

# The Journal of Phytopharmacology

(Pharmacognosy and phytomedicine Research)

## Review Article

ISSN 2320-480X  
JPHYTO 2020; 9(2): 130-138  
March- April  
Received: 26-02-2020  
Accepted: 10-03-2020  
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doi: 10.31254/phyto.2020.9210

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## Use of Orchids in treating Diabetes and related diseases: A review

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### ABSTRACT

Diabetes is one of the most common diseases and is one of the main causes of morbidity and mortality in world. The number of diabetic patients showed a sharp rise from 347 million to 400 million in seven years (2008 to 2015). India is one of the frontrunner countries in harbouring this disease. Herbal drugs are always been intriguing for the treatment of diabetes. Several polyherbal formulations, single drugs have been assigned to possess anti-diabetic potentials. Among the plant families, Orchidaceae is not only one of the most interesting, also have been praised for their medicinal values since ages. This review tries to encompass the uses of orchids in diabetes and related disorders. Nearly 19 species belonging to 12 genera of orchids are traditionally used in treating Diabetes and related pathophysiological conditions across the Globe. Some of them, if validation is concerned, are proven experimentally to show anti-diabetic and anti-hyperglycaemic potentials on standard animal models. Pharmacological studies revealed that as many as 17 species included in 6 genera of orchids are evaluated so far for anti-diabetic potential. With forbidden gaps in the traditional belief and pharmacological profile currently, there remains indeed a potential area for bio-prospecting of orchid group for their ant-diabetic property.

**Keywords:** Orchids, Traditional Medicine, Diabetes, Hyperglycaemia.

### INTRODUCTION

Diabetes is one of the common forms of disorders presently found amongst human population. Three types of diabetes are recognised, namely, (i) Type I Diabetes or Insulin-dependent type, (ii) Type II Diabetes or Non-insulin dependent type and (iii) Gestational Diabetes [1]. There could be another type, which is supposed to be non-specific and may be caused by several factors and develop secondarily. Pancreatic inflammation, Cystic fibrosis, Down's syndrome, Haemochromatosis due to medical treatments including administration of corticosteroids, diuretics and pancreatectomy might account for this secondary diabetes [2]. However, it is documented that this disease is one of the major causes of mortality and morbidity and is increasing day by day, mainly because of sedentary life-style and obesity [1].

Presently, approximately 9.2% women of the world and 9.8% men of the world are suffering with Diabetes, with an estimated total number of patients of 347 million according to 2008 census [3] and 400 million according to 2015 census [4]. Specifically, nearly 4% pregnant women potentially develops gestational diabetes and Type II Diabetes accounts for nearly 85 to 90% cases in developed countries and even more in developing nations [2]. Some estimates predict that the number of diabetes affected patients may reach up to 592 million by the end of 2030 [5]. In 2012, an estimate showed, there were nearly 1.5 million deaths directly due to diabetes worldwide [5]. India is also in the top position in harbouring maximum number of Diabetic patients and second in prediabetic patients [6].

Diabetes mellitus (DM) is a common metabolic disorder with multiple aetiology, which is characterised by the consistent and chronic hyperglycaemia and improper metabolism of fat, proteins and more prominently carbohydrates [7]. This results from many reasons, like (i) insulin secretion defects, (ii) defect in insulin action or sometimes, (iii) both [7].

Chronic hyperglycaemia, which is often associated with DM and other forms of Diabetes, may lead to various complications, such as retinopathy, nephropathy, neuropathy, and increased risk of cardiovascular diseases [3]. Current uses of standard drugs, with unpleasant side-effects, include insulin-sensitizers (like Thiazolidinediones) or insulin-secretagogue (like Sulfonylureas), or  $\alpha$ -glucoside inhibitors [8]. Common side-effects also include severe hypoglycaemia, lactic acidosis, peripheral oedema, abdominal discomforts [8], inhibition of hepatic regeneration, obesity, and osteoporosis [5].

In order to combat such serious issue, large number of experiments, mainly on cell-lines and animals have been and are being conducted throughout the world since ages. Herbal drugs, of several plant origins have also been regularly evaluated to treat diabetes and related many disorders both *in vitro* and *in vivo* (for review, please see [1, 2, 4, 5, 8, 9]). It is documented that out of more than 2,50,000 higher plants, only 2,500 species have been so far screened for anti-diabetic potentials across the globe [5]. It is worth mentioning that according to World ethno botanical documentation, nearly 800 medicinal plants are used to treat or prevent diabetes, out of which nearly 450 are clinically experimented, of which nearly 109 plants possess complete mode of action [9]. Apart from single drug, several polyherbal formulations are also mentioned to treat diabetic conditions [9]. This may include several groups of plants including orchids, since they are known for their therapeutic potentials since long times (for general reference please see [10]).

However, there are no single review on the use of Orchid (Family - Orchidaceae) members in preventing or treating particularly diabetes and related pathophysiological conditions. Thus, this review specifically targets the use of Orchidaceae family members as a probable potent source of future anti-diabetic drugs.

## METHODOLOGY

Search of data for this review was primarily from the standard websites. In order to procure pertinent literature without having any author bias, combinations of keywords like "Orchids", "Orchidaceae", "Hyperglycemia" were incorporated with "Diabetes" in Google Scholar, Science Direct, Elsevier, Pubmed Central, BMC. Peer reviewed journal articles, Thesis and dissertations, Abstracts, were in the inclusion criteria for the literature search. Language bias was not incorporated in order to obtain maximum information available.

## DISCUSSION

Although the number differ significantly (from 800 to 1200), it is undoubtedly known that several plants are utilised to manage DM worldwide [5]. More than 400 herbal drugs in the form of whole plant materials, plant parts or derivatives from plant parts have been incorporated in more than 700 mono-herbal or polyherbal formulations worldwide to treat Diabetes [2]. Indigenous medicinal systems, including folklore medicines of practically every country has incorporated drugs of herbal origin for managing DM and related disorders. Ethnomedicinal reviews and documentations revealed the use of as many as 19 species encompassed in 12 genera of orchids for this which are furnished in Table 1.

### Experimental validation of anti-diabetic potential of orchids

It is clear that traditional belief suggests the use of several orchids in treating diabetes by tribal communities across the globe. Some of these orchids have also been validated by several scholars throughout the world experimentally, while some are still under study.

As evident from literature, most of these animal models on Diabetes were chemically induced. Frequently, Streptozotocin (STZ) or 2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose and Alloxan or (2,4,5,6-Tetraoxypyrimidine; 5,6-dioxuracil)[3] are preferred in the researches with orchids (Table 2) with few experimental scenario where high fat diet and Adrenalin were used to induce diabetic conditions. From the available data following points may be summarised (Table 2):

1. There are as many as 17 species of orchids included in 6 genera, which have been evaluated so far for this property.
2. Most common genus which has been worked out extensively is *Dendrobium* with 9 species.
3. Only single search hit a preliminary clinical trial performed by Xu and colleagues where capsule of *Anoectochilus roxburghii* were used on human subjects [42].

A traditional medicine, named *Dendrobium* compound (DC), a complex mixture of *Dendrobium* orchids, has been experimented on animal model to elucidate anti-diabetic potential [11]. In the experimental model, animals were subjected to high-sugar, high-fat diet with 30 mg/kg body weight Streptozotocin to induce diabetes. It was observed that blood glucose level was significantly reduced in the animals when treated with DC [11]. In addition, there was notable increase in Glucagon-like Peptide-1 (GLP-1) in the blood. After a high-sugar load for 2 hr, the GLP-1 reduced in DC treated animals [11]. From these experiments, it was concluded that DC might work as a hypoglycaemic product via GLP-1 signaling pathway [11]. Previous studies indicated that DC could bring apoptosis in the Islet cells [12]. Molecular studies showed that there was significantly increase in the mRNA of two genes Bcl-2 and Bax in Islet cells in those diabetic animals treated with DC [12].

### Diabetic Retinopathy

One of the major concern and complicated problem with Diabetes mellitus is Diabetic Retinopathy (DR) [13]. Gong and colleagues have evaluated STZ-induced diabetic *in vivo* model and showed the following major findings [13]:

1. With 30 to 300 mg per kg body weight, ethanolic crude extract of *D. chrysotoxum* orchid increased retinal vessels.
2. Expression of mRNAs of vascular endothelial growth factor (VEGF) and VEGF-receptor-2 (VEGFR-2) significantly increased after treatment of herb. Elevated serum VEGF level was decreased.
3. Expression of mRNAs of Matrix Metalloproteinase (MMP) 2 and 9 (MMP-2 and MMP-9) were also shown to have been decreased along with basic Fibroblast Growth Factor (bFGF), Platelet derived Growth Factor (PDGF) A/B, Insulin-like Growth Factor-1 (IGF-1), Interleukin-1 $\beta$  and IL-6.
4. Further, the extract also decreased the increased phosphorylation of p65 and the increased expression of Intercellular Adhesion molecule-1 (ICAM-1).
5. Anti-inflammatory potential of this orchid extract is supposed to be via NF- $\kappa$ B signaling pathway.

In conclusion it was shown that the herb might alleviate angiogenesis during the process of diabetic retinopathy, which could be via inhibiting the expressions of VEGF/VEGFR-2, and some other pro-angiogenic factors, like that of MMP-2/9, PDGF, bFGF, IGF-1 [13].

On the other hand, Yu and colleagues, using STZ-diabetic model elucidated that [14]:

1. With the administration of 30 or 300 mg per kg body weight, the disrupted Blood-Retinal Barriers (BRBs) were attenuated.
2. The increased mRNA expression of retinal Intercellular Adhesion molecule-1 (ICAM-1), TNF- $\alpha$ , Interleukin-6 (IL-6) and IL-1 $\beta$  were eventually reduced with herbal treatment.
3. Additionally, there was increased serum TNF- $\alpha$ , IL- $\gamma$ , IL-6, IL-12, IL-2, IL-1 $\beta$ , IL-8, IL-3 and IL-10, were also down regulated.
4. Conversely, mRNA expressions of the proteins Occludin and Claudin-1, which are typically Tight Junction Proteins, in the retina were up regulated.
5. Phosphorylated p65,  $\kappa$ B and  $\kappa$ B-Kinase activities were also down regulated during the treatment.
6. In another attempt, Yu and colleagues have evaluated the inflammatory interleukins and many markers and following significant inferences were drawn [15]:
7. There were significant change in the IL-6 and IL-1 $\beta$ , Tumour Necrosis Factor (TNF- $\alpha$ ), Early Growth Response-1 (Erg-1), Tissue Factor (TF) and Serpine-1 in the retina of affected animals followed by herbal intervention.

Two major conclusions were postulated as the putative mechanism of action of this orchid in preventing Diabetic retinopathy as [14, 15]:

1. The orchid might prevent STZ-induced diabetic retinopathy via modulation of Tight Junction Proteins as well as via inhibiting the inflammatory cytokines which inhibit the retinal inflammation.
2. The ameliorative effect might as well be via inhibiting blood-retinal barrier breakdown and thereby reducing the expression of pro-inflammatory cytokines and coagulation related signals.

In fact, significant role of inflammation in the pathophysiology of DR has been postulated by Li and colleagues [16]. It is postulated that this increase in TNF- $\alpha$  leads to abnormality in tight-junction proteins and damage the blood-retinal barrier eventually. Herbal polysaccharides, isolated from *Dendrobium candidum* was shown to possess preventive role in this pathway. Significant finding of the experiments of Li and colleagues may be summarized as [16]:

1. Diabetes was induced by intraperitoneal injection of STZ to animals. Blood-retinal barrier (BRB) permeability was evaluated by Evans Blue leakage which was measured after perfusing the same through cardiac chamber and eyes.
2. The retinal leakage of Evans Blue was significantly lower in treated animals as compared to Diabetic models, nearly 22.12, 17.99, 21.26 and 30.45 for 100, 200 and 300 mg/Kg/day and diabetic rats.
3. In addition, TNF- $\alpha$  expression was significantly lowered in treated group, while expression of the zonula occludens-1 (ZO-1), occludin and Claudin-5 proteins were significantly increased.

From these experiments, it was concluded that polysaccharides could attenuate the BRB condition via TNF- $\alpha$  expression and by up-regulating various tight-junction proteins in retina of diabetic rats [16].

### Diabetic Nephropathy

Diabetic nephropathy (DN) is one of the important 'long-term microvascular complication of uncontrolled hyperglycemia, which develops in approximately 30% to 40% of all Diabetes Mellitus patients'. It is one of the major end-stage-renal diseases [17].

In order to evaluate one of the common TCM drug, named 'Tiepi Shihu' (dried stem of *Dendrobium officinale*), Zhao and Han have shown that aqueous extract of this orchid could be used in treating DN by preventing insulin resistance [17]. Following summary can be furnished to establish major findings:

1. Animals were administered aqueous extract of orchid at 5 ml/Kg/day and 10 ml/kg/day doses. In the control group, 0.0042 g/kg/day dimethylbiguanide was administered.
2. Diabetes Mellitus was induced STZ, 30 mg/kg, every 2 weeks, twice.
3. Treatment of herb reduced urinary glucose level, and altered the albuminuria (albumin concentration in urine), serum creatinin level, blood urea-nitrogen concentration to a significant level.
4. There was no effect on the total cholesterol, triglyceride, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels of the liver.
5. Significant change in certain protein, like that of TLR-2, TLR-4, and MyD88 mRNA expression due to the treatment with the herb was observed.

From these findings along with others, several positive conclusions were made [17]:

1. The orchid extract does not have any significant effect on blood lipids and liver functions.
2. Extract might promote insulin secretion from the Beta-cells of Pancreas, thus alter the serum insulin level and act as

- hypoglycemic, simultaneously inhibit Glucagon secretion from Alpha-cells, thereby controlling serum glucagon level.
3. Elevation of FINS protein and depletion of level of GLU the herb-administered animals suggested probable action on the pancreatic enzymes.
4. DN inhibitory effect herb was associated to TLRs, which have direct relation with pancreatic secretion. This was also supported by the decrease of IL-6 and IL- $\beta$  expression.
5. Finally, down-regulation of the levels of hs-CRP, TNF- $\alpha$ , and IL-6 suggested that the orchid inhibit the expression of TLRs to alleviate inflammatory response in rats with DN.

### Major inference

From the above discussion and the tabular information, it can be inferred that a marked forbidden gap exists between the folklore uses and scientific validation of potential, as far as anti-diabetic properties of orchids are concerned, which may be summarised as follows:

1. While some genera like *Acampe*, *Agrostophyllum*, *Arundina*, *Cyrtorchis*, *Eria*, *Geodorum*, *Papilionanthe*, and *Spiranthes* are used for treating diabetes by various tribes, they are not yet validated experimentally (Table 1).
2. The species of *Prosthechea* scientifically validated is not which is used in traditional belief. The converse is also true.
3. *Eulophia* species, especially *E. ochreatea* and *E. epidendreae*, which are not used to treat diabetes by tribal communities, possess significant potential, as evidences showed (Table 2).
4. Several species of *Dendrobium*, viz. *D. denneanum*, *D. loddigesii*, *D. nobile* are experimentally shown to possess significant anti-diabetic potentials, which are not being used by tribes.

Thus, in order to bridge the gap, (i) more extensive research programmes are recommended worldwide, which would club the modern science with the ancient traditional belief, and (ii) enrichment of tribal knowledge by experimental proofs and value-addition to communities by personal communications are needed, along with strategic conservation of this goldmine for future generation.

Another important aspect of exploring the anti-diabetic potential of orchids has revealed that even though, several orchids are either traditionally utilised or are experimentally shown to possess anti-diabetic properties, the number of actual formulae in order to cure the disease is yet not been adapted by the scientific community. There might be several reasons, as summarised hereunder, for the same:

- I. *In vitro* as well as *in vivo* models are evaluated to show the anti-diabetic potentials. However, actual clinical trials are scanty or altogether absent (in this case only one documented).
- II. Development of monoherbal or polyherbal formulations using these herbs are not reported, documented yet.
- III. Similarly, reports of single isolated molecule with significant potentials are scanty.
- IV. One may insight that, if developed, such a Polyherbal formulation might not be as efficient as single herb or isolated compound.
- V. There might remain some problem with subject trial, like ethical issues, availabilities of subjects, clinical application, which need to be addressed in order to proceed for an end-to-end solution.

The last aspect, which might be imagined for herbal medicine and its research, is that the pharmacokinetic parameters are quite difficult to elucidate. How a single compound of herbal origin is absorbed, eliminated, retained and converted *in vivo*, and what are the behaviours when synergistic or antagonistic effects are viewed, is what is exactly needed once we come up with some specific compound or formulations.

**Table 1:** Ethnomedicinal uses of Orchids in Diabetes and related disorders

SN	Name of Orchid	Part used (used as)	Country (or State in India)	Pathological condition (to treat)	Reference
1	<i>Acampe praemorsa</i> (Roxb.) Blatt. & McCann	Whole plant decoction	South Indian states	Diabetes	[18,19]
2	<i>Agrostophyllum callosum</i> Rchb.f.	Tuber, chewed	Sikkim	Diabetes	[20]
3	<i>Anoectochilus formosanus</i> Hayata	Whole plant, Decoction	China	Diabetes	[21]
4	<i>Anoectochilus roxburghii</i> (Wall.) Lindl.	Whole plant, Decoction	China	Diabetes	[21, 22]
5	<i>Arundina graminifolia</i> (D.Don) Hochr.	Root decoction	North East Himalayan Belt, India	Diabetes	[23, 24]
6	<i>Cyrtorchis arcuata</i> (Lindl.) Schltr.	Dried powder of whole plant	Africa	Diabetes	[25, 26, 24, 27]
7	<i>Dendrobium aphyllum</i> (Roxb.) C.E.C. Fisch.	Whole plant	Bangladesh	Diabetes	[28]
8	<i>Dendrobium aurantiacum</i> (F.Muell.) F.Muell.	Infusion of leaves or decoction	Australia	Diabetes	[24]
9	<i>Dendrobium formula</i> ( <i>Herba Dendrobii</i> )	Whole plants in a polyherbal formula	China	Diabetes	[29]
10	<i>Dendrobium candidum</i> Wall ex Lindl.	Leaves decoction	Nagaland, NE Himalayan Belt, India	Diabetes	[23]
11	<i>Dendrobium chrysotoxum</i> Lindl.	Whole plant in many forms	China	Diabetes	[30]
12	<i>Dendrobium officinale</i> Kimura et Migo	Whole plant in many (nearly 190) polyherbal formulae	China	Diabetes	[17, 31]
13	<i>Eria tomentosa</i> (J.Koenig) Hook.f.	Whole plant	Bangladesh	Diabetes	[28]
14	<i>Geodorum densiflorum</i> (Lam.) Schltr.	Whole plant or pseudobulbs, consumed	Bangladesh	Diabetes	[28, 32]
15	<i>Nervilia plicata</i> (Andrews) Schltr.	Whole plant, decoction	Southern India	Diabetes	[33]
16	<i>Papilionanthe teres</i> (Roxb.) Schltr.	Whole plant, consumed	Bangladesh	Diabetes	[28]
17	<i>Prosthechea karwinskii</i> (Mart.) J.M.H.Shaw.	Leaves are chewed and pseudobulbs infusion taken	America, Mexico	Diabetes	[34]
		Leaves and pseudobulbs, decoction	America and Mexico	Hyperglycemia	[35]
18	<i>Spiranthes acaulis</i> (Sm.) Cogn.	Whole plant in early stages of diabetes	Latin America, Caribbean	Diabetes	[36]
19	<i>Spiranthes australis</i> (R.Br.) Lindl.	Decoction of whole plant	China, Trinidad, Tobago	Urinary problems and Diabetes	[24]
20	<i>Spiranthes sinensis</i> (Pers.) Ames.	Whole plants and root decoction	China	Diabetes	[37]

**Table 2:** Pharmacological evidences to prove anti-diabetic potential of Orchids

SN	Genus and Species	Model description	Major finding	Isolated Bioactive compound(s)	Inference or Conclusion by the scholar	Inference	Reference
1	<i>Anoectochilus formosanus</i> Hayata, and <i>A. roxburghii</i> (Wall.) Lindl.	Animal model: Streptozotocin induced diabetic model  <i>In vitro</i> Cell line model: mouse liver cells (FL83B)	Significant reduction in fasting glucose, total triglycerides, total cholesterol after 21 day administration  In the cells, induced by TNF- $\alpha$ (40 ng/ml) were co-treated with various concentrations of the extracts, the anti-insulin resistance changed significantly; hot water extract is more effective in glucose uptake and anti-insulin resistance as compared to other extracts	Crude extract  Hot water, Cold Distilled water and Ethanolic extracts	Potent anti-hyperlipidemic and anti-oxidant  Anti-insulin resistant potential	Combination of <i>in vivo</i> and molecular analysis may further be taken to provide an end-to-end solution of such scenario  Further elucidation of Mechanism of action is absolutely necessary to formulate some potent medicine	[38, 10]  [39]
2	<i>Anoectochilus roxburghii</i> (Wall.) Lindl.	Animal model: Alloxan induced hyperglycemic mice	Crude extract significantly antagonize the increase in blood glucose triggered by adrenaline and exogenous glucose in mice;	No significant role in Beta cells injury	Anti-diabetic	Elucidation of mechanism of action might provide some clue to its activity	[40, 22, 41]

		Animal model: Streptozotocin induced diabetes	n-Butanol extract at 600 mg/kg reduce blood glucose level	Hypoglycemic potential is related with anti-oxidant properties	Anti-diabetic and anti-oxidant	Further elucidation of mechanism of action might provide a clue to new formulation	[22]
		Clinical trial	Significant change in diabetic-Type-2 condition of subjects	Capsules of herb	Potent anti-diabetic	So far documented the only clinical trial for the herb which was done under medical supervision on human subjects. Such work provides clear clue, when combined with pharmacokinetic behaviour of isolated compounds in human system	[22, 42]
		<i>In vivo</i> model	Significant reduction in body's antioxidant properties	Polysaccharides	Anti-diabetic	Further elucidation of Mechanism of action is absolutely necessary to formulate some potent medicien	[22, 43]
		<i>In vivo</i> model	At a dose of 15 mg/kg scavenges free-radicals and reduces serum NO level and repairs damaged insulin cells in vivo	Kinsenoside	Anti-oxidant	Relation between oxidative stress and diabetes in order to cure the later through the former needs to be elucidated	[22, 44]
3	<i>Anoectochillus burmannicus</i>	<i>In vitro</i> cell line model: mature 3T3-L1 adipocytes	there was reduction in glucose uptake due to the presence of TNF- $\alpha$ ; significant increase in glucose uptake (up to 40%) when the TNF- $\alpha$ adipocytes were treated with <i>A. burmannicus</i> extract;	Crude extract	A direct relation between anti-inflammatory substances and Metabolic syndrome (MS). The anti-TNF- $\alpha$ -blockage has been shown to improve the insulin-resistance in autoimmune diseases like Rheumatoid Arthritis; while IL-1-receptor antagonists are known to increase insulin-sensitivity in Type-2 Diabetes	Further isolation of bioactive chemicals along with mechanism isolation might give some satisfactory results in near future	[45]
4	<i>Dendrobium candidum</i> Wall ex Lindl.	<i>In vivo</i> model	Anti-hyperglycemic potential; Stimulate Beta cells and inhibit Alpha cells of Pancreas	Not reported	Glucagon inhibitory and Insulin stimulatory effect	Reported to be priliminary study	[23, 46]
5	<i>Dendrobium aqueum</i> Lindl.	<i>In vitro</i> Biochemical analysis	Antiglycation with thiol-group protection in vitro	Not reported	Potential protect thiol-groups dueing glycation	Basic biochemical analysis and needs to be further evaluated with animal, cell lines to find an end-to-end solution	[47]
6	<i>Dendrobium chrysotoxum</i> Lindl.	Animal model: Alloxan induced hyperglycemic mice	Hypoglycemic potentia; Blood glucose level in Hyperglycemic mice 360 mg/dl; that of treated 303.6 and 231.7 mg/dl per 200 and 500 mg/Kg	Polysaccharides of pseudobulbs	Hypoglycemic activity <i>in vivo</i>	Characterisation of Polysaccharides and further experimentation in vivo as well as clinical trial to be addressed in order to develop new potent medicine from this orchid	[48]
7	<i>Dendrobium huoshanense</i> C.Z.Tang et S.J.Cheng	Animal model: Streptozotocin induced diabetic cataract in animals	Anti-cataract potential and increased opacity of lens in treated animals; iNOS gene expression regulatory	Polysaccharides of pseudobulbs	Diabetic anti-cataract potential	Combination of <i>in vivo</i> and molecular analysis may further be taken to provide an end-to-	[49]

		Animal model: Alloxan induced diabetic animals	Chemical induced oxidative stress level declined; serum insulin level, fasting glucose level and glycosylated serum protein level improved	Polysaccharides of pseudobulbs	Anti-diabetic and potential anti-oxidant <i>in vivo</i>	end solution of such scenario Oxidative stress might be one of the major aspect inducing a damage in the Pancreatic cells. Further correlation of these two at molecular level might provide an useful solution to combat diabetes	[50]
8	<i>Dendrobium formosum</i> Roxb. Ex.Lindl.	<i>In vitro</i> Cell line model	In L6-myoblast cells of rats glucose uptake improved enhanced by bioactive molecule	Lucianthridin (at a dose of 1µg/ml)	Potent anti-diabetic and anti-obesity compound	Purification, characterisation and further mechanism of action elucidation might be beneficial	[51]
9	<i>Dendrobium denneanum</i> Kerr.	<i>In vivo</i> Alloxan-induced animal model	Significant reduction of blood glucose level at 30 mg/Kg, 100 mg/Kg and 300 mg/Kg doses; increase glucose tolerance	Polysaccharides of pseudobulbs	Anti-diabetic potential	Combination of <i>in vivo</i> and molecular analysis may further be taken to provide an end-to-end solution of such scenario	[52]
10	<i>Dendrobium officinale</i> Kimura et Migo	Animal model: Alloxan induced diabetic animals	Significantly reduces the Fasting Blood Glucose level, Glycosylated Serum Protein level and at the same time increases Serum Insulin level in Alloxan-induced diabetic mice model, at a dose of 50 mg/Kg, 100 mg/Kg and 200 mg/Kg	Polysaccharides specifically rich in Glucose, Mannose and Arabinose	Hypoglycemic activity <i>in vivo</i>	Combination of <i>in vivo</i> and molecular analysis may further be taken to provide an end-to-end solution of such scenario	[31]
		Animal model: Alloxan induced hyperglycemic mice	Reduced MDA and increased GSH concentration; attenuation of liver and kidney	Polysaccharides of pseudobulbs	Anti-diabetic through oxidative stress reduction and via blood-lipid balancing potential	Exact role of oxidative stress in the pathophysiology of diabetes and diabetic damage of organs need to be further elucidated along with attenuating potential of Polysaccharides of this herb	[50]
		Animal model: Streptozotocin and Adrenalin induced hyperglycemia	Crude extract at 0.125 g/Kg and 0.25 g/Kg increased Beta cells, decreased Alpha cells activities in Pancreas; alleviated adrenalin-induced hyperglycemia at 0.5 g/Kg and 1.0 g/Kg doses	Crude extract	Hypoglycemic activity <i>in vivo</i>	Isolation, Characterisation of bioactive chemicals from the crude extract along with Pharmacokinetic studies might provide some clue to the best activity	[46]
		Animal model: Antidiabetic rats	Total falvonoid at a dose of 35 mg/Kg, total Polysaccharide at a dose of 100 mg/Kg and total aqueous extract at a dose of 6 g/Kg; significantly down-regulate the phosphorylation of JNK at Thr-183/Tyr-185 residues and upregulate the phosphorylation of AKT at Ser-473 residue in the Islet tissues of Pancreas	Flavonoid, Polysaccharides of crude aqueous extract	Hypoglycemic activity <i>in vivo</i>	Elucidation of mechanism of action with evaluation of synergistic or antagonistic pharmacokinetic behaviours of these molecules might further be attempted	[31]
11	<i>Dendrobium nobile</i> Lindl.	Animal model: Adrenalin and high-fat diet induced diabetes	Treatment with v10 mg/Kg to 80 mg/Kg of alkaloid increased expression of PGC1, glucose metabolism,	Alkaloids	Alkaloid have significatn role in glucose and lipid metabolism	Since there were increase in anti-oxidant genes alongside, the putative role of	[53]

			Glut2 and FoxO1 expressions; increase in fatty acid oxidation genes like Cpt1 $\alpha$ and Acox1; down-regulation of Sterol regulatory element-binding protein-1 (Srebp-1) Lipolysis promoting gene, ATGL			oxidative stress in pathophysiology of diabetes might get a clearer view when further analysed using more sophisticated approach	
12	<i>Dendrobium loddigesii</i> Rolfe.	Animal model: mutant db/db mouse	Reduction in blood glucose level, low density lipoproteins (LDL-C); significant increase in serum insulin	Polyphenols	Polyphenols could attenuate the fatty liver syndrome and improved diabetic retinopathy	Further evaluation of isolated compounds, mechanism of action and molecular analysis needs to be clubbed	[54]
13	<i>Eulophia epidendraea</i> (J.Koenig ex Retz.) C.E.C.Fisch	Animal model: Alloxan monohydrate induced diabetic model	Reduction in glucose level	Crude Methanolic extract	Hypoglycemic activity in vivo	Reported to be preliminary study	[55]
14	<i>Eulophia ochreatea</i> Lindl.	<i>In vitro</i> Biochemical analysis	Antiglycation potential, alpha-amylase inhibitory activity and antioxidant	Not reported	Anti-glycation; Anti-oxidant	Reported to be preliminary study	[56]
15	<i>Nervilia plicata</i> (Andrews) Schltr.	Animal model: Streptozotocin induced diabetic model	Crude extract at 5 mg/Kg dose restored damage in kidney tissue, reduce serum urea and creatinine levels; reduced lipid peroxidation in kidney	Crude Ethanolic extract	Anti-diabetic and Anti-oxidant	Further evaluation of isolated compounds, mechanism of action and molecular analysis needs to be clubbed	[33]
16	<i>Prosthechea michuacana</i> (Lex.) W.E.Higgins	Animal model: Streptozotocin induced diabetic model	Crude extract at a dose 200 and 400 mg per Kg reduced blood glucose level from 50.64% to 35.57% and from 57.10% to 47.78%, respectively; Triglyceride levels and total cholesterol levels also showed significant decline, 37.5% and 41.56% at 200 mg/Kg dose and 46.27% and 46.08% at 400 mg/Kg dose; decrease hyperinsulinemia by nearly 24%	Crude Hexane extract	Anti-diabetic	Further evaluation targeting the kinetic behaviour of each molecules isolated and characterised might provide an excellent arena to find new formulation and might as well go for end-to-end solution to combat diabetes	[57]
		Both <i>In vitro</i> and <i>In vivo</i> models	<i>In vitro</i> , these compounds could inhibit formation of AGEs by trapping reactive methylglyoxal of Bovine Serum Albumin; significant inhibitory effect on Glycated Haemoglobin (GHb and HbA1c)	$\alpha$ - $\alpha'$ -Dihydro-3',5',2-trimethoxy-3-hydroxy-4-acetyl-4'-isopentenyl stilbene, Gigantol (or 5-[2-(3-hydroxy-5-methoxyphenyl)ethyl]-2-methoxyphenol) and a novel type of phenanthrene-derivative like 4,6,7-Trihydroxy-2-methoxy-8-(methylbut-2-enyl)phenanthrene-1-1'-4',6',7'-trihydroxy-2'-methoxy-8'-(methylbut-2-enyl)-phenanthrene	Strong inhibitory effects for Advanced Glycation (AGE) and antioxidant		[58]
		Animal model: Streptozotocin induced Type-2 diabetic model	Significant increase in serum and pancreatic insulin level after 30 days administration; reduction in serum cholesterol, triglyceride, blood glucose levels	24-Methyl-24-hydroxy-5 $\alpha$ -lanosta-9(11)-25-dien-3 $\alpha$ -acetate (compound 1) and 24-Methyl-24-hydroxy-5-lanosta-9(11)-en-3 $\alpha$ -acetate	Significant hypoglycemic and hypolipidemic potentials		[59]
17	<i>Orchis anatolica</i> Boiss.	Animal model	Reduction in the total blood cholesterol (LDL) (198.89 mg/dL	Crude Ethanolic extract	Potent anti-diabetic, anti-hyperglycemic and	Further evaluation of isolated compounds,	[60]

in control and 174.07 mg/dL in treated group), total triglycerides (104.42 mg/dL in control and 89.19 mg/dL in treated group), Creatinin Kinase (443.93 IU/L in control and 367.50 IU/L in treated group); no change in Aspartate Amino Transferase (AST), Alanine Aminotransferase (ALT) and total Bilirubin content;	anti-hyperlipidemic herb	mechanism of action and molecular analysis needs to be clubbed in order to select a potent formulation for diabetes
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## CONCLUSION

In the present scenario, in light of available published data, this review on the use of orchids in treating diabetes can clearly demonstrate that herbal medicines, especially of orchid origin may prove good in future. Not only directly anti-diabetic, several orchid-derived drugs which are anti-oxidant, anti-inflammatory, ameliorative are being explored worldwide. If in future, there has to be any long-term cure or remedy for diabetes, it must come from drugs or herbal origin, in which Orchidaceae play a pivotal role. Reports suggest that the use of orchids in chemical or diet induced diabetic models of animals is quite promising. However, the future prospect is yet to open a new door when, if possible, a new bioactive molecule would come out to combat a common and complicated disease like Diabetes.

## ACKNOWLEDGEMENT

The author is deeply in gratitude to Dr. Bipinraj K., Assistant Professor, RGITBT, BVDU, Pune, for his encouragement and sincere help.

## Conflict of interest

No conflict of interest.

## Financial support and sponsorship

Nil.

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**HOW TO CITE THIS ARTICLE**

Mukherjee S, Jagtap S. Use of Orchids in treating Diabetes and related diseases: A review. *J Phytopharmacol* 2020; 9(2):130-138.