Journal of Translational Science

Review Article

ISSN: 2059-268X

Dendrobium in Diabetes: A comprehensive review of its phytochemistry, pharmacology, and safety

Jack Wan Hei[1], Wan Hung[2], Zhang Yanbo[1] and Zhang-Jin Zhang[1]*

[1]School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong, Sassoon Road, Pokfulam, Hong Kong

[2]School of Nursing, LKS Faculty of Medicine, The University of Hong Kong, Sassoon Road, Pokfulam, Hong Kong

Abstract

Dendrobium, which is one of the frequently used medicinal herbs in Traditional Chinese Medicine (TCM) for treating diabetes, has aroused lots of attention on its potential alternative in the treatment of diabetes. This review aims to provide a comprehensive study on its phytochemical constituents, safety and pharmacological effects on treating diabetes and its complications with the underlying mechanisms uncovered. A comprehensive search of published medical literature from 2000 to 2020 was conducted by searching PubMed, Science Direct, Scopus, Web of Science and Google Scholar databases with keywords dendrobium, diabetes, phytochemistry, pharmacology and safety were used. Results showed that dendrobium exhibited anti-diabetic effects such as reducing gluconeogenesis, regulating lipid, protecting islet cells, anti-obesity, antioxidant and anti-inflammation on treating diabetes and its complications through the regulation of AMPK-GLUT4-PPARα; cAMP-PKA and Akt/Fox01; cRaf-MEK1/2-ERK1/2; IRS1-PI3K-Akt-Fox01/GSK 3β; MAPK; NF-κB; PI3k/Akt signaling pathway. The main chemical constituents of dendrobium species, which exert anti-diabetic, were polysaccharides. Most of the compounds of dendrobium species improved diabetes by antioxidant activity. No side effect of dendrobium species was reported in experimental studies. Therefore, our study suggested that dendrobium may offer a new potential alterative for prevention and treatment of diabetes and its complication. Well-designed clinical trials are needed for future studies.

Abbreviations: AC: Adenylate Cyclase; Akt: Protein Kinase B; Ala: Alanine; ALT: Alanine Transaminase; AR: Aldose Reductase; AST: Aspartate Aminotransferase; AUC: The Area Under the Curve; bFGF: Basic Fibroblast Growth Factor; BG: Blood Glucose; BUN: Blood Urea Nitrogen; BW: Body Weight; CA/CDCA: Cholic Acid/Chenodeoxycholic Acid; CAT: Catalase; CK: Creatine Kinase; Citr: Citrate; Create: Creatine; CREA: Creatinine; CTGF: Connective Tissue Growth Factor; DPPH, 2,2-Diphenyl-1-Picrylhydrazyl; ERG: Electroretinogram; FBG: Fasting Blood Sugar; FFAs: Free Fatty Acids; FN: Fibronectin; FINS: Fasting Insulins; Fox01: Forkhead Box Protein 01; GDH: Glucose Dehydrogenase; Gln: Glutamine; GLU: Glucagon; GLUT1: Glucose Transporter 1; GLUT2: Glucose Transporter 2; GLUT4: Glucose Transporter 4; G6Pase: Glucose-6-Phosphatase; GSK 3β: Glycogen Synthase Kinase 3 Beta; GSH: Glutathione; GSH-PX: Glutathione Peroxidase; GSP: Glucose Regulated Protein; HG: High Glucose; HIF-1α: Hypoxia-Inducible Factor 1-Alpha; HOMA-IR: Homeostasis Model of Assessment Insulin Resistance; Hs-CRP: High-sensitivity CRP; HW/BW: Heart to Body Weight Ratio; ICAM-1: Intercellular Adhesion Molecule 1; IFN-γ: Interferon-γ; IGF-1: Insulin-like Growth Factor 1; IL-1β: Interleukin-1β; IL-6: Interleukin-6; Ile: Isoleucine; INS: Insulin InsR: Insulin Receptor; iNOS: Inducible Nitric Oxide Synthase; KB: Ketone Body; LDL: Low-Density Lipoprotein; LDL-C: Low Density Lipoprotein Cholesterol; LDH: Lactate Dehydrogenase; Leu: Leucine; MDA: Malondialdehyde; MMP 2/9: Matrix Metalloproteinase-9; MT-1: Metallothionein-1; MyD88, Myeloid Differentiation Primary Response 88; 2-NBDG: 2-[*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2deoxyglucose; NF-κB: Nuclear-Factor Kappa β; Nqo1: NADPH Quinore Oxidoreductase-1; OGTT: Oral Glucose Tolerance Test; P-AMPK: Adenosine Monophosphate (AMP)-Activated Protein Kinase Phosphorylation; PEPCK: Phosphoenolpyruvate Carboxykinase; PDGF A/B: Platelet-Derived Growth Factor A/B; PGC1α: Alpha Susbunit of Peroxisome Proliferators-Activated Receptor-Gamma Coactivator-1; PKA: protein Kinase A; PI3K: Phosphoinositide-3-Kinase; PPARα: Peroxisome Proliferator-Activated Receptor α; ROS: Reactive Oxygen Species; SCr: Serum Creatine; SOD: Superoxide Dismutase; Tau: Taurine; TC: Total Cholesterol; Tch: Blood Lipids; TG: Triglycerides; TLR-4: Toll-Like Receptors; TNF-α: Tumor Necrosis Factor-α; T-SOD: Total Superoxide Dismutase; UA: Uric Acid; Val: Valine; VEGF: Vascular Endothelial Growth Factor.

Introduction

Diabetes mellitus is characterized by high blood glucose level as a result of insufficient insulin for the body's needs [1]. It is generally accepted that type 1 diabetes is due to the pancreas not producing enough insulin while type 2 diabetes is due to the cells of body not responding properly to the insulin produced [2]. Diabetes has become a worldwide major health-care problem as hyperglycemia increase the risk of complications such as diabetic retinopathy, diabetic cataract, diabetic nephropathy, diabetic cardiomyopathy etc [3]. However, diabetes is a chronic disease which cannot be cured and repaired because if the progressive reduction in beta-cell mass and inversible beta cell failure [4]. Due to the advance effect of drugs, current treatment for diabetes is not satisfactory [5]. As traditional Chinese medicinal herbs are relative cost-effective, multi-target and

***Correspondence to:** Professor Zhang-Jin Zhang, School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong, Sassoon Road, Pokfulam, Hong Kong, E-mail: zhangzj@hku.hk

Key words: dendrobium, diabetes, phytochemistry, pharmacology, safety

Received: March 29, 2021; **Accepted:** April 23, 2021; **Published:** April 26, 2021

has low risk of advance effect, they become a potential candidate for diabetic drug development [6].

Dendrobium, which is one of the major genera of Orchidaceae, has both ornamental and medicinal value. There are more than 1400 species worldwide and are widely distributed in tropical and subtropical regions such as Asia, Europe and Oceania [7]. In China, there are about 80 kinds of dendrobium which are mainly distributed in the southwest, east and south of China [8].

Dendrobium is an important flower plants with high economic value. Its stems and flowers have been valued as precious food and herb medicine with healthy benefit and therapeutic effects. In traditional Chinese medicine, fresh of dry stems of some species of Dendrobium's plants are harvested for medicinal purposes, collectively known as SHIHU. Its medicinal value has been first recorded in ancient Chinese medical book "Shen Nong's Materia Medica" thousands of years ago [9].

Dendrobium is a valuable medicinal herb commonly used for nourishing yin and clearing heat in traditional Chinese medicine theory. It has the functions of moistening lung and benefiting stomach, clearing heat and brightening eyes, tonifying deficiency and strengthening body [10]. Thus, it can be used to benefit stomach, nourish body fluid, moisten lung and relieve cough. Recently, many researchers studied the chemical constituents and pharmacological effects of Dendrobium plants. It was found that the chemical constituents of Dendrobium plants include polysaccharides, alkaloids, bibenzyls, phenols, Phenanthrenes etc [11]. Several studies showed that Dendrobium has anti-aging, anti-cancer, digestion promotion, blood pressure reduction, cataract treatment and vasodilation effect [12]. At present, there are more than 50 kinds of medicinal Dendrobium such as dendrobium officinale, dendrobium huoshenense, dendrobium loddigesii, dendrobium aphyllum, dendrobium candidum, dendrobium crepidatum, dendrobium draconis etc [13]. In this review paper, the search was done in PubMed, Science Direct, Scopus, Web of Science and Google Scholar databases a 20-year period between 2000 to 2020 with keywords search of dendrobium, diabetes, phytochemistry, pharmacology and safety. Recently, many researchers are interested in studying dendrobium species. However, there is no review paper focusing on the mechanism of therapeutic effects of dendrobium species on diabetes and its complications. Although some studies suggested that dendrobium can treat diabetes, there is lack of studies about the comprehensive mechanism of dendrobium's anti-diabetic effects. Therefore, our review is the first study to fully understand the role of dendrobium in diabetes by studying its phytochemistry and pharmacological mechanisms on treating diabetes and its various complications. **It also provides an interesting and illuminating insights to the readers who intend to perform clinical trials on dendrobium species in the future.**

Phytochemistry of dendrobium: Nowadays, more than 50 compounds had been identified and isolated from dendrobium [14]. It was found that the chemical constituents of dendrobium are mainly polysaccharides, alkaloids, phenols, phenanthrenes and alkaloids [15]. The compounds which show anti-diabetic effects are listed in Table 1.

Table 1 summarizes compounds which exert anti-diabetic effect in different species of dendrobium. Several chemical structures of these compounds involved in anti-diabetic activity are illustrated in Figure 1-4. These compounds include polysaccharide, phenanthenes, stilbenes, bibenzyl, polyphenol, indolizidine alkaloids. Most of these compounds showing anti-diabetic effects are polysaccharides. Besides, most of these compounds alleviate diabetes by antioxidant activity, implying a potential candidate for studying diabetes in the future.

Pharmacological activities of dendrobium in the management of diabetes

Reducing gluconeogenesis: In normal physiological conditions, liver glycogen synthesis and gluconeogenesis maintain a dynamic equilibrium [16]. However, when liver appears insulin resistance, which is defined as a pathological state that human body cannot respond to insulin normally, liver gluconeogenesis increases and hepatic glycogen synthesis decreases. Then, the balance between gluconeogenesis and glycogen synthesis is disrupted. After that, liver glycogen output increases and high blood glucose levels id resulted eventually. Thus, reducing gluconeogenesis is one of the targets to control blood glucose [17]. Dendrobium mixture, which includes **15 g dendrobium, 20 g astragalus, 8 g schisandra, 15 g pueraria, 15 g salvia, 15 g rehmannia and 8 g earthworms**, improved insulin resistance and liver functions via regulating the PI3K/Akt signaling pathways. It is evidenced by Fox01, PEPCK, G6Pase decreased expression and InsR, PI3K, Akt increased expression. Thus, Dendrobium may improve liver glycogen and decrease blood glucose [18]. A water extract of dendrobium officinale was showed to up-regulate energy and amino

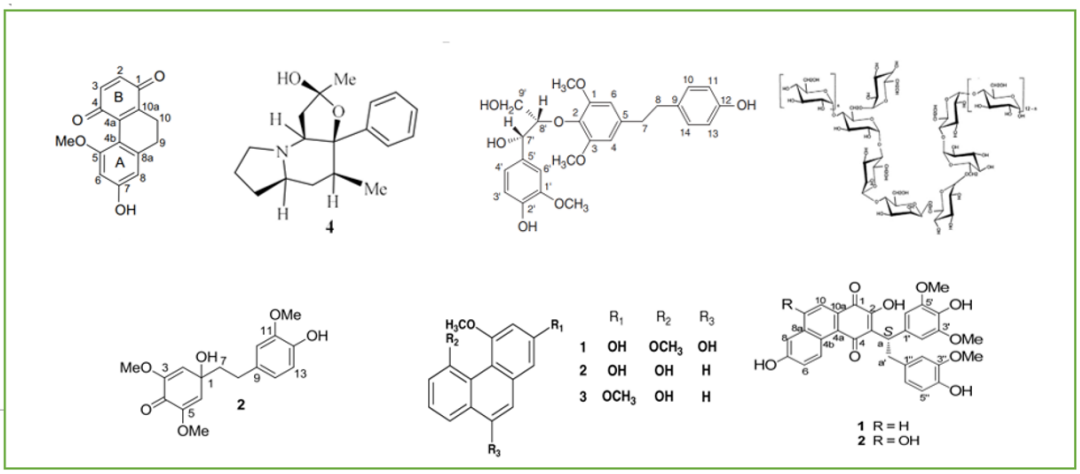

Table 1. The contents of compounds in different species of Dendrobium that exhibited anti-diabetic activities

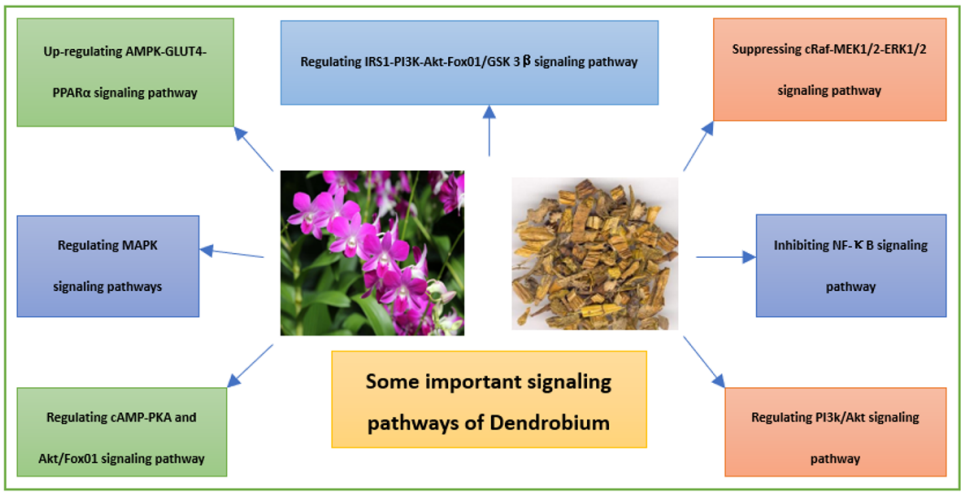

Figure 2. Animal studies about the antidiabetic effects of *Dendrobium* and its ingredients

Table 1. The contents of compounds in different species of Dendrobium that exhibited anti-diabetic activities

Species	Compound name	Types	Molecular formula	Molecular weight	IC_{50}	Function	Reference
Dendrobium officinale	DOP-1-1	Polysaccharide	an O-acetylated glucomannan of β-D configuration in pyranose sugar forms	1.78X105 Da	Nil	Anti-inflammation and anti-oxidant	[57]
Dendrobium officinale	DOPA-1	Polysaccharide	D-mannose,D-glucose,a backbone consisting 1,4-linkedβD-Man*p* and 1,4-linkedβ-D-Glc*p* with *O*-acetyl group	394 kDa	Nil	Anti-oxidant	[34]
	DOPA-2	Polysaccharide	D-mannose,D-glucose,a backbone consisting 1,4-linkedβD-Man*p* and 1,4-linkedβ-D-Glc*p* with *O*-acetyl group	362 KDa	Nil	Anti-oxidant	
Dendrobium huoshenense	DHPD1	Polysaccharide	glucose,arabinose,galactose,mannose,xylose with C-2,C-6 of glycosyl residues	3.2X103 Da	Nil	Antiglycation	[58]
Dendrobium huoshenense	DHPIA	Polysaccharide	Mannose,glucose,a trace of galactose,backbone contain (1 → 4)-linked α-D-Glc*p*, (1 → 6)-linked α-D-Glc*p* and (1 → 4)-linked β-D-Man*p*, with a branch of terminal β-D-Gal*p*	6700 Da	Nil	Anti-oxidant	[59]
Dendrobium loddigesii	loddigesiinols A(1)	Phenanthnenes	$C_6H_{14}O_3$	Nil	2.6μM	Anti-oxidant	[60]
	loddigesiinols B(7)	Phenanthnenes	$C_{25}H_{22}O_6$	Nil	10.9μM	Anti-oxidant	
	loddigesiinols D(9)	Stibenes	$C_{17}H_{16}O_7$	Nil	69.7μM	Anti-oxidant	
Dendrobium loddigesii	loddigesiinols G	Polyphenols	$C_{31}H_{26}O_9$	Nil	16.7μM	α-glucosidase inhibitory activity	[61]
	loddigesiinols H	Polyphenols	$C_{31}H_{26}O_{10}$	Nil	10.9μM	α-glucosidase inhibitory activity	
	loddigesiinols I	Polyphenols	$C_{31}H_{26}O_8$	Nil	2.7μM	α-glucosidase inhibitory activity	
	loddigesiinols J	Polyphenols	$C_{31}H_{28}O_8$	Nil	3.2 uM	α-glucosidase inhibitory activity	
Dendrobium aphyllum	aphyllals B	Bibenzyl	$C_{17}H_{20}O_6$	Nil	nil	Anti-oxidant	[62]
	Aphyllals A	Phenanthrene	$C_{15}H_{14}O_4$	Nil	nil	Anti-oxidant	
Dendrobium candidum	dendrocandins J	Bibenzyl	$C_{31}H_{30}O_8$	Nil	36.8 uM	Anti-oxidant	[63]
	dendrocandins K	Bibenzyl	$C_{30}H_{27}O_8$	Nil	70.2 uM	Anti-oxidant	
	dendrocandins L	Bibenzyl	$C_{30}H_{22}O_8$	Nil	45 uM	Anti-oxidant	
	Dendrocandins M	Bibenzyl	$C_{26}H_{29}O_8$	Nil	60.5 uM	Anti-oxidant	
	dendrocandins N	Bibenzyl	$C_{25}H_{25}O_7$	Nil	87.6 uM	Anti-oxidant	
	dendrocandins O	Bibenzyl	$C_{25}H_{26}O_8$	Nil	50.4 uM	Anti-oxidant	
	dendrocandin P	Bibenzyl	$C_{30}H_{28}O_8$	Nil	22.3 uM	Anti-oxidant	
	dendrocandin Q	Bibenzyl	$C_{30}H_{28}O_8$	Nil	30.3 uM	Anti-oxidant	
Dendrobium crepidatum	isocrepidanine	Indolizidine alkaloids	$C_{20}H_{27}NO_4$	Nil	345.4 uM	Hypoglycemic effect	[64]
Dendrobium draconis	5-methoxy-7-hydroxy-9,10-dihydro-1,4-phenanthrenequinone	Phenanthrenequinone	$C_{15}H_{12}O_4$	Nil	283.3uM	Anti-oxidant	[65]

Reducing gluconeogenesis			
↑Energy and amino acid metabolism	↓ gluconeogenesis	↓Glycogen degradation rate	↑Glycogen synthesis

Figure 3. The chemical structures and names of compounds isolated from different species of *Dendrobium* that exhibited anti-diabetic activities

↑Citr, GIN, Creat, Ala, Leu, Ile, Val, Gln, GSH, Tau	↑IRS-1, PI3K, Akt ↓6Pase, PEPCK, ↓Fox01	↓GP, GP bonding site	↑GS ↓GSk 3β

Figure 4. Medicinal plants *Dendrobium* used in treatment of diabetes and its complications with their mechanism of actions

acid metabolism as well as increase liver glycogen. It can reduce gluconeogenesis [19]. A study conducted by Hong-Yan Wang et al. showed that a polysaccharide from dendrobium huoshanense (GXG) could enhance glycogen synthesis and reduce gluconeogenesis via insulin-mediated IRS1-PI3K-Akt-Fox01/GSK 3βsignaling pathway. This study suggested that Dendrobium may reduce glycogen degradation rate by improving stability of liver glycogen structure [20]. In another study, a polysaccharide of dendrobium officinale (DOP) (100,200,400 mg/kg for 4 weeks) strengthened the fragile diabetic liver glycogen by inhibiting cAMP-PKA signaling pathway. Besides, it inhibited hepatic glycogen degradation and hepatic gluconeogenesis [21]. In brief, dendrobium has been evidenced to alleviate diabetes through reducing gluconeogenesis. The underlying mechanisms may be attributed to the regulation of PI3K/Akt, PI3K-Akt-Fox01/GSK 3β, cAMP-PKA signaling pathway (Figure 5). *Dendrobium* alleviates diabetes through reducing gluconeogenesis, glycogen degradation rate and increasing energy and amino acid metabolism as well as glycogen synthesis. **Lipid regulation**: Obesity is one of the causes of type 2 diabetes as lipid deposition in liver may lead to insulin resistance [22]. Besides, lipotoxicity may increase islet cell apoptosis and restrict the muscle's usage of glucose capacity. Thus, it is important for diabetic patient to prevent dyslipidemia [23]. An extract of dendrobium nobile lindl. (DNLA) (15mg/kg for 18 weeks) was demonstrated to reduce the absorption of cholesterol by decreasing CA/CDCA ratio and increase the excretion of cholesterol by enhancing the taurine-conjugated bile acids [24]. A study conducted by Qiong Zhang et al. suggested that the extract of dendrobium finbriatium (100mg/kg,200 mg/kg for 4 weeks) could reduce lipid accumulation and lipotoxicity-induced hepatocyte apoptosis in rat. It also prevented islet cell apoptosis [25]. In a cell study of Xue-Wen Li et al., a shihurine-rich extract of D. loddigesii decreased the intracellular accumulation of oil droplets and triglycerides. It also increased 2-NBDG uptake of 3Ts-L1 cells [26]. Another study about dendrobium nobile lindl. revealed that an alkaloid of DNLA could increase lipid metabolism gene expression and decrease lipid synthesis regulator Srebp 1 [27]. Collectively, dendrobium alleviates diabetes by regulating the absorption and excretion of cholesterol. It can also reduce the toxicity of bile acids and lipid accumulation (Figure 6). *Dendrobium* alleviate diabetes by reducing the lipid accumulation, the toxicity of bile acids, absorption of cholesterol as well as increasing excretion of cholesterol.

Protecting islet cells*:* The pancreas, which is a mixed gland formed by exocrine tissue, can synthetize and secrete inactive digestive enzymes. The endocrine tissue of pancreas is represented by the islets of Langerhaous consisted of alpha, gama, epsilon and beta cells [28]. Apoptosis is a form of beta cells death that happen in diabetes. A vitro study of a shihumine-rich extract of D. loddigesii showed that after 9 weeks of administration, the quantity of islet cells and the adipose cell size increased by up-regulating AMPK-GLUT4-PPARα signaling pathway. The expression of cleaved caspase-3 was also inhibited. Thus, it could prevent islet cell apoptosis [29]. In summary, dendrobium alleviates diabetes by protecting islet cells through the regulation of AMPK-GLUT4-PPARα signaling pathway. *Dendrobium* can protect islet cells and prevent islet cell apoptosis (Figure 7).

Anti-oxidant: Oxidative stress is defined as an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage [30]. If excess reactive oxygen species is produced,β-cell maturation and apoptosis increases. Then insulin synthesis and secretion will be decreased. Both diabetes and obesity can increase the production of reactive oxygen species, resulting in oxidative stress [31]. A rich polyphenol extract of D. loggigesii (DJP) (25 mg/kg,50 mg/kg,100mg/kg for 8 weeks) was demonstrated to reduce the oxidative stress in db/db mice [32]. Another study using 1g/kg of the extract from dendrobium officinale to fed STZ rat for 5 weeks. Although there was no effect on blood glucose level and bodyweight, the glutathione peroxidase (GSH-PX) increased, implying the protective effects of this extract of dendrobium was related to antioxidant activity [33]. A cell study separated two polysaccharide fractions (DOPA-1 and DOPA-2) from stems of dendrobium officinale and tested the ability against H2O2-induced oxidative injury, DOPA-1 and DOPA-2 were found to suppress apoptosis and ameliorate oxidative lesions [34]. Another study about Alkaloids of dendrobium nobile lindl. (DNLA) showed that it could increase the expression of antioxidant gene MT-1 and Nqo1 in livers of mice through Nrf2-antioxidant pathway [27].

In short, dendrobium exerts anti-oxidant effects through Nrf2-antioxidant pathway. It also increases glucose metabolism genes and anti-oxidant genes. *Dendrobium* exerts anti-oxidant effects through increasing glucose metabolism genes and anti-oxidant genes (Figure 8).

Anti-inflammation: Low-grade inflammation can lead to insulin resistance and is a main cause of Type 2 diabetes as pro-inflammatory macrophages may reduce the insulin sensitivity of liver, skeletal muscle and pancreatic β cells [35].

A rich polyphenol extract of D. loddigesii (DJP)was demonstrated to have anti-inflammation effect by reducing IL-6 and TNF-α [32]. Another study suggested that the extract of dendrobium fimbriation (DFE) could downregulate 588 differentially expressed genes (DEGs) and 74% of them were related to inflammatory, implying it may have anti-inflammation effect [25].

Lipid regulation			
↓ Lipid accumulation	↓ The toxicity of bile acids	↓ Absorption of Cholesterol	↑ Excretion of Cholesterol

Figure 5. The diagram illustrates reducing gluconeogenesis of *Dendrobium*

↓ TC, TG, oxidative capacity ↑ Glycogen storage ↓ Atp5g1, Cyp7a1, Srebp1	↓ LCA, DCA, CA, CDCA ↑ Fxr, Cyp3a11	↓ CA/CDCA ratio ↓ Apoa1	↑ ATGL ↑ TDCA, THDCA, TCDCA, TUDCA, TMCAs

Figure 6. The diagram illustrates lipid regulation of *Dendrobium*

Protect islet cells
↑ Quantities of islet cells, serum insulin levels
↓ Cleaved caspase-3

Figure 7. The diagram illustrates lipid regulation of *Dendrobium.*

In brief, Dendrobium showed anti-inflammation effect by regulating NF-κβ signaling pathway. *Dendrobium* showed anti-inflammation effect by regulating NF-κβ signaling pathway (Figure 9).

Diabetic cardiovascular complications: Cardiovascular complications are notable causes of death in diabetic patients [26]. Diabetic cardiomyopathy is a serious diabetic complication as it is notable causes of death in diabetic patients. It is mainly manifested as myocardial dysfunction without other heart disease and may eventually lead to heart failure [36]. Chronic sustained hyperglycemia and insulin resistance may induce myocardial infarction and chronic pressure overload in diabetic patients with diabetic cardiomyopathy [37]. A dendrobium officinale extract (DOE), after 8 weeks of (75mg/kg, 150mg/kg, 300mg/kg) administration, was demonstrated that it could inhibit oxidative stress, cardiac lipid accumulation and pro-inflammatory cytokines in order to reduce cardiac fibrosis [38]. In a cell study conducted by Jing-yi Zhang et al., dendrobium officinale polysaccharides (DOY-GY) could exert cardioprotective effects on H2O2 induction-H9C2 cardiomyocytes through PI3K/Akt and MAPK pathways [39]. Collectively, dendrobium alleviates diabetic cardiovascular complications by reducing inflammation, cardiac fibrosis, cardiac oxidative stress, myocardial injury and apoptosis. The underlying mechanism may be associated with PI3K/Akt and MAPK pathways. *Dendrobium* alleviates diabetic cardiovascular complications by reducing inflammation, cardiac fibrosis, cardiac oxidative stress, myocardial injury and apoptosis (Figure 10).

Diabetic nephropathy: Diabetic nephropathy is an important chronic micro-vascular complication of diabetes and may lead to end-stage renal disease [40]. Diabetic nephropathy is induced by diabetes and kidney dysfunction will be developed by disturbing renal tubular, glomeruli and its filtration barrier. Kidney functions continues to decline until end-stage renal failure was resulted [41]. Diabetes influences body's metabolism and blood circulation, generating excess reactive oxygen species. which injure glomeruli and cause albuminuria [42]. The glomerular filtration barrier, which is composed of the fenestrated endothelium, the glomerular basement membrane and the epithelial podocytes, becomes more damaged in the progression of diabetic nephropathy. After administrating dendrobium candidum (0.2,0.4,0.8g/kg) for 8 weeks, it was found that it could improve pathological change in kidney and alleviate diabetic nephropathy by regulating VEGF, GLUT-1 and CTGF expression [43].

In vitro and vivo study of diabetic nephropathy, a methanolic extract of dendrobium monilfone (DM) was demonstrated to exert lipid lowering effect in HFD-induced obesity in mice as well as to inhibit the kidney cell damage induced by oxidative stress [44].

Another study using the extract of dendrobium officinale (5 ml/kg,10 ml/kg) for 4 weeks, result showed that it could alleviate diabetic nephropathy by preventing insulin resistance and reducing TLRs and inflammatory response [45]. Glucomannans, which is an extract of dendrobium officinale stem, could balance the disturbed glucose, lipid, amino acid metabolism and normalize the architecture of kidney corpuscle and tubular system after 4 weeks of drug (160 mg/kg) administration [46].

In summary, dendrobium alleviates diabetic nephropathy by reducing inflammation, oxidative stress, insulin resistance, renal dysfunction and diabetic kidney lesion. *Dendrobium* improves diabetic nephropathy by reducing oxidative stress, renal dysfunction, insulin resistance, inflammatory response and diabetic kidney lesions (Figure 11).

Diabetic retinopathy: Diabetic retinopathy is a common diabetic complication. It is characterized by hard exudates, microaneurysms, macular edema and retinal hemorrhage [47]. The ethanol extract of D. Chrysotoxum (30 mg/kg,300 mg/kg for 1 month) was demonstrated to breakdown the blood retinal barrier, inhibit retinal inflammation and prevent the decrease of tight junction protein such as occludin and claudin-1 [48]. In vivo and vitro study by Zengyang Yu et al., erianin,

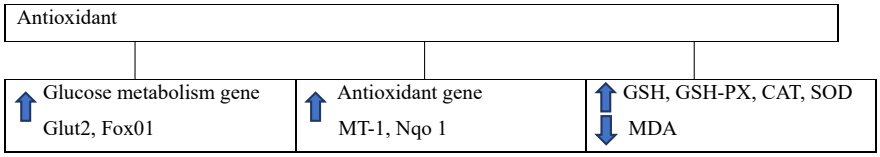

Figure 8. The diagram illustrates anti-oxidant of *Dendrobium*

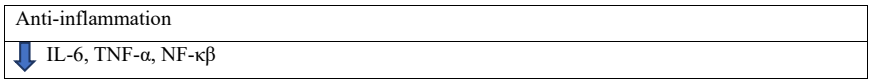

Figure 9. The diagram illustrates anti-inflammation of *Dendrobium*.

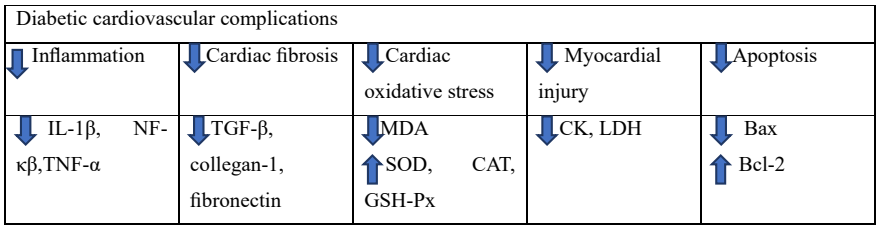

Figure 10. The diagram illustrates diabetic cardiovascular complications of *Dendrobium*

which was extracted from dendrobium chrysotoxum Lindl., could inhibit retinal neoangiogenesis by abrogating HG-induced VEGF expression. It could also block ERT1/2-mediated HIF-α activation in retinal endothelial and microglial cells [49]. Another study also found that the ethanol extract of dendrobium chrysotoxum Lindl could alleviate retinal angiogenesis and ameliorate retinal inflammation by inhibiting NFκβ signaling pathway [50]. To conclude, dendrobium alleviates diabetic retinopathy by reducing retinal neoangiogenesis and tight junction protein. It can also reduce pro-angiogenic factor and inflammation. *Dendrobium* alleviates diabetic retinopathy by reducing inflammation, retinal neoangiogenesis, tight junction proteins and pro-angiogenic factor (Figure 12).

Diabetic Cataract: Cataract is the leading cause for impaired vision and blindness in patients with diabetes [51]. Hyperglycemia-associated increase in osmotic pressure and oxidative damage are the main causes for the development and progression of diabetic cataract [52].

In a cell study conducted by Jie Wu et al., a gigantol from dendrobium chrysotoxum Lindl. was showed to inhibit AR gene expression and aldose reductase in Human lens epithelial cells (HLECs) [53]. Another study showed that gigantol from dendrobium aurantiacum var dennam could prevent galactose-induced damage to the rat lens by repressing the gene expression and activity of AR & iNOS. It could also delay lens turbidity and keep lens transparent [54]. To sum up, dendrobium alleviates diabetic cataract by reducing damage of osmotic pressure stress and oxidative damage. *Dendrobium* improves diabetic cataract by reducing oxidative damage and damage caused by osmotic pressure stress (Figure 13).

Safety of Dendrobium: In the "Shen Nong's Materia Medica", dendrobium is classified as "Top-tier" medicinal herb which is regarded as an effective medicinal herb without observable toxicity. The safety of medicinal herb is important because the intake of heavy metal elements into human body is harmful. One study conducted by Yingdan Yuan et al. showed that the dosage of 12g d^{-1} dendrobium, which is prescribed in the Chinese Pharmacopoeia 2010 edition, is in accordance with the recommended daily intake of trace elements recommend by the Food and Drug Administration of the United States [55]. Another study by Li-Chan Yang et al. assessed the 90 days oral toxicity and genetic safety of the aqueous extract of Dendrobium Taissed Tosnobile in 90 sprague-dawley (SD) rats, no abnormal changes were observed in clinical signs and body weight. Also, no significant difference between treatment and control group was found in biochemistry parameter, urinalysis and hematology throughout the study period [56-65]. Therefore, when taken according to the dosage prescribed by the pharmacopoeia does not cause any adverse effects and trace elements poisoning.

Conclusion and outlook

Dendrobium is one of the most frequent used medicinal herbs for treating diabetes in TCM clinical practices. Table 2 and Table 3 summarizes its hypoglycemia effects in animal studies and cell-based studies. In recent studies, there are more than 50 compounds isolated and identified from dendrobium. The types of compounds, which show anti-diabetic activities, include polysaccharide, phenanthenes, stilbenes, bibenzyl, polyphenol, indolizidine alkaloids. Most of the compounds showing anti-diabetic effects are polysaccharides. The signaling mechanisms of dendrobium treating diabetes may be involved in the regulation of AMPK-GLUT4-PPARα; cAMP-PKA and Akt/Fox01; cRaf-MEK1/2-ERK1/2; IRS1-PI3K-Akt-Fox01/GSK 3β; MAPK; NF-κB; PI3k/Akt which are illustrated in Figure 2.

Moreover, dendrobium can reduce gluconeogenesis, regulate lipid, protect islet cells, anti-obesity, antioxidant and anti-inflammation. It can also treat various diabetic complications such as diabetic cardiovascular, diabetic nephropathy, diabetic retinopathy and diabetic cataract.

Dendrobium is considerably safe and well tolerate at the recommend dose as there are no side effects had been reported in clinical trial. However, as there are insufficient clinical trial studies the

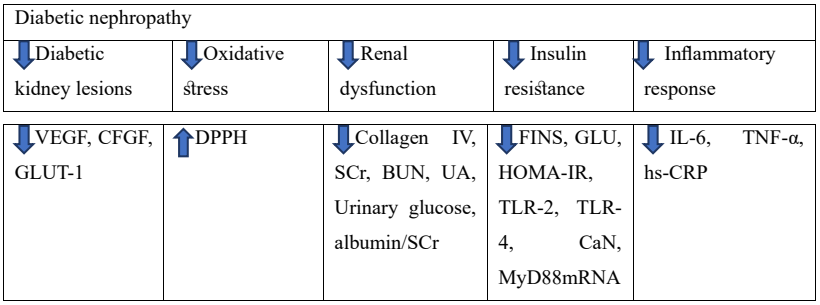

Figure 11. The diagram illustrates diabetic nephropathy of *Dendrobium*

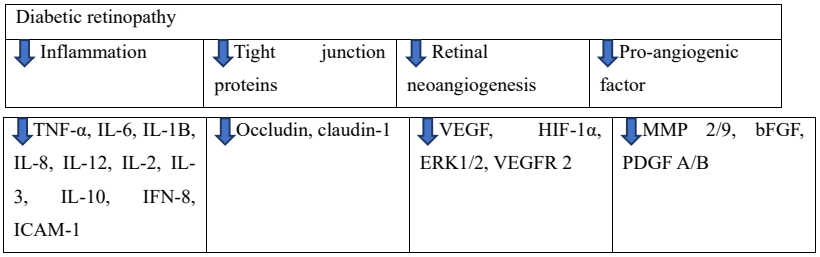

Figure 12. The diagram illustrates diabetic retinopathy of *Dendrobium*

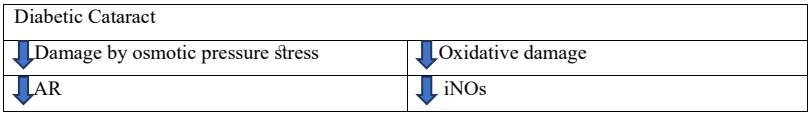

Figure 13. The diagram illustrates diabetic cataract of *Dendrobium*

Table 2. Animal studies about the antidiabetic effects of *Dendrobium* and its ingredients

Species	Extract	Topic	Duration	Model	Pathways	Results
Dendrobium nobile Lindl. (Si Huang, et al. 2019)	DNLA	Hepatic lipid homeostasis	18 weeks	C57BL/6 mice	Reducing cholesterol absorption and increasing cholesterol excretion	Reducing liver TC,TG; Increasing hydrophilicity; Reducing hepatic level of free bile acids(LCA,DCA,CA,CDCA); Increasing taurine-conjugated bile acids (TMCAs, TCDCA,TUDCA,THDCA); Reducing CA/CDCA ratio; Up-regulating Cyp27al,Cyp3all,Fxr,Shp.
Dendrobium officinale kimura & Migo (Hong Zheng, et al. 2017)	DOWE	Type 2 diabetes	4 weeks	STZ	Up-regulating energy and amino acid metabolism	Reducing BG; Increasing liver glycogen; Increasing Citr, GIN, Creat, Ala, Leu, Ile, Val, Gln, GSH, Tau in liver
Dendrobium loggigesii (Xue-Wen Li, et al. 2019)	DLS	Type 2 diabetes	8 weeks	db/db mice	Up-regulating AMPK-GLUT4-PPARα	Reducing BW, FBG, serum lipid level; Improving oral glucose; Increasing serum INS level; Decreasing TG & TC; Increasing quanties of islet cells; Increasing adipose cell size; Inhibiting expression of cleaved caspase-3; Increasing P-AMPK, PPARα, GLUT4.
Dendrobium aurantiacum var. denneanum (Hua Fang, *et al.*2015)	Gigantol	Diabetic cataract	60 days	Wistar rats	Reducing osmotic pressure and ameliorating oxidative damage	Repressing the gene expression and ability of AR & iNOS; keep lens transparent; delay lens turbidity; Reducing amount of AR and iNOS in lens epithelial cells.
Dendrobium candidum (Jingzhi Chang *et al.*2019)	Nil	Diabetic nephropathy	8 weeks	STZ	Regulating expression of VEGF, GLUT-1, CTGF	Reducing kidney index, SCr, BUN,24 hr urine protein; Decreasing VEGF; Decreasing GLUT-1 & CTGF renal cortex expression; Improving pathological changes in kidney
Dendrobium chrysotoxum lindl. (Zengyang Yu *et al.*2015)	DC	Diabetic retinopathy	1 month	STZ	Inhibiting retinal inflammation and preventing the decrease of tight junction protein	Decreasing breakdown of blood retinal barrier; Increasing expression of occludin & cludin-1 protein; Reducing the increased retinal mRNA expression of ICAM-1,TNFα,IL-6,IL-1β; Alleviating the increased ICAM-1 and phosphorylated p65,IκB,IκB kinase; Reducing the increased serum level of TNFα,IFN-γ,IL-6,IL-1β,IL-8,IL-12,IL-2,IL-3,IL-10

Dendrobium huoshanense (Hong-Yan Wang *et al.*2019)	GXG	Type 2 diabetes	5 weeks	STZ	Regulating insulin-mediated IRS1-PI3K-Akt-Fox01/GSK 3β signaling	Reduce FBG, glycosylated serum protein & serum INS; Improving glucose tolerance & insulin sensitivity; Improving pancreaticβ-cell quantity and function; Improving regulation of hepatic glucose metabolism; Up-regulating IRS1-PI3K-Akt phosphorylation; Down-regulating FoxO1/GSK 3βphosphorylation; Enhancing glycogen synthesis; Reducing gluconeogenesis.
Dendrobium mixture (XinJun Lin, *et al.*2018)	Nil	Type 2 diabetes	12 weeks	Wistar rats.	Regulating PI3k/Akt signaling pathway	Reducing FBG, GSP, InsR, Tch, TG, ALT, AST; Reducing Fox01, PEPCK, G6Pase; Increasing InsR, PI3K, Akt; Improving liver function & insulin resistance
Dendrobium moniliforne (Woojung Lee, *et al.*2012)	DM	Diabetic nephropathy	9 weeks	Male C57BL/6 mice	Inhibiting kidney cell damage induced by oxidative stress	Reducing elevated serum glucose, TC, renal lipid accumulation; Reducing renal dysfunction biomarkers like SCr & renal collagen IV deposition
Dendrobium nobile Lindl. (Yun-Yan Xu, *et al.*2017)	DNLA	Diabetic liver	8 days	male kunming mice	Increasing liver glucose and lipid metabolism gene metabolism	Increasing PGC1α mRNA and protein levels; Increasing glucose metabolism gene Glut2, FoxO1; Increasing fatty acidβ-oxidation genes Acox1 & Cpt1a; Reducing lipid synthesis regulator Srebp1; Increasing lipolysis gene ATGL; Increasing antioxidant gene MT-1 & Nqo1 in liver; Increasing PPARα & GLUT4; Increasing Nrf2-antioxidant gene expressions
Dendrobium officinale kimura et Migo (Ming Zhao, *et al.*2018)	DO	Diabetic nephropathy	4 weeks	STZ	Preventing insulin resistance and reducing TLRs & inflammatory response	Decreasing glomerular volume; Reducing urinary glucose, albuminuria, SCr, albuminuria/SCr, Bun; Reducing the expression levels of CaN, TLR-4, MyD88, hs-CRP, TNF-α, IL-6, the level of FINS, GLU, HOMA-IR.
Dendrobium officinale kimura et Migo(Zhihao Zhang, *et al.*2016)	DOE	Diabetic cardiomyopathy	8 weeks	STZ	Inhibiting oxidative stress, pro-inflammatory cytokines and cardiac fibrosis	Reducing HW/BW; Reducing CK,LDH,TC,TG; Reducing MDA,T-SOD; Reducing cardiac injury; Reducing cardiac lipid accumulation and deposition of collagen; Downregulating TGF-β,collagen-1,FN,NF-κB,TNF-α,IL-1β
Dendrobium officinale kimura et Migo (Yage Liu, *et al.* 2020)	DOP	Type 2 diabetes	4 weeks	STZ	Regulating glycogen-mediated cAMP-PKA and Akt/FoxO1 signaling pathway	Inhibiting hepatic glycogen degradation & hepatic gluconeogenesis; Reversing the instability of liver glycogen structure; Suppressing serum glycogen; Reducing BW, FBG, OGTT; Restoring pancreatic islet morphology; Reducing insulin-positive cell ratio in pancreatic islet cells; Inactivating AC & reducing the expression of PKA.
Dendrobium officinale kimura et Migo (Shao-zhen Hou, *et al.* 2016)	DO	Type 1 diabetes	5 weeks	STZ	Inhibiting oxidative stress	Reducing TC, TG, BUN, CREA; Increasing the amplitudes of ERGa- and b- waves and Ops; Hypoalgesia and histopathological changes of vital organs induced by hyperglycemia; Increasing GSH-PX
Dendrobium loggigesii (Xue-Wen Li, *et al.* 2018)	DJP	Type 2 diabetes	8 weeks	db/db mice	Reducing inflammation & oxidative stress	Reducing BG, BW, LDL-C; Increasing insulin level; Improving fatty liver & DN; Reducing MDA; Increasing SOD, CAT, GSH; Reducing IL-6, TNF-α; Reducing intestinal flora balance; Increasing Bacteroidetes to firmicute ratios
Dendrobium chrysotoxum lindl. (Zengyang Yu, *et al.* 2016)	Erianin	Diabetic retinopathy	2 months	STZ	Inhibiting retinal neoangiogenesis	Abrogating retinal neovascularization
Dendrobium chrysotoxum lindl. (Chen-Yuan Gong, *et al.* 2014)	DC	Diabetic retinopathy	2 months	STZ	Inhibiting NF-κB signaling pathway	Ameliorating increased retinal vessels; Reducing increased retinal mRNA expression of VEGF & VEGFR2; Decreasing elevated serum VEGF level; Reducing retinal mRNA expression of MMP 2/9; Reducing serum levels of MMP2/9, IL-1β, IL-6, IGF-1, bFGF, PDGF A/B; Decreasing increased phosphorylation of p65; Reducing increased expression of ICAM-1
Dendrobium officinale kimura et Migo (Haihong Chen, *et al.* 2019)	Glucomannans	Diabetic kidney disease	4 weeks	STZ	Normalizing the architecture of kidney corpuscle and tubular system	Reducing FBG, serum INS, glycated serum protein; Reducing concentrations of serum LDL, TC, TG, nonesterified fatty acid; Reducing UA, Creat, urea in serum, glycosuria, KB, protein in urine; Normalizing the architecture of glomerulus.
Dendrobium aphyllum (Huifan Liu, *et al.* 2019)	DAP	Type 2 diabetes	30 days	kunming mice	Up regulating the expression of glucose transporters	Decreasing BP; Increasing enzyme activities, G6Pase, GDH; Upregulating GLUT1, GLUT2 in colon. Incrementing 4 types short chain fatty acids and the health-promoting microbiota diversity
Dendrobium fimbriatum (Qiong Zhang, *et al.* 2020)	DFE	Type 2 diabetes	4 weeks	Sprague-Dawley rats	Prevent β cell apoptosis and decreasing hepatic lipid accumulation	Reducing FBG; Reducing AUC value of blood glucose level; Increasing serum & pancreatic INS; Reducing serum FFAs; Downregulating 588 differentially expressed gene,74% related to inflammatory; Preventing islet cell apoptosis; Improving energy metabolism, lipid transport, oxidoreductase activity in liver; Reducing lipid accumulation & lipotoxicity-induced hepatocyte apoptosis.

Table 3. Cell-based studies about the antidiabetic effects of *Dendrobium* and its ingredients

Species	Extract	Topic	Model	Pathways	Results
Dendrobium loggigesii (Xue-Wen Li, *et al.*2019)	DLS	Type 2 diabetes	3T3-L1 cell	Up-regulating AMPK-GLUT4-PPARα	Decreasing intracellular accumulation of oil droplets; Decreasing TG; Increasing 2-NBDG uptake.
Dendrobium moniliforne (Woojung Lee, *et al.*2012)	DM	Diabetic nephropathy	LLC-PK1 renal epithelial cells	Inhibiting kidney cell damage induced by oxidative stress	Increasing DPPH radical scavenging activity; Reducing LLC-PK1 kidney cell damage induced by oxidative stress
Dendrobium chrysotoxum lindl. (Zengyang Yu, *et al.*2016)	Erianin	Diabetic retinopathy	RF/6A cells & microglia BV-2 cells	Suppressing cRaf-MEK1/2-ERK1/2 and PI3K-Akt signaling cascades in retinal endothelial cells	Blocking high glucose-induced VEGF, HIF-1α translocation into nucleus, ERK1/2 activation; Inhibiting HG-induced tube formation and migration; Inhibiting HG-induced VEGF expression; Inhibiting ERK1/2-mediated HIF-1α activation; Abrogating VEGF-induced angiogenesis
Dendrobium chrysotoxum lindl. (Jie Wu, *et al.*2017)	Gigantol	Diabetic cataract	Human lens epithelial cells	Inhibiting AR gene expression	Reducing AR gene expression; Bounding to insert AR gene base pairs of the double helix
Dendrobium officinale kimura et Migo (Jing-yi Zhang, *et al.*2017)	DOP-GY	Diabetic cardiomyopathy	H9c2 cardiomyocytes	Exerting cardioprotective effects via PI3K/Akt and MAPK pathways	Increasing survival rate; cutting LDH leakage; Reducing lipid peroxidation damage; Improving activity of endogenous antioxidant enzymes; Inhibiting production of ROS; Declining mitochondrial membrane potential; Downregulating pro-apoptosis protein; Upregulating anti-apoptosis protein
Dendrobium officinale kimura et Migo (Kaiwei Huang, *et al.*2016)	DOPA-1 & DOPA-2	Oxidative stress	RAW 264.7 macrophages	Ameliorating H2O2-induced oxidative injury	Activating splenocyte & macrophage; Promoting cell viability; Suppressing apoptosis; Ameliorating oxidative lesions.

effect of dendrobium on diabetes, further investigation, especially well-planned randomized clinical trial, are still needed to study the effect of dendrobium on treating diabetes.

This study combines the experimental evidence of dendrobium both in vivo and in vitro with TCM theory. Result shows that dendrobium may offer a new therapeutic promise to cure diabetes and its complications. Potential chemical structure with anti-diabetic effects is also demonstrated for further investigation. Well-designed clinical trials are anticipated in the future studies.

Conflict of interest

The authors declare no competing interests.

Funding

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

References

1. Nowotny K, Jung T, Höhn A, Weber D, Grune T, et al. (2015) Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. *Biomolecules* 5: 194-222. [Crossref]
2. Lee MS (2014) Role of innate immunity in the pathogenesis of type 1 and type 2 diabetes. *J Korean Med Sci* 29: 1038-1041.
3. Kato M, Castro NE, Natarajan R (2013) MicroRNAs: potential mediators and biomarkers of diabetic complications. *Free Radic Biol Med* 64: 85-94. [Crossref]
4. Alejandro EU, Gregg B, Blandino-Rosano M, Cras-Méneur C, Bernal-Mizrachi E, et al. (2015) Natural history of β-cell adaptation and failure in type 2 diabetes. *Mol asp of med* 42: 19-41.
5. Kleinberger JW, Pollin TI (2015) Personalized medicine in diabetes mellitus: current opportunities and future prospects. *Annals of the NY Academy of Sci* 1346: 45. [Crossref]
6. Bai L, Li X, He L, Zheng Y, Lu H, Li J, et al. (2019) Antidiabetic potential of flavonoids from traditional Chinese medicine: a review. *Am J Chin Med* 47: 933-957.
7. Xu H, Wang Z, Ding X, Zhou K, Xu L, et al. (2006) "Differentiation of Dendrobium species used as "Huangcao Shihu" by rDNA ITS sequence analysis,". *Planta Medica* 72: 89-92. [Crossref]
8. Lam Y, Ng TB, Yao RM, Shi JXu, K, Sze SCW, et al. (2015) Evaluation of chemical constituents and important mechanism of pharmacological biology in Dendrobium plants. *Evid Based Complementary Altern Med* 2015; 2015.
9. Han YUE, Hui Zeng, Kan Ding (2020) A review of isolation methods, structure features and bioactivities of polysaccharides from Dendrobium species. *Chin J Nat Med* 18: 1-27. [Crossref]
10. Da Silva JAT, Ng TB (2017) The medicinal and pharmaceutical importance of Dendrobium species. *Appl Microbiol Biotechnol* 101: 2227-2239.
11. Cakova V, Bonte F, Lobstein A (2017) Dendrobium: Sources of Active Ingredients to Treat Age-Related Pathologies. *Aging and Dis* 8: 827-849. [Crossref]
12. Luo QL, Tang ZH, Zhang XF, Zhong YH, Yao SZ, et al. (2016) "Chemical properties and antioxidant activity of a water-soluble polysaccharide from Dendrobium officinale," *International J Biological Macromolecules* 89: 219-227.
13. Ng TB, Liu J, Wong JH, Ye X, Sze SCW, Tong, Y, et al. (2012) Review of research on Dendrobium, a prized folk medicine. *Appl Microbiol Biotechnol* 93: 1795-1803.
14. Tang H, Zhao T, Sheng Y, Zheng T, Fu L, et al. (2017) Dendrobium officinale Kimura et Migo: a review on its ethnopharmacology, phytochemistry, pharmacology, and industrialization. *Evid Based Complementary Altern Med* 2017; 2017.
15. Xu J, Han QB, Li SL, Chen XJ, Wang XN, et al. (2013) Chemistry, bioactivity and quality control of Dendrobium, a commonly used tonic herb in traditional Chinese medicine. *Phytochem Rev* 12: 341-367.
16. Petersen MC, Vatner DF, Shulman GI (2017) Regulation of hepatic glucose metabolism in health and disease. *Nat Rev Endocrinol* 13: 572-587. [Crossref]
17. Artunc F, Schleicher E, Weigert C, Fritsche A, Stefan N, et al. (2016) The impact of insulin resistance on the kidney and vasculature. *Nat Rev Nephrol* 12: 721.
18. Lin X, Shi H, Cui Y, Wang X, Zhang J, et al. (2018) Dendrobium mixture regulates hepatic gluconeogenesis in diabetic rats via the phosphoinositide 3 kinase/protein kinaseβsignaling pathway. *Experimental Ther Med* 16: 204-212. [Crossref]
19. Zheng H, Pan L, Xu P, Zhu J, Wang R, et al. (2017) An NMR-Based Metabolomic Approach to Unravel the Preventive Effect of Water-Soluble Extract from Dendrobium officinale Kimura & Migo on Streptozotocin-Induced Diabetes in Mice. *Molecules* 22: 1543.
20. Wang HY (2019) Dendrobium huoshanense polysaccharide regulates hepatic glucose homeostasis and pancreatic β-cell function in type 2 diabetic mice. *Carbohydr Polym* 211: 39-48.
21. Liu Y, Yang L, Zhang Y, Liu X, Wu Z, et al. Dendrobium officinale polysaccharide ameliorates diabetic hepatic glucose metabolism via glucagon-mediated signaling pathways and modifying liver-glycogen structure. *J Ethnopharmacol* 248: 112308.

22. Leitner DR, Frühbeck G, Yumuk V, Schindler K, Micic D, et al. (2017) Obesity and type 2 diabetes: Two diseases with a need for combined treatment strategies-EASO can lead the way. *Obes Facts* 10: 483-492. [Crossref]

23. Wang W, Zhang D, Zhao H, Chen Y, Liu Y, et al. (2010) Ghrelin inhibits cell apoptosis induced by lipotoxicity in pancreatic β-cell line. *Regulatory Pept* 161: 43-50.

24. Huang S, Wu Q, Liu H, Ling H, He Y, et al. (2019) Alkaloids of dendrobium nobile lindl. Altered hepatic lipid homeostasis via regulation of bile acids. *J Ethnopharmacol* 241: 111976.

25. Zhang Q, Li J, Luo M, Xie GY, Zeng W, et al. (2020) Systematic transcriptome and regulatory network analyses reveal the hypoglycemic mechanism of Dendrobium fimbriatum. *Mol Ther Nucleic Acids* 19: 1-14.

26. Li C, Li Y, Gai Z (2019) Bile acids and farnesoid X receptor: novel target for the treatment of diabetic cardiomyopathy. *Curr Protein Pept Sci* 20: 976-983.

27. Xu YY, Xu YS, Wang Y, Wu Q, Lu YF, et al. (2017) Dendrobium nobile Lindl. alkaloids regulate metabolism gene expression in livers of mice. *J Pharm Pharmacology* 69: 1409-1417. [Crossref]

28. Abdulreda MH, Rodriguez-Diaz R, Cabrera O, Caicedo A, Berggren PO, et al. (2016) The different faces of the pancreatic islet. *In Pancreat Islet Isolation. Springer, Cham* 2016: 11-14.

29. Li XW, Huang M, Lo K, Chen WL, He YY, et al. (2019) Anti-Diabetic Effect of a Shihunine-Rich Extract of Dendrobium loddigesii on 3T3-L1 Cells and db/db Mice by Up-Regulating AMPK–GLUT4–PPARα. *Molecules* 24: 2673.

30. Touyz RM, Rios FJ, Alves-Lopes R, Neves KB, Camargo LL, et al. (2020) Oxidative stress–A unifying paradigm in hypertension. *Canadian J Cardiol* 2020.

31. Niemann B, Rohrbach S, Miller MR, Newby DE, Fuster V, et al. (2017) Oxidative stress and cardiovascular risk: obesity, diabetes, smoking, and pollution: part 3 of a 3-part series. *J Am Coll Cardiol* 70: 230-251. [Crossref]

32. Li XW, Chen HP, He YY, Chen WL, Chen JW, et al. (2018) Effects of rich polyphenols extract of Dendrobium loddigesii on anti-diabetic, anti-inflammatory, anti-oxidant, and gut microbiota modulation in db/db mice. *Molecules* 23: 3245.

33. Hou SZ, Liang CY, Liu HZ, Zhu DM, Wu YY, et al. (2016) Dendrobium officinale prevents early complications in streptozotocin-induced diabetic rats. *Evid Based Complementary Altern Med* 2016; 2016.

34. Huang K, Li Y, Tao S, Wei G, Huang Y, et al. (2016) Purification, characterization and biological activity of polysaccharides from Dendrobium officinale. *Molecules* 21: 701.

35. Kojta I, Chacińska M, Błachnio-Zabielska A (2020) Obesity, Bioactive Lipids, and Adipose Tissue Inflammation in Insulin Resistance. *Nutr* 12: 1305.

36. Oktay AA, Aktürk HK (2020) Diabetes, Cardiomyopathy, and Heart Failure. In Endotext [Internet]. *MDText. com, Inc.* 2020.

37. Spillmann F, Altmann C, Scheeler M, Barbosa M, Westermann D, et al. (2002) Regulation of cardiac bradykinin B1-and B2-receptor mRNA in experimental ischemic, diabetic, and pressure-overload-induced cardiomyopathy. *International immunopharmacol* 2: 1823-1832. [Crossref]

38. Zhang Z, Zhang D, Dou M, Li Z, Zhang J, Zhao X (2016) Dendrobium officinale Kimura et Migo attenuates diabetic cardiomyopathy through inhibiting oxidative stress, inflammation and fibrosis in streptozotocin-induced mice. *Biomedicine & Pharmacotherapy* 84: 1350-1358.

39. Zhang JY, Guo Y, Si JP, Sun XB, Sun G B, et al. (2017) A polysaccharide of Dendrobium officinale ameliorates H2O2-induced apoptosis in H9c2 cardiomyocytes via PI3K/AKT and MAPK pathways. *International J Biological Macromolecules* 104: 1-10.

40. Chan G, Tang SC (2013) Current practices in the management of diabetic nephropathy. j. r. Coll. *Physician Edinb* 43: 330-332. [Crossref]

41. Higgins GC, Coughlan MT (2014) Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy. *Br J Pharmacology* 171: 1917-1942.

42. Ha H, Lee HB (2003) Reactive oxygen species and matrix remodeling in diabetic kidney. *J Am Soc Nephrology* 14(suppl 3): S246-S249.

43. Chang J, Zhou Y, Cong G, Guo H, Guo, et al. (2019) Dendrobium candidum protects against diabetic kidney lesions through regulating vascular endothelial growth factor, Glucose Transporter 1, and connective tissue growth factor expression in rats. *J Cell Biochemistry* 120: 13924.

44. Lee W, Eom DW, Jung Y, Yamabe N, Lee S, et al. (2012) Dendrobium moniliforme attenuates high-fat diet-induced renal damage in mice through the regulation of lipid-induced oxidative stress. *Am J Chin Med* 40: 1217-1228. [Crossref]

45. Zhao M, Han J (2018) Dendrobium officinale Kimura et Migo ameliorates insulin resistance in rats with diabetic nephropathy. *Med Sci Monit Basic Res* 24: 84.

46. Chen H, Nie Q, Hu J, Huang X, Zhang K, et al. (2019) Glucomannans alleviated the progression of diabetic kidney disease by improving kidney metabolic disturbance. *Mol Nutr & Food Res* 63: 1801008.

47. Karst SG, Lammer J, Radwan SH, Kwak H, Silva PS, et al. (2018) Characterization of In vivo retinal lesions of diabetic retinopathy using adaptive optics scanning laser ophthalmoscopy. *International J Endocrinol* 2018; 2018.

48. Yu Z, Gong C, Lu B, Yang L, Sheng Y, et al. (2015) Dendrobium chrysotoxum Lindl. alleviates diabetic retinopathy by preventing retinal inflammation and tight junction protein decrease. *J Diabetes Res* 2015; 2015.

49. Yu Z, Zhang T, Gong C, Sheng Y, Lu B, et al. (2016) Erianin inhibits high glucose-induced retinal angiogenesis via blocking ERK1/2-regulated HIF-1α-VEGF/VEGFR2 signaling pathway. *Sci Rep* 6: 34306.

50. Gong CY (2014) Ethanol extract of Dendrobium chrysotoxum Lindl ameliorates diabetic retinopathy and its mechanism. *Vasc Pharmacology* 62: 134-142.

51. Flaxman SR, Bourne RR, Resnikoff S, Ackland P, Braithwaite T, et al. (2017) Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *The Lancet Global Health* 5: e1221-e1234. [Crossref]

52. Zhang P, Xing K, Randazzo J, Blessing K, Lou MF, et al. (2012) Osmotic stress, not aldose reductase activity, directly induces growth factors and MAPK signaling changes during sugar cataract formation. *Experimental Eye Res* 101: 36-43.

53. Wu J, Li X, Wan W, Yang Q, Ma W, et al. (2017) Gigantol from Dendrobium chrysotoxum Lindl. binds and inhibits aldose reductase gene to exert its anti-cataract activity: An in vitro mechanistic study. *J ethnopharmacol* 198: 255-261.

54. Fang H, Hu X, Wang M, Wan W, Yang Q, et al. (2015) Anti-osmotic and antioxidant activities of gigantol from Dendrobium aurantiacum var. denneanum against cataractogenesis in galactosemic rats. *J Ethnopharmacol* 172: 238-246. [Crossref]

55. Yuan Y, Yu M, Zhang B, Liu X, Zhang J, et al. (2019) Comparative nutritional characteristics of the three major Chinese Dendrobium species with different growth years. *PloS One* 14: e0222666.

56. Yang LC, Liao JW, Wen CL, Lin WC (2018) Subchronic and Genetic Safety Assessment of a New Medicinal Dendrobium Species: Dendrobium Taiseed Tosnobile in Rats. *Evid Based Complementary Altern Med* 2018; 2018.

57. He TB, Huang YP, Yang L, Liu TT, Gong WY, et al. (2016) Structural characterization and immunomodulating activity of polysaccharide from Dendrobium officinale. *Int J Biol Macromol* 83: 34-41.

58. Qian XP, Zha XQ, Xiao JJ, Zhang HL, Pan LH, et al. (2014) Sulfated modification can enhance antiglycation abilities of polysaccharides from Dendrobium huoshanense. *Carbohydr Polym* 01: 982-989.

59. Tian CC, Zha XQ, Pan LH, Luo JP (2013) Structural characterization and antioxidant activity of a low-molecular polysaccharide from Dendrobium huoshanense. *Fitoterapia* 91: 247-255.

60. Ito M, Matsuzaki K, Wang J, Daikonya A, Wang N, et al. (2010) New phenanthrenes and stilbenes from Dendrobium loddigesii. *Chem Pharm Bull (Tokyo)* 58: 628-633.

61. Lu Y, Kuang M, Hu GP, Wu RB, Wang J, et al. (2014) Loddigesiinols G-J: α-glucosidase inhibitors from Dendrobium loddigesii. *Molecules* 19: 8544-8555.

62. Yang D, Liu LY, Cheng ZQ, Xu FQ, Fan WW, et al. (2015) Five new phenolic compounds from Dendrobium aphyllum. *Fitoterapia* 100: 11-18. [Crossref]

63. Li Y, Wang CL, Zhao HJ, Guo SX (2014) Eight new bibenzyl derivatives from Dendrobium candidum. *J Asian Nat Prod Res* 16: 1035-1043.

64. Xu X, Li Z, Yang R, Zhou H, Bai Y, et al. (2019) Crepidatumines C and D, Two New Indolizidine Alkaloids from Dendrobium crepidatum Lindl. Ex Paxt. *Molecules* 24: 3071.

65. Sritularak B, Anuwat M, Likhitwitayawuid K (2011) A new phenanthrenequinone from Dendrobium draconis. *J Asian Nat Prod Res* 13: 251-255. [Crossref]