Antidiabetic Molecular Mechanisms of Active Compounds from Several Orchids

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Abstract: Hyperglycemia condition that leads to diabetes causes various complications. Various active compounds from plants have been studied for their antidiabetic abilities. One of them is the orchid plant. Besides being used as decoration, orchids contain several active compounds that have been proven to be used in medicine, including diabetes. This article discusses the antidiabetic mechanism of several active compounds obtained from orchids. Publication regarding orchid plant for diabetes were found in databases such as PubMed, Google Scholar, Wiley, Science Direct, Medline, Scopus, and Springer. Keywords used in this study were “orchid”, “diabetes”, “hyperglycemia”, “compound” and “herbal”. Out of the 447 collected articles (published in the period between 2011 and 2022), 416 were excluded due to non-relevant studies. There were 31 eligible studies included in this article. In conclusion, the antidiabetic mechanisms of the orchid extracts were as antioxidant, anti-inflammatory and anti-glycation agents, increasing insulin action, influencing lipid metabolism, and inhibiting α-amylase and α-glucosidase activity.

Keywords: Active compound; Antidiabetic; Mechanism; Orchid

Introduction

Hyperglycemia in diabetics can increase the generation of Advanced Glycation End Products (AGEs), a glycated protein molecule whose interaction with its receptor, RAGE, can induce the formation of Reactive Oxygen Species (ROS) through NADPH oxidase activation. One example of AGES is H2O2, of which its excessive production can activate nuclear factor kappa b (NFkB) and further causes diabetes complications (Yulianti et al., 2021, 2022). There are some studies of medicinal plants that were traditionally used to treat diabetes. Their antidiabetic activities such as improved insulin sensitivity and hypoglycemic activities. These abilities are believed due to their phenolic, flavonoids, terpenoids, alkaloids, and glycosides compounds (Salleh et al., 2021). Some plants have antioxidant abilities and are used as effective herbal medicines. While their antidiabetic compounds increase insulin secretion of pancreatic tissues or decrease the intestinal absorption of glucose (Kooti et al., 2016).

Orchids are member of Angiosperm group and belong to Orchidaceae family (Tsering et al., 2017). There are 4000 species of orchids found in Indonesia (Martha & Rahayu, 2022). Orchidaceae is a flowering plant comprises of 25,000 to 35,000 species from 750 to 850 genera (Musharof Hossain, 2011). Orchids are usually used preferably for decorative flower rather than for its medicinal use. Chemical compounds from this species include polysaccharides, revesteral, stilbenoids, while the polyphenol compounds are alkaloids, flavonoids, terpenoids, dibenzyl derivatives and phenanthrenes (Ashu Rajeshbhai & Ingalhalli, 2022; Joshi et al., 2020; Martha Pérez Gutiérrez, 2010; Singh et al., 2012). Orchids has the ability of antidiabetics, anti-inflammation, antioxidant, antimicrobes, anticancer, neuroprotection, and antiallergy (Ashu Rajeshbhai &
Ingalhalli, 2022; Minh et al., 2016). Minh et al. (2016) found that some compounds, from hybrid Phalaenopsis spp. namely phenolic, vanillic acid, protocatechuic acid, caffeic acid, p-hydroxybenzoic acid, syringic acid, ferulic acid, vanillin, p-coumaric acid, sinapic acid, benzoic acid, and ellagic acid have potentials as antioxidants. Orchidaceae, as a big plant family, is well known as a source of bioactive compounds, which has been studied for its new bioactive natural products (Kuo et al., 2022). This article reviews some orchids with their medicinal properties, which can be used as antidiabetics along with their particular mechanisms, using the most recent investigations available on literatures. Many studies have been carried out on the benefits of orchids for the treatment of diabetes, but have not discussed all the possible mechanisms that can be carried out by the active compounds contained in these orchids.

Method

Scientific databases such as Science Direct, PubMed, Google Scholar, Medline, Wiley, Scopus, and Springer were utilized to find publication regarding orchid plant for diabetes. The keywords used in this study included “orchid”, “diabetes”, “hyperglycemia”, “compound” and “herbal”. Out of the 447 collected articles (published in the period between 2011 and 2022), 416 were excluded due to non-relevance studies.

Inclusion and Exclusion Criteria

The search was restricted to only articles written in English language. All studies found during the search were evaluated by three different authors independently. After compliance with inclusion criteria, the eligibility screening was done by reading title and abstract of all articles to remove irrelevant studies. Most of the unselected journals were due to the plants studied do not belong to the Orchidaceae, or even though they are known as orchid trees or orchid, but they have no antidiabetic activities. Some of the journals were the same journal, or not in English. There were ultimately 31 eligible studies that included in this article. The data extraction was performed by classifying the articles to answer the research questions. Research design and method should be clearly defined.

Result and Discussion

Inclusion Studies on Antidiabetics Mechanism of Orchids Extract

There are several types of orchids that have been found to demonstrate antidiabetic abilities. The antidiabetic ability shown by these orchids are through various mechanisms (Table 1 Antidiabetes properties of some orchids and heir mechanisms). The antidiabetic activity of orchids were found using different extraction methods, plant parts and research methods (in vitro and in vivo).

Table 1 shows various antidiabetic activities possessed by the compounds found from the extraction of various plant parts from orchids. Almost all parts of the plant can be used and have antidiabetic activity. The parts of the orchid plants used in these studies included flower parts, leaves, stems, roots, and even some studies used all parts of the plant. The active compounds were obtained using various solvents, namely chloroform, ethanol, methanol, hexane, ethyl acetate and water. This shows that the active compounds produced in these studies have different polarities, from polar to non-polar. Solvent polarity affected phytochemical substances obtained from the isolation and purification steps of plant material. Phytochemicals are extracted in solvents of different polarity as no single solvent (Nawaz et al., 2020). There are several antidiabetic mechanisms carried out by active compounds extracted from orchids, which are as follows:

Antioxidant Activity

The extract of some orchids, Dendrobium huoshanense, D. officinale, D. nobile, D.chrysotoxum, P. karwinskii, Prosthechea michuacana (Lex.) W.E. Higgins, Dendrobium crepidatum, Dendrobium aquum Lindl, Dactylorhiza romana subsp. Georgica, Dendrobium officinale, Anacamptis pyramidalis (L.) Rich, Bauhinia variegata, Gastrodia elata Blume, Maxillaria tenuifolia, Eulophia ochreata L, Gymnadenia orchidis Lindl and Grammatophyllum speciosum Blume have an activity as antioxidant. The antidiabetic activities were done by controlling and scavenging free radicals to offer cell protection against oxidative stress (Gutierrez, 2013; Hunyadi, 2019) as well as acting as antioxidant via their hydrogen-donating ability (Paudel et al., 2019). They are capable of donating hydrogen to a free radical in order to remove odd electron, which is responsible for the radical’s reactivity (Mukherjee et al., 2012; Nimse & Pal, 2015). Many of compounds have antioxidant properties which act through either enzymatic or non-enzymatic pathways (Safari et al., 2018). Table 1 shows several species of orchids containing flavonoids. Flavonoids as antidiabetic compounds act as antioxidants because they have three benzene rings and one hydroxyl group (Ahmed et al., 2020; Yeh et al., 2017). The antioxidant activity of phenolic compounds varies, their biological activity depends on the structure of these compounds, their combination with other compounds, their solubility, absorption and metabolism (Francenia Santos-Sánchez et al., 2019; Ji et al., 2020).
Table 1. Antidiabetes Properties of Some Orchids and Heir Mechanisms

<table>
<thead>
<tr>
<th>Orchid</th>
<th>Part of the plant</th>
<th>Model description</th>
<th>Major finding</th>
<th>Control</th>
<th>Isolated Bioactive compound</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td><em>Dendrobium huoshanense</em> (DHP), D. officinale (DOP), D. nobile (DNP) and D. chrysotoxum (DCP)</td>
<td>freeze-dried stems</td>
<td>alloxan induced diabetic Male Kunming mice</td>
<td>hypoglycemic and antioxidative activities between four <em>Dendrobium</em> polysaccharides</td>
<td>metformin</td>
<td>polysaccharides</td>
<td>(Pan et al., 2014)</td>
</tr>
<tr>
<td><em>Prosthechea karwinskii</em> (Mart.) J.M.H. Shaw</td>
<td>leaves extract (100, 200, and 300 mg/kg p.o.)</td>
<td>Metabolic syndrome was induced in Wistar rats through administration of a 40% sucrose diet for 20 weeks</td>
<td>decreasing weight gain, abdominal and pericardial fat deposits, insulin resistance, triglycerides, TNF-α, HS-CRP, and adiponectin</td>
<td>metformin (200 mg/kg p.o.)</td>
<td>quinic acid, neochlorogenic acid, chlorogenic acid, rutin, kaempferol-3-0-β-rutinoside, and embelin</td>
<td>(Barragán-Zarate et al., 2021)</td>
</tr>
<tr>
<td><em>Prosthechea michuacana</em> (Lex.) W.E. Higgins (PM)</td>
<td>bulbs hexane extract</td>
<td>streptozotocin (STZ) and nicotinamide-induced type 2 diabetic male CD1 mice</td>
<td>anti-diabetic effect by stimulating insulin-dependent and by protecting pancreatic β-cells from oxidative stress and also an anti-obese, anti-insulin resistance and antihyperglycemic pro-drug.</td>
<td>glibenclamide</td>
<td>triterpenes (tetracyclic triterpenoids: 24-methyl, 24-hydroxy-5α-lanosta-9(11), 25-dien-3α-acetate and 24-methyl-24-hydroxy-5-lanosta-9 (11)-en-3α-acetate)</td>
<td>(Gutierrez, 2013)</td>
</tr>
<tr>
<td><em>Dendrobium crepidatum</em></td>
<td>Ethanol and acetone stem’s extracts</td>
<td>DPPH (2,2-diphenyl-1-picrylhydrazyl), in vitro</td>
<td>inhibiting DPPH free radicals</td>
<td>ascorbic acid</td>
<td>tetracosane, triacantone, stigmasterol, and some phenol derivatives (2-methoxy-4-vinylphenol, 2-methoxy-5-(1-propenyl)-phenol, p-meslyoxyphenol, and 2,6-dimethoxy-4-(2-propenyl)-phenol)</td>
<td>(Paudel et al., 2019)</td>
</tr>
<tr>
<td><em>Malaxis rheedei</em> SW</td>
<td>whole plant methanol extract</td>
<td>α-amylase and α-glucosidase activities with</td>
<td>inhibiting the enzymes like salivary, amylase and glucosidase and shows potential</td>
<td>flavonoid, tannin, glycoside, resin, steroids,</td>
<td></td>
<td>(Haridas et al., 2017)</td>
</tr>
<tr>
<td>Orchid</td>
<td>Part of the plant</td>
<td>Model description</td>
<td>Major finding</td>
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<td>Isolated Bioactive compound</td>
<td>Reference</td>
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<tr>
<td>Orchis anatolica</td>
<td>roots, ethanol</td>
<td>Alcohol extract</td>
<td>reducing glucose level, reducing cholesterol and triglycerides levels</td>
<td>metformin</td>
<td>flavonoid</td>
<td>(Khouri &amp; Daradka, 2013)</td>
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<tr>
<td>Dactylorhiza hatagirea (D. hatagirea)</td>
<td>root, whole plant</td>
<td>Alloxan monohydrate induced wistar albino rats.</td>
<td>reducing blood glucose, lipid parameters and significantly increasing body weight.</td>
<td>glibenclamide</td>
<td>flavonoids (quercetin), carboxylate and saponins</td>
<td>(Choukarya et al., 2019)</td>
</tr>
<tr>
<td>Dendrobium gibsonii</td>
<td>whole-plant</td>
<td>α-glucosidase inhibition assay</td>
<td>α-glucosidase inhibitory activity as a noncompetitive inhibitor of α-glucosidase</td>
<td>acarbose, dihydrodengibisin, dengrogbisol, ephemeronanthol A, dengibisin, nobilone, aloifol I, lusianthridin, denchrysan A, and 4-methoxy-9H-fluorene-2,5,9-triol</td>
<td>flavonoids, triallate, theobromate, and tannins</td>
<td>(Thant et al., 2020)</td>
</tr>
<tr>
<td>Dendrobium formosum</td>
<td>whole plant</td>
<td>L6 myoblasts</td>
<td>Compounds 1 and 12 showed higher α-glucosidase inhibitory activity. Lusianthridin (6) and orlistat</td>
<td>acarbose and confusarin (1), hircinol (2), erianthridin (3), (Inthongkaw et al., 2017)</td>
<td></td>
<td>(Inthongkaw et al., 2017)</td>
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</tbody>
</table>

### Key Findings

- **Dendrobium aqueum Lindl**
  - Aqueous extracts of pseudobulbs.
  - Antioxidant activity using DPPH, the protein glycation inhibitory using albumin/fructose glycation model.
  - DPPH free-radical scavenging potential and antiglycation potential.
  - Gallic acid, protocatechuic acid, catechin, p-hydroxybenzoic acid, chlorogenic acid, caffeic acid, epicatechin, syringic acid, vanillin, p-coumaric acid, o-coumaric acid, ferulic acid, sinapic acid, benzoic acid, routine, rosmarinic acid, cinnamic acid, quercetin, kaempferol and luteolin.

- **Dactylorhiza romana subsp. Georgica**
  - Tuber extracts.
  - Phosphomolybdic test method, DPPH scavenging activity, α-amylase and α-glucosidase activity.
  - Antioxidant and antimicrobial agent, or enzyme inhibitor.

- **Prosthechea karwinskii**
  - Pseudobulbs, leaves and flowers.
  - 40% sucrose induced MS male Wistar rats.
  - Reducing glucose level, reducing cholesterol and triglycerides levels.

- **Dendrobium officinale**
  - Stem.
  - Type 2 diabetic rats.
  - Ameliorate the symptoms of oxidative stress, inflammation, and hepatic lipid accumulation of liver.

- **Dactylorhiza hatagarea (D. hatagarea)**
  - Hydroalcoholic extract of roots.
  - Alloxan monohydrate induced wistar albino rats.
  - Reducing blood glucose, lipid parameters and significantly increasing body weight.

- **Orchis anatolica**
  - Roots ethanol extraction.
  - Alloxan induced diabetic rat.
  - Antihyperglycemic effect, correct some biochemical markers induced by diabetes.
<table>
<thead>
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<tbody>
<tr>
<td><em>Roxb. ex Lindl</em></td>
<td></td>
<td></td>
<td>moscatilin (11) had higher activity than insulin.</td>
<td>gigantol (4), nudol (5), lusianthridin (6), coelonin (7),</td>
<td>dihydroconiferyl dihydro-p-coumarate (8), batatasin III (9), 2,5,7-trihydroxy-4-methoxy-9,10-dihydrophenanthrene (10), moscatilin (11), and 5-methoxy-7-hydroxy-9,10-dihydro-1,4-phenanthrenequinone (12)</td>
<td>(Mahomodally et al., 2020)</td>
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<tr>
<td><em>Anacamptis pyramidalis</em></td>
<td></td>
<td>The antioxidant potential was evaluated by DPPH, ABTS, CUPRAC and FRAP assays.</td>
<td>Enzymes inhibition activity against ACh, BChE, tyrosinase, α-glucosidase, and α-amylase</td>
<td>Disaccharide, Citric acid, Parishin G, Roseoside, Gastrodin derivative, Parishin B, Parishin C, Dihydroxybenzoic acid derivative, Caffeic acid derivative, Acacetin derivative, Oxodihydroxyoctadecenoic acid, Trihydroxyoctadecenoic acid</td>
<td></td>
<td>(Mahomodally et al., 2020)</td>
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<tr>
<td><em>Prosthechea michuacana</em></td>
<td>bulbs</td>
<td>Hyperglycemic and antihyperlipemic activity, improving the hyperinsulinemia and produces a significant change on AGEs formation in vitro with aminoguanidine, antihyperglycemia in vivo with glibenclamide and tolbutamide</td>
<td>Predominantly AGEs</td>
<td></td>
<td></td>
<td>(Gutierrez &amp; Hoyo-Vadillo, 2011)</td>
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<td><em>(Lex.) WE Higgins</em></td>
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<tr>
<td><em>Bauhinia variegata</em></td>
<td>Young B. variegata L. (var. Candida) leaves</td>
<td>STZ induced diabetic rats</td>
<td>anti-diabetic effect through restoring the normal architecture of pancreatic β-cells in addition to the antioxidant and hypolipidemic effect</td>
<td>Polyphenol</td>
<td></td>
<td>(Abdel-Halim et al., 2020)</td>
</tr>
<tr>
<td><em>Gastrodia elata</em> Blume (GE)</td>
<td>GE, fermented by Saccharomyces cerevisiae</td>
<td>High Glucose induced human umbilical vein endothelial cells (HUVECs)</td>
<td>protect against the oxidative stress, and inflammatory conditions in endothelial cells, caused by HG</td>
<td>Phenolic compounds (gastrodin, p-hydroxybenzyl alcohol (HBA), p-</td>
<td></td>
<td>(Kwon et al., 2012)</td>
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<td><em>Maxillaria teuifolia</em></td>
<td>EtOAc extract of the flower</td>
<td>Anti-oxidant activity were determined in ferric thiocyanate method. α-glucosidase inhibitory activity compared with synthetic inhibitor</td>
<td>suppressing carbohydrate disintegration and could prevent damage to organisms by oxidative stress</td>
<td>acarbose</td>
<td>3,4-dihydroxybenzoic acid methyl ester (1), flavanthrinid (2), vanillic acid (3) and mangiferin (4)</td>
<td>(C. Li, 2021)</td>
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<tr>
<td><em>Diaphananth e bidens (D. bidens)</em> (AFZEL. EX SW) SCHRTR</td>
<td>methanol leaf extract</td>
<td>STZ induced hyperglycemic rats</td>
<td>reducing blood glucose tolbutamide</td>
<td>saponins, steroids, tannins and terpenoids</td>
<td>polysaccharides of <em>B. striata</em></td>
<td>(Ottah et al., 2012)</td>
</tr>
<tr>
<td><em>Bletilla striata</em></td>
<td>polysaccharides of B. striata</td>
<td>high fat diet (HFD)-fed mice</td>
<td>reducing obesity and metabolic disorders in HFD-fed mice</td>
<td>polysaccharides of B. striata</td>
<td>polysaccharides</td>
<td>(Hu et al., 2020)</td>
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<tr>
<td><em>Dendrobium ofcinale</em></td>
<td>leaves hot water extraction, alcohol sedimentation and chromatographic separation</td>
<td>inflammatory cell model by LPS acting THP-1 cells</td>
<td>protecting THP-1 cells from LPS-stimulated cytotoxicity, inhibiting reactive oxygen species formation, suppressed toll-like receptor-4 (TLR-4), myeloid differentiation factor (MyD88) and tumour necrosis factor receptor-associated factor-6 (TRAF-6) mRNA and protein expression</td>
<td>polysaccharides</td>
<td>polysaccharides</td>
<td>(Zhang et al., 2018)</td>
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<tr>
<td><em>Dendrobium candidum</em></td>
<td>dry dendrobium</td>
<td>human corneal epithelial cells (HCEC)</td>
<td>improving the proliferative activity of HCEC cells under the high glucose environment and reduce the apoptosis of cells by regulating the expression of bax and bcl-2. Protecting and repairing corneal epithelial cells damage in high glucose.</td>
<td>polysaccharide</td>
<td>polysaccharide</td>
<td>(Q. Li et al., 2017)</td>
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<td><em>Aerides multiflora</em></td>
<td>dried powder from the whole plants macerated with MeOH</td>
<td>The liberation of p-nitrophenol from the substrate p-nitrophenol-α-D-glucopyranoside (PNPG).</td>
<td>compound revealed a non-competitive inhibition and suggested as a candidate structure for α-glucosidase inhibitor</td>
<td>Aerimultin, Dihydroisnapyl dihydroferulate, 6-Methoxy coelonin, Gigantol, Imbricatin, Agrostonin, Dihydroconiferyl dihydro-p-coumarate, 5-Methoxy-9,10-dihydrophenanthrene-2,3,7-triol, Acarbose</td>
<td>(Thant et al., 2021)</td>
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<td>Eulophia ochreata L</td>
<td>Tubers extracted</td>
<td>antioxidant activity using DPPH radical scavenging activity, total antioxidant</td>
<td>antioxidant activity and favorable α amylase inhibitory activity</td>
<td>ascorbic acid</td>
<td>Phenolic and flavonoids compounds</td>
<td>(Jagtap et al., 2012)</td>
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<td></td>
<td>with methanol and distilled water</td>
<td>capacity using phosphomolybd enum method, amylase inhibition assay using the chromogenic DNSA method, antiglycation activity using BSA-fructose assay, Nitroblue tetrazolium assay was used to determine the fructosamine antioxidant activity.</td>
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<tr>
<td>Gymnadenia orchidis Lindl</td>
<td>fibrous root</td>
<td>STZ induced adult female albino mice of BALB C</td>
<td>inhibiting glycation of the hemoglobin, normalizing the lipid profile of diabetic animals, improving antioxidant status and reducing lipid peroxidation, recovering DNA stand breakage</td>
<td>Terpenoids</td>
<td></td>
<td>(Arzoo et al., 2018)</td>
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<tr>
<td>Grammatophyllum speciosum Blume</td>
<td>ethanol extracts prepared from leaf, rhizome+root and pseudobulbs</td>
<td>antioxidant activity using DPPH assay, α-glucosidase inhibition assay was undertaken according to a modified Lebowitz (1998).</td>
<td>DPPH free radical scavenging activity and α-Glucosidase inhibitory activity</td>
<td>Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) and Acarbose</td>
<td></td>
<td>(Rungruchkanont &amp; Chatsuwan, 2019)</td>
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<tr>
<td>Dendrobium christyanum Rchb.f</td>
<td>A methanolic extract from the dried root</td>
<td>in vitro α-glucosidase inhibitory and glucose uptake stimulatory activities</td>
<td>Compounds 4 and 6 appear to be potential hypoglycemic agents since they possess both α-glucosidase inhibitory and glucose uptake stimulatory activities.</td>
<td>Acarbose</td>
<td>Methyl haematommate (1), methyl 2,4-dihydroxy-3,6-dimethylenzoate (3), ndocosyl 4-hydroxy-trans-cinnamate (4), vanillin (5), coniferyl aldehyde (6), 4,5-dihydroxy-2-methoxy-9,10-dihydrophenanthrene (7), gigantol (10), and doricinolic acid (13).</td>
<td>(San et al., 2020)</td>
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<tr>
<td>Dactylorhiza hatagirea</td>
<td>methanolic leaf extract</td>
<td>α-amylase and α-glucosidase inhibition</td>
<td>inhibiting α-Amylase and α-Glucosidase enzymes, elevating relative expression</td>
<td>Acarbose</td>
<td>Metformin</td>
<td>(Alsawalah et al., 2019)</td>
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</table>
**Antiglycation Potential**

Four orchids of this study, *Gymnadenia orchidis* Lindl, *Eulophia ochreata* L, *Dendrobium aquaticum* Lindl, and *Prosthechea michuacana* (Lex.) WE Higgins have antiglycation activity. Protein glycation is a biomarker for diagnosis of diabetes. Glucose is a directed glycating agent of amino group in proteins, which modifies N-terminal and side chain amino groups. Afterwards, at later stage, AGEs, are formed by the degradation of fructosamines and by the reaction of reactive dicarbonyl metabolites, such as methylglyoxal (MGO) (Rabbani & Thornalley, 2021). Inhibition of MGO formation is known as one of the antiglycation mechanisms to inhibit AGE formation. In addition to inhibiting its formation, the antiglycation mechanism can also be carried out by acting as a scavenger for this molecule (Jung et al., 2019). Protein glycation and oxidative stress caused by chronic hyperglycemia are the major factors in diabetic complication. Some substances prevent the formation of AGEs by acting as an antioxidant, inhibiting sugar autoxidation, binding to amino groups, early degradation of Maillard Reaction Products (MRP), and by reducing sugars, so that these sugars cannot bind to the amino groups of a protein (Yulianti et al., 2021).

Another mechanism of action of antiglycation compounds is by binding to their receptors, this can cause cellular mechanisms due to the interaction of AGEs with their receptors to be inhibited (Sindhuja et al., 2021). Orchids also contain polyphenols, such as *Bauhinia variegate* (Abdel-Halim et al., 2020). Polyphenols are one of the antiglycation compounds that increase the work of peroxisome proliferator-activated receptors (PPAR), which controls carbohydrate and lipid metabolism, and has been shown to reduce RAGE expression (Di Sotto et al., 2019).

**Stimulating Insulin, Anti-insulin Resistance and Elevating GLUT4 Receptor**

Insulin is a peptide hormone that binds plasma membrane-bound receptors in target cells. This hormone promotes glucose utilization and storage by increasing glucose transport and glycogen synthesis in skeletal muscle, activating glycogen synthesis, increasing lipogenesis and decreasing gluconeogenic gene expression in liver, as well as suppressing lipolysis and increasing glucose transport and lipogenesis in white adipocyte tissue (Petersen & Shulman, 2018). There are some orchids from this study that improve the
insulin signaling namely Dactylorhiza hatagirea, Prosthechea michuacana (Lex.) W.E. Higgins and Prosthechea karwinskii. Targets of these compounds that affect insulin signaling include insulin receptor substrate, phosphatidylinositol 3-kinase, glucose transporter, activated protein kinase (AMPK), glycogen synthase kinase 3, MAPKs, JNK, NF-kB, protein tyrosine phosphatase 1B, nuclear factor-E2-related factor 2, and peroxisome proliferator-activated receptors (J. Li et al., 2019). Maintenance and enhancement of β-cell function has the potential to improve diabetes. Specific growth factors, cell cycle mediators, and nuclear factors have been proposed to regulate β-cell homeostasis (Chang et al., 2013).

Anti-Adipogenic Properties

Lipid metabolism, such as increased lipogenesis and decreased lipolysis in adipose tissue occurs largely as a response of glucose homeostasis to insulin stimulation (M. Li et al., 2022). Orchids Prosthechea karwinskii, Prosthechea michuacana (Lex.) W.E. Higgins, Dendrobium officinale, Dactylorhiza hatagirea, Prosthechea michuacana (Lex.) WE Higgins, Bauhinia variegate, Bletilla striata, Gymnadenia orchis Lindl, Calanthe fimbriata Franch, Dendrobium delacourii have the properties to improve lipid metabolism in diabetes. Polyphenols, besides functioning as antioxidants also have antidiapogenic abilities. Reduction of adipose tissue is carried out through the mechanism of inhibiting cell proliferation, increasing cell apoptosis, inhibiting differentiation from pre-adipose to adipose, inhibiting cellular lipid accumulation and increasing lipolysis (Nam et al., 2019).

Inhibiting α-Amylase

α-Amylase catalyzes the hydrolysis of starch which will produce glucose as the final product. The catalytic activity of this enzyme can be controlled to reduce glucose production at the postprandial stage, which could be of therapeutic benefit to diabetics (Khadayat et al., 2020). Some α-Amylase inhibitor show their mechanisms by interacting with the key active site residues through an array of hydrophobic interactions and hydrogen bonds (Ogunyemi et al., 2022). Malaxis rheedei SW, Anacamptis pyramidalis (L.) Rich, Eulophia ochreata L, Dactylorhiza hatagirea are some orchids with antidiabetic property as an α-Amylase inhibitor. Based on table 1, the orchid Dactylorhiza romana subsp. Georgica (Kotiloğlu et al., 2020) and Dactylorhiza hatagirea (Choukarya et al., 2019) contain quercetin compounds. Quercetin is a compound that has been shown to act as an inhibitor for α amylase. The inhibition mechanism carried out by this compound is by forming molecular interactions with the enzyme binding sites (Oso & Olaoye, 2020).

Inhibiting α-Glucosidase

Glucosidases are required for starch digestion. Hence, α-glucosidase inhibitor is one of the methods for treating diabetes by suppressing the digestion of carbohydrates, thus slowing down the process of glucose assimilation which will lead to a significant reduction of plasma glucose and postprandial insulin levels (Choudhury et al., 2018). Some orchids in this study which have this property are Malaxis rheedei SW, Dendrobium gibsonii, Dendrobium formosum Roxb. ex Lindl, Anacamptis pyramidalis (L.) Rich, Maxillaria tenusifolia, Aerides multiflora, Grammatophyllum spectiosum Blume, Dendrobium christyanum Rchf, Dactylorhiza hatagirea, Dendrobium delacourii. Previous study has showed competitive mode of inhibition mechanism of α-Glucosidase inhibitor from some plant substances (Lianza et al., 2022).

Antiinflammation

Metabolic inflammation is involved in diabetes and its complications (such as diabetic nephropathy, retinopathy and neuropathy). Systemic inflammation occurs as a result of an increase in proinflammatory cytokines (IL-6, IL-1β, TNF-α), which are elicited by chemokines. Increased recruitment of inflammatory cells in metabolic networks, and activation of inflammatory responses occur due to NF-kB activation and signaling of AMPK and PPAR-γ (Kong et al., 2021). Prosthechea karwinskii, Dendrobium officinale, Gastrodia elata Blume have the antiinflammation activity. Bioactive compounds from plants that can regulate AKT, mTOR, adenosine monophosphate, AMPK, AGEs, growth factors, proinflammatory cytokines (IL-1β and TNF-α), oxygen species, and various other signaling mechanisms related to diabetes can be projected as an effective therapy (Kaabi, 2022).

Conclusion

In conclusion, orchid has been widely used in traditional medicine. All parts of these plants can be extracted and contain some active substances. Several studies have reported some antiadiabetic mechanisms of several species of orchids. These anti-diabetic mechanisms include being antioxidants, anti-glycation and anti-inflammation, increasing insulin action, influencing lipid metabolism, and inhibiting α-amylase and α-glucosidase.

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EY, ISM and LS constructed the idea for this manuscript and planned the methods. EY, ISM and LS had responsibility in extracting the data from the journals, data management and reporting. EY and TCH analyzed and interpreted the extracting datas. EY had responsibility in the construction of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest
There is no conflict of interest.

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