effect of on diabetic encephalopathy in streptozotocin-induced experimental T1DM in rats [47]. Hypericumperforatum extract can protect against learning and memory deficits in diabetic rats [48]. FlosPuerariae extract ameliorates cognitive impairment in streptozotocin-induced diabetic mice [49]. Oral administration of Ficusdel to idea leaf extract to diabetic rats attenuates spatial learning and memory impairment [15]. Pomegranate (Punicagranatum L.) flower improves learning and memory performances caused by T1DM in rats [50].The extracts of seeds of Garcinia kolamay prevent cognitive dysfunctions caused by T1DM in rats [51].Mango leaf extract improves cognitive impairment caused byT2DM in mice [52]. Salvia officinalis L. indicates preventive effects against learning and memory deficit induced by diabetes in rats [37]. An drographispaniculata extract indicates beneficial effects on cognitive functions in streptozotocin-induced diabetic rats [34].Urticadioica extract attenuates recognition memory deficit in streptozotocin-induced diabetic mice [53,54].Radix PolygoniMultiflori, a famous Traditional Chinese Material, shows the protective effect on diabetic encephalopathy in rats [55]. Ethanol extract of Clitoreaternatea, a herb from Indian folklore, improves diabetes-induced cognitive decline in rats [56].The alcoholic extracts of roots of the Salaciareticulata W. and Clitoreaternatea L. prevent learning and memory impairment in the streptozotocin-induced young diabetic rats [57].

3.2. Prescriptions

ZiBuPiYin recipe improves cognitive decline in Zucker diabetic fatty rats [58] and db/db diabetic fatty mice [59,60]. Huanglian-Wendan Decoction indicates protective effects against cognitive deficits in rats with diabetic encephalopathy [61]. LiuweiDihuang Decoction shows neuro protective effect against cognition deficits of diabetic encephalopathy in rat [62].Treatment with Chinese Jinzhida recipe improves cognitive function in the T2DM rat model [63]. Kangen-karyu, a Chinese herbal prescription, attenuates cognitive deficits in T2DMdb/db mice [64]. Chotosan, a Kampo formula, ameliorates cognitive deficits in T2DM mice [65] and juvenile-onset T1DM rats [66].

4. Action Mechanism of the Compounds against DACD

4.1 Anti-Inflammation and/Oranti-Oxidation

A lot of reports verify that oxidative stress and inflammation are involved in the pathogenesis of chronic diabetic complications, including DACD. Actually, neuro protection of most natural products against DACD is achieved through anti-inflammation and anti-oxidation efficacy. Chronic treatment with Curcumin, Sesamol or Lycopene improved cognitive deficit of diabetic rats in Morris Water Maze (MWM) test, and attenuate oxidative stress and inflammation in the cerebral cortex and hippocampal regions of diabetic rats [6, 26, 42]. Carvacrolcould remarkably attenuate DACD in rats, which was related to inhibition of oxidative stress, inflammation, and apoptotic cascades caused by diabetes [33]. Tocotrienolameliorated the memory of streptozotocin-induced diabetic rats through inhibiting oxidative-nitrosative stress, and NF-κB mediated neuro inflammatory cascades [28]. Chrysin remarkably alleviated diabetes-associated cognitive deficits in rats, which was linked with suppression of oxidative stress, inflammation and apoptotic cascades[13].Chronic treatment with oxymatrine alleviatedDACD in rats, which was associated with inhibition of oxidative stress, inflammation and apoptotic cascades[25].Supplementation of naringin improved learning and memory performances of rats through inhibition

of oxidative stress and inflammation, which might be mediated by PPAR gamma activation in T1DM or T2DM [10, 11]. Puerarin possessed neuro protection to ameliorate cognitive deficits in streptozotocin-induced diabetic rats by anti-inflammatory, antioxidant and anti-apoptotic effects [14].Luteolin could inhibit apoptosis of hippocampal nerve cells in rats with diabetic encephalopathy, which was mediated by an indirect anti-oxidative effect, and the inhibition of activation of apoptosis-related factors [8]. Huperzine A ameliorated DACD in rats via inhibiting oxidative stress, inflammation and apoptosis[23].Chronic treatment with Berberine improved cognitive performance of the diabetic rats, accompanied by the lowered hyperglycemia, decreased lipid peroxidation, and elevated reduced glutathione level [20].GinsenosideRg5improvedstreptozotocin-induced learning and memory impairments in rats, which was associated with attenuating neuro inflammatory responses[40].Our previous report indicated that chronic ginsenosideRe treatment decreased the escape latency and increased percentage of time spent in the target quadrant of the diabetic rats in MWM test. Furthermore, ginsenosideRe treatment attenuated oxidative stress and inflammation, as evidenced by the reduced levels of TNF-alpha and malondialdehyde in two brain areas, as well as the enhanced GSH levels in serum of diabetic rats [39]. Chronic green tea epigallocatechingallate could dose-dependently ameliorate learning and memory deficits in streptozotocin-diabetic rats through attenuation of oxidative stress and modulation of nitric oxide [12].Quercetin treatment ameliorated cognitive dysfunction in the diabetic rats likely due to its anti-oxidant efficacy, which was comparable to vitamin C [7].Cinnamic acid improved memory by reducing the oxidative stress in the brain of diabetic mice[36].Beneficial effects of crocin on streptozotocin-induced memory dysfunction in rats may be attributed to its anti diabetic and antioxidant activity[19].Long-term oral supplementation of catalpol improved neuronal injury and cognitive dysfunction in T1DM rats by attenuating oxidative stress and its anti diabetic activity [29]. Danshensuameliorated the learning and memory deficits in diabetic mice, which was due to suppression of NF-κB mediated neuro inflammatory cascades [35]. Calycosin had a beneficial effect on the amelioration, prevention and treatment of DACD in rats through attenuating oxidative stress damages [16]. Aucubinameliorated diabetic encephalopathy and loss of hippocampal neurons in rats by regulating endogenous antioxidant enzymatic activity [30].

4.2. Protecting the Central Cholinergic System

Resveratrol alleviated memory impairment and prevented the increase in acetyl cholinesterase activity in diabetic rats, demonstrating that Resveratrol could modulate cholinergic neurotransmission and consequently improve cognition [27].Gugulipid had significant protective affect against streptozotocin-induced memory deficits in mice, which could be attributed to anti-oxidant and anti-acetyl cholinesterase activity of gugulipid [43].Tocotrienolameliorated the memory of streptozotocin-induced diabetic rats through decreasing acetyl cholinesterase activity[28]. Chronic treatment with luteolin improved neuronal injury and cognitive performance in diabetic rats by attenuating oxidative stress and choline esterase activity [9].Quercetin treatment ameliorated cognitive dysfunction in the diabetic rats, which was associated with its anti-acetyl cholinesterase effect, and was comparable to donepezil (a typical acetyl cholinesterase inhibitor) [6].Cinnamic acid improved memory by attenuating cholinergic dysfunction in the brain of diabetic mice [36].Huperzine A ameliorated DACD in rats via regulating the activities of choline acetylase and acetyl cholinesterase [23].

4.3. Restoring Hippocampal Synaptic Plasticity

Berberine improvement of learning and memory in streptozotocin-diabetic rats was associated with hippocampal synaptic plasticity restoration and anti-apoptotic effect [21].Caffeine, a mixed antagonist of adenosine A(1) and A(2A) receptors, attenuated memory impairment of mice via preventing synaptic dysfunction and astrogliosis in T2DM [24].L-3-n-Butylphthalide could improve the cognitive function in the rats with T1DM by up-regulating the protein expression and mRNA level of hippocampal NR2B, one of the subunits of N-methyl-D-aspartate receptor (an important factor for the formation of long-term potentiation) [44]. Calycosin had a beneficial effect on the amelioration, prevention and treatment of DACD in rats, accompanied by inhibiting reductions in the expression of synapsin, postsynaptic density protein (PSD-95), and brain-derived neurotrophic factor [16].

4.5. Affecting Neurotrophic Factors and Associated Signaling Pathways

Calycosin had a beneficial effect on the amelioration, prevention and treatment of diabetes-associated cognitive deficits in rats, through increasing brain-derived neurotrophic factor expression and activating the PI3K/Akt/GSK-3beta pathway [16].Luteolin could improve diabetic encephalopathy in rats, which was mediated by an indirect anti-oxidative effect, the inhibition of activation of apoptosis-related factors and the activation of PI3K/Akt signal pathway [8].Huperzine A ameliorated DACD in rats via elevating protein and mRNA levels of brain-derived neurotrophic factor [23].Neuro protection of aucubin in primary diabetic encephalopathy in rats was related to inhibiting apoptosis by modulating the expressions of Bcl-2 and Bax genes [31]. Berberine could improve the behavioral results of db/db diabetic mice in Morris water maze, Y-maze spontaneous alternation test, and fear conditioning test, which were achieved by increasing the protein expression of SIRT1 and down regulating endoplasmic reticulum stress-

associated proteins, accompanied by the increased synapse- and nerve-related protein expression (PSD-95, synaptophysin, and nerve growth factor) and the decreased protein expression of inflammatory factors (TNF-α and NF-κB) in the hippocampus of db/db mice [22].

5. Summary and Outlook

In the past decade, substantial effort has been put into seeking the effective therapy of diabetes-associated cognitive dysfunction for more safety reasons, including natural products. Many natural products, including compounds, the extracts, and prescriptions, had been reported to show beneficial effects on cognitive impairment caused by diabetes, whatever T1DM or T2DM, and the action mechanisms were mainly focused on anti-inflammation and/or anti-oxidation, as well as improvement of functions of the central cholinergic system. However, there are still some aspects needing to be strengthened. Firstly, the assessment means for cognitive dysfunction are simplex, mainly Morris water maze task; others include across-arm maze test, novel object recognition task, passive avoidance test, and open field test, etc. Moreover, the above mentioned ways were seldom used together. Secondly, action mechanisms in the above studies are simple and shallow, deep molecular mechanisms should be further elucidated. Nevertheless, these researches laid a certain foundation for the future study. Finally, large clinical trials are urgently needed to further assess their efficacy as DACD-improving agents.

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