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Review Article

South Korean medicinal plants and their isolated phytocompounds for the management of diabetes mellitus

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Abstract

Objective: Diabetes mellitus is one of the leading causes of death worldwide. Given the numerous limitations of modern treatments, new effective therapeutic approaches are of great interest. This review provides up-to-date information on preclinical and clinical studies on antidiabetic plants in South Korea.

Materials and Methods: Data were obtained from reliable databases such as PubMed, Scopus, SciFinder and Google Scholar. The structures of antidiabetic compounds isolated from plants used as antidiabetics in South Korea were drawn using Chemical Sketch Tool-RCSB-PDB.

Results: We compiled 134 studies (116 preclinical and 18 clinical) on antidiabetic plants in South Korea. Plants like *Panax ginseng*, *Aloe vera*, *Momordica charantia*, *Viscum album* and *Zingiber mioga* were mostly used, while protopanaxadiol, protopanaxatriol, phellopterin, imperatorin, bergapten and curcumin were among the most potent secondary metabolites discussed. Leaves were the most frequently utilized part of the plants, representing 24.28%, followed by roots (22.86%), whole plants (10%), fruits (8.57%), seeds (5.72%), stems (5.72%), aerial parts (2.85%), branches (2.85%), and other parts like flowers, rhizomes, husks, arrowroot and pericarpium, accounting for 1.43% each. Maceration was the most common extraction method (85%), while oral administration was the main route. This route is usually safe, easy and economical, and promotes a rapid physiological response, thus enhancing the efficacy of the formulation.

Conclusion: The antidiabetic properties of many plants have been experimentally proven, but few clinical trials have been conducted on these plants, despite their folk use in the treatment of diabetes in South Korea. Further efficacy studies in humans are of great interest.

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Introduction

Diabetes mellitus (DM) is a chronic disease linked to a disorder of assimilation, utilization, and storage of sugars from food, and characterized by chronic hyperglycemia (Smith et al. 2022). It is a serious public health problem because it affects people everywhere regardless of age group, country, or sex. Studies have shown that the prevalence of DM worldwide has more than quadrupled since 1990. In fact, by 2024, more than 800 million people worldwide were living with DM, with type 2 diabetes accounting for approximately 90% of cases (Zhou et al. 2024). South Korea is among the countries where DM is a public health concern, with a prevalence of 12.5% among people aged 19-29 years and 14.8% among those aged 30 years and above, estimated at approximately 5.4 million people in 2022 (Ha et al. 2024). Genetic predisposition and lifestyle contribute significantly to the development of DM. The progression of DM is characterized by the inability of body cells to efficiently metabolize sugar, which is attributed to inadequate insulin action on target tissues, resulting either from insulin insensitivity or deficiency in its production. The failure of insulin to process sugar arises when the pancreas fails to generate a sufficient amount of insulin or when the body is unable to effectively utilize the insulin it produces (Marshall 2020). The body is prompted to decompose its own fats, proteins, and glycogen in order to generate sugar, resulting in elevated blood sugar levels and the production of surplus by-products known as ketones by the liver. Untreated DM results in chronic damage and eventual failure of multiple organs, which can lead to disability and an increased risk of early mortality. The extent of damage caused by hyperglycemia to various organ systems may be associated with the duration of the disease and the effectiveness of its management (Cloete 2022).

The optimal control of blood glucose level in diabetic patients is the primary goal of diabetes treatment. Although synthetic oral antidiabetic agents, combined with insulin, serve as the primary means of managing diabetes, they do not completely reverse the progression of its complications, and may even worsen the condition due to their significant side effects. Nowadays, significant advancements have been achieved in the management of DM through the use of oral antidiabetic medications, but the outcomes remain imperfect. Various limitations such as drug resistance, adverse reactions, and potential toxicity have been identified. Thus, new effective and safe plant-based agents are of great interest. Many experimental studies have been conducted on antidiabetic plants in South Korea. For instance, our research group reported the antidiabetic potentials of some plants such as *Hibiscus cannabinus* (Mariadoss et al. 2021) and *Cirsium setidens* (Shin et al. 2022) used in the management of DM in Korean traditional medicine. To our knowledge, there is no previous review that describes in depth the activities of South Korean antidiabetic plants, despite their use in Korean traditional medicine. Thus, the present study was conducted to provide updated information on preclinical and clinical studies of South Korean medicinal plants and their isolated phytocompounds for the management of DM. Based on the data collected in previous studies, the mechanism of action of selected antidiabetic plants and phytocomponents is also discussed. This study is innovative, as there is no similar report in the literature. This work connects ethnomedicinal uses and experimental and clinical investigations on South Korean antidiabetic plants, which is useful for the development of high-quality plant-based antidiabetic agents.

Materials and Methods

Experimental and clinical data on South Korean antidiabetic plants and their isolated phytocompounds were obtained from various online databases such as Web of Science, Google Scholar, SciFinder, Science Direct, Springer Link, Taylor & Francis, PubMed, and Scopus. Furthermore, the books, book chapters, and proceedings served as supplementary sources. To collect information on experimental studies on South Korean medicinal plants utilized for diabetes treatment, the following search terms were used: "plant extracts and diabetes in Korea", "traditional treatment of diabetes in Korea" and "hypoglycemic plants in South Korea". Information on phytocompounds isolated from South Korean plants with antidiabetic properties was obtained using the following search terms: "GC-MS or LC-MS analysis of Korean antidiabetic plants", "chemical profile of Korean antidiabetic plants", "phytochemical screening of Korean antidiabetic plants", "antidiabetic molecules from Korean plant extracts", "silica chromatography of Korean antidiabetic plants, and "nuclear magnetic resonance and mass spectroscopy of Korean antidiabetic plants". Information related to clinical data on South Korean plants was obtained using the search terms: "clinical studies on South Korean medicinal plants", "safety of antidiabetic plants in Korea", "phytotherapy in diabetic subjects in Korea", "antidiabetic capsules in Korea", "complementary antidiabetic drugs in Korea", and "diabetes and randomized controlled trials in Korea". We searched for all studies published from 2010 to 2024. The structures of antidiabetic compounds isolated from Korean antidiabetic herbs were drawn using Chemical Sketch Tool-RCSB PDB using the SMILES of each molecule obtained from the PubChem database.

Results

General data, publication trends, and extraction procedures of plants with antidiabetic potential in South Korea

We gathered all the antidiabetic plants and isolated phytocomponents with antidiabetic potential in South Korea. This literature review allowed us to compile 134 studies conducted on antidiabetic plants across different regions of South Korea. Of the 134 studies, 116 were experimental, while 18 studies were clinical. Also, 91 experimental studies were conducted on the evaluation of the antidiabetic activity of a single plant extract using *in vitro*, *in vivo*, and *in silico* approaches. Ten experimental studies were focused on the development of polyherbal formulations with antidiabetic potentials using selected South Korean herbs, while 15 studies were conducted on specific antidiabetic compounds isolated from South Korean plants. Sixteen clinical studies were conducted on the antidiabetic properties of capsules or tablets based on South Korean antidiabetic plant extract, while 2 studies were carried out on polyherbal antidiabetic formations. Overall, 68 antidiabetic plants of South Korean origin were identified. Twelve polyherbal antidiabetic formulations and 39 antidiabetic phytocompounds from South Korean plants were pooled (Figure 1).

The publication trend of experimental and clinical studies on South Korean medicinal plants with antidiabetic potentials is summarized in Figure 2A and B.

In South Korea, although medicinal plants have been used in the treatment of diabetes for centuries, scientific publications are more recent. Based on our findings, leaves are the most frequently utilized part of the plants, representing 24.28%, followed by roots (22.86%), whole plants (10%), fruits (8.57%), seeds (5.72%), stems (5.72%), aerial parts (parts of a plant that are above ground) (2.85%), branches (2.85%), and other parts such as flowers, rhizomes, outer skins, husks, arrowroot, inner barks, and pericarpium, accounting for 1.43% each (Figure 2C).

As shown in Figure 2D, maceration is the most common extraction method, accounting for 85%, followed by decoction (11.25%), powder (2.5%), and infusion (1.25%). Regarding the type of solvent used in the preparation, aqueous extract is the most frequent, representing 36.84%, followed by ethanol (35.53%), methanol (7.89%) or water/ethanol (7.89%), water/acetone (1.33%), and hexane (1.32%), having an equal percentage with ethyl acetate (1.32%) (Figure 2E).

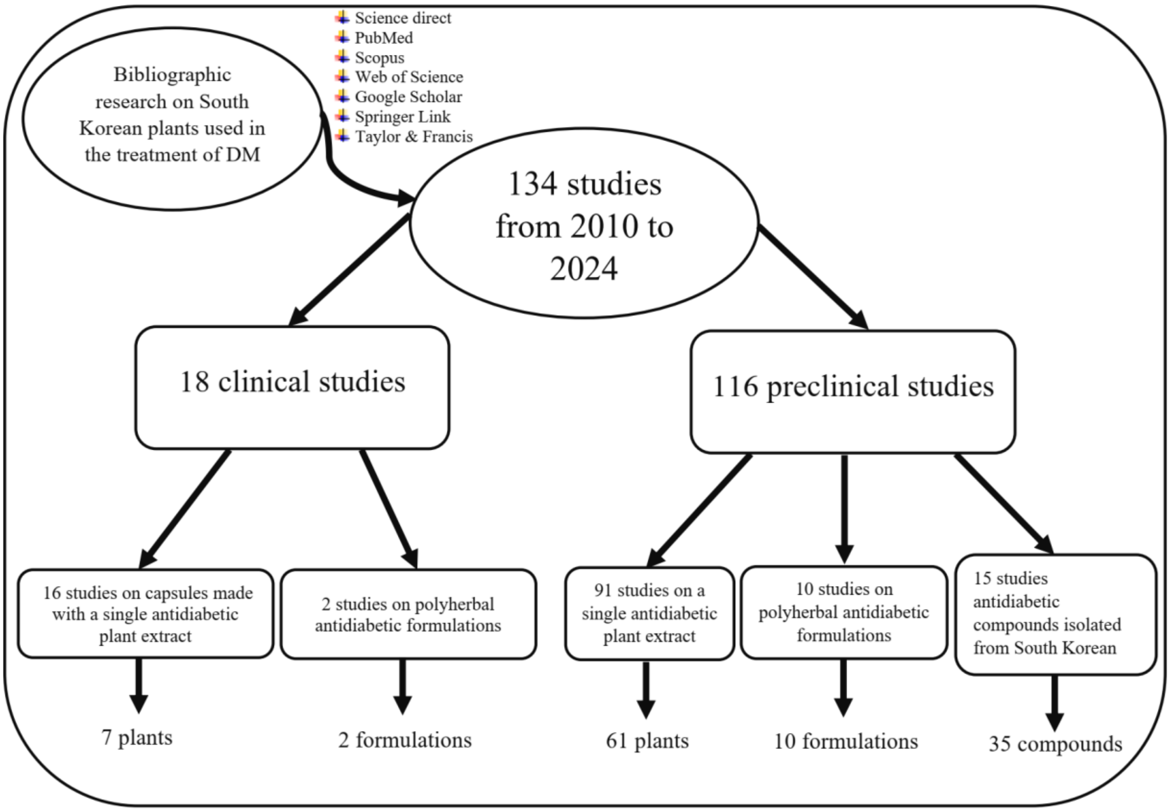

Figure 1. Summary of the bibliographic research of this study.

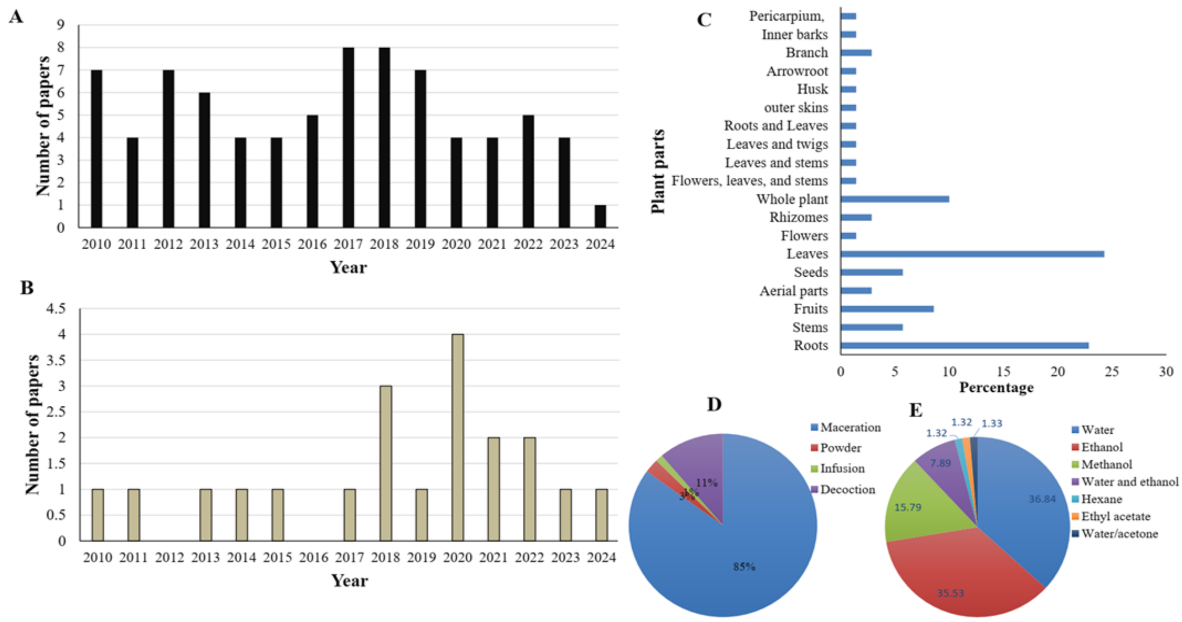

Figure 2. Publication trends, and preparation of extracts with antidiabetic potential in South Korea. A and B: Number of articles published each year on preclinical and clinical studies, respectively; C: Percentage of plant parts used; D: Mode of preparation; and E: Type of solvent used.

South Korean empirical formulas for the treatment of DM

South Korean traditional medicine is very rich and diverse. The use of plant extracts in the management of DM in South Korea dates back centuries, but experimental and clinical studies are more recent. Various Korean empirical formulas used in the treatment of DM in South Korea are summarized in Table S1. A total of 57 antidiabetic formulations are grouped.

Preclinical evidence of South Korean antidiabetic plants

Various plant extracts with antidiabetic properties in South Korea are summarized in Table 1. Some of them such as *Momordica charantia*, *Panax ginseng*, *Sasa borealis*, *Vigna nakashimae*, and *Vitis vinifera* have been also clinically studied.

Polyherbal antidiabetic formulation

Some experimental studies have described the antidiabetic properties of various South Korean polyherbal formulations (Table S2). For instance, a formulation composed of 7 plant extracts was found to regulate glycemia, insulinemia, cholesterol profile, and hemoglobin A1C (HbA1c) levels in mice, activate peroxisome proliferator-activated receptor γ (PPARγ)-dependent luciferase activity and adenosine monophosphate–activated protein kinase (AMPK) in C2C12 cells, and stimulate I kappa B kinase/nuclear factor kappa B (IKKb/NFκB) signaling and prevent endoplasmic reticulum (ER) stress in HepG2 cells (Yeo et al. 2011). In the study of Lee et al (2000), an improvement in the level of thiobarbituric acid reactive substances (TBARS) and carbonylated proteins, as well as the reduced and oxidized glutathione (GSH/GSSG) ratio, was observed in diabetic rats administered intraperitoneally with the aqueous extract of the mixture of *Phellodendron cortex* and *Aralia cortex*. In another study, Jung et al (2021) showed that the mixture of *Coptidis Rhizoma, Salviae Miltiorrhizae Radix,* and *Cinnamomi Cortex* significantly reduced the calorie intake in high fat diet (HFD) mice, and normalized glycemia, insulinemia, lipid profile, and liver markers in diabetic mice, indicating the possibility of being exploited in the management of obesity and diabetes. Similarly, a mixture of *Ligularia fischeri* leaves and *Momordica charantia* fruits promoted adipocyte differentiation in 3T3-L1 cells, improved glucose uptake and insulin metabolism in C2C12 cells, and exhibited an antidiabetic effect in mice (Baek et al. 2018). The antidiabetic studies of two novel herbal preparations revealed significant improvement in diabetes-related parameters in alloxan-induced diabetic rats (Kim et al. 2006) and streptozotocin (STZ)-induced diabetic mice (Kim et al. 2014). A mixed grain formulation composed of the ethanolic extracts of oat, sorghum, adzuki bean, finger millet, and proso millet improved the fasting blood glucose level and insulin immunoreactivities with an effect comparable to that of metformin, thus supporting the use of this formulation in Korean traditional medicine (Yang et al. 2023) (Table S2).

Some antidiabetic compounds isolated from South Korean medicinal plants

There are few studies on the antidiabetic potentials of compounds isolated from Korean antidiabetic plants (Table S3, Figure 3). For instance, the antidiabetic potential of phellopterin, imperatorin, and bergapten isolated from the aqueous/methanol fraction of *Angelica dahurica* was reported in diabetic mice (doses: 0.5, 1, and 2 mg/kg) and 3T3-L1 cells (doses: 12.5, 25, 50 and 100 mg/ml) (Han et al. 2018). It has been reported that the antidiabetic effect of *Panax ginseng* is attributed to its content of ginsenosides such as protopanaxadiol and protopanaxatriol. Indeed, Deng et al (2017) investigated the antidiabetic potentials of these ginseng-specific saponins in HFD/STZ-induced type 2 diabetes mellitus (T2DM) mice. It was found that protopanaxadiol and protopanaxatriol, administered at the doses of 50 and 150 mg/kg/day, significantly decreased fasting blood glucose (FBG) and improved insulin resistance, lipid profile, antioxidant markers, and proinflammatory cytokines after 10 weeks of oral treatment. The antidiabetic effect of protopanaxadiol was higher than that of protopanaxatriol. Curcumin, one of the main constituents of *Curcuma longa*, has been shown to exhibit a potent antidiabetic effect in diabetic mice, due to its ability to prevent insulin resistance (You et al. 2013; Kim et al. 2018b). On the other hand, erianin isolated from *Dendrobium chrysotoxum* prevents diabetes complications such as retinopathy and peripheral neuropathy (Yu et al. 2016), while fisetin extracted from *Cotinus coggygria* stimulates glucose consumption, regulates insulin metabolism, and inhibits gluconeogenesis (Kim et al. 2012a). Fustin, gallic acid, 3′,4′,7-trihydroxyflavone, and fisetin isolated from the ethanolic extract of *Rhus verniciflua* heartwoods showed better antioxidant activity than α-tocopherol (control), due to their electron donation ability (Kim et al. 2010). They also exhibited remarkable α-glucosidase inhibitory activity, comparable to that of acarbose (10-50 µg/ml), indicating their antidiabetic action. In a similar study, four cucurbitane triterpenoids called C1-C4 isolated from *Momordica charantia*, exhibited strong antidiabetic activities in STZ-induced diabetic mice and C2C12 cells (Han et al. 2018).

Clinical studies of South Korean medicinal plants

In this section, we describe clinical trials on the antidiabetic properties of *Diospyros kaki*, *Aloe vera*, *Momordica charantia*, *Sasa borealis*, *Vigna nakashimae*, *Vitis vinifera*, *Panax ginseng*, *Panax quinquefolius*, and a polyherbal formulation composed of Daeshiho-tang, Bojungikgi-tang, Jowiseunggi-tang, and Hoechunyanggyeok-san (Table S4).

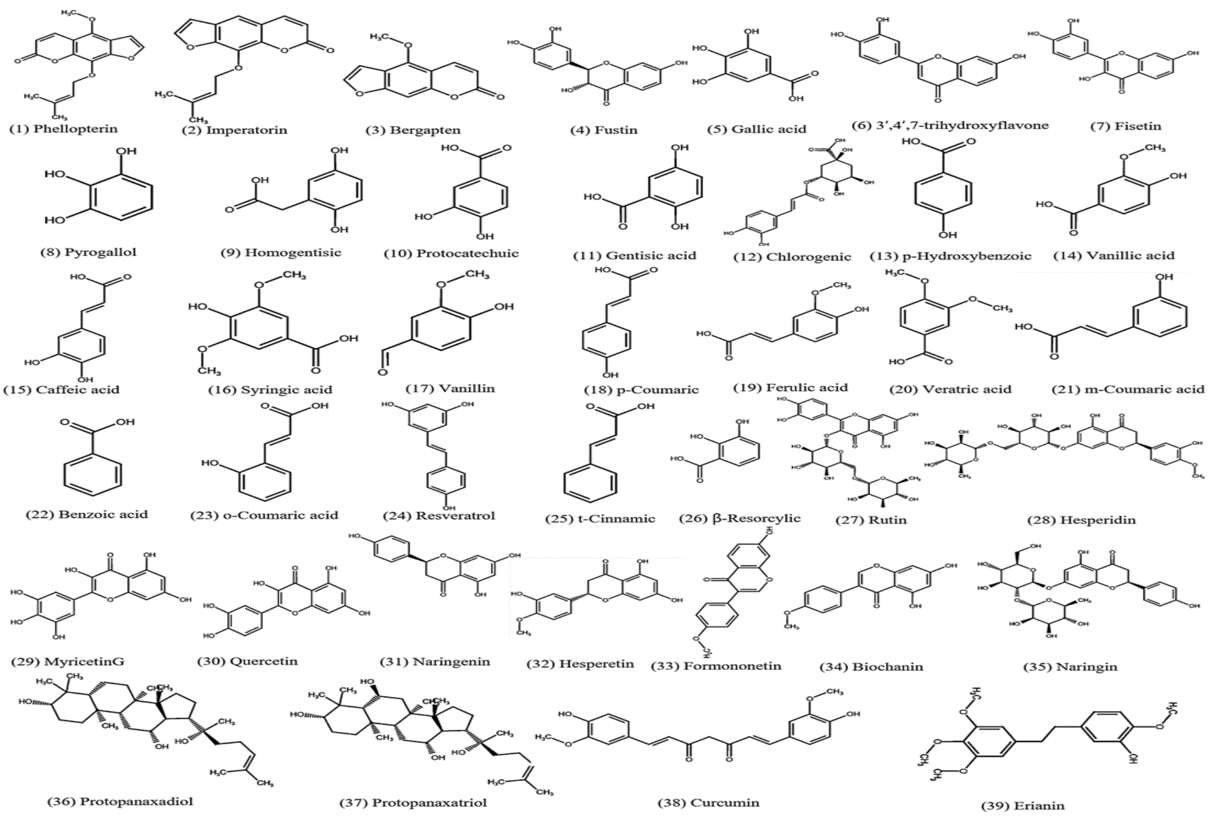

Figure 3. Chemical structures of selected antidiabetic compounds isolated from South Korean antidiabetic plants

Table 1. Preclinical evidence of South Korean antidiabetic plants.

Scientific Name	Plant part	Extract tested	Model(s)	Dose range	Administration	Duration (weeks)	Positive control	Pharmacological activity	Reference
Acanthopanax senticosus	Stem	Maceration (ethanol)	*In vivo* (Rats)	0.1% and 0.5% diet	*Oral*	14	-	Improvement of HbA1c, FBG, glucose level, antioxidant markers and proinflammatory cytokines.	Kwon et al. 2016
Allium cepa	Outer skins	-	*In vitro* and *in silico*	-	-	-	-	Glucosidase and protein tyrosine phosphatase inhibitory activities, and strong binding potential with PTP1B.	Vu et al. 2020
Allium sativum	Husk	Maceration (ethanol)	*In silico*	-	-	-	-	Anti-T2DM synergistic action through PPAR signaling pathway.	Oh et al. 2022
Angelica dahurica	Roots	Maceration (methanol)	*In vivo* (Mice) *In vitro* (CHO-K1 cells)	300 mg/kg/day	*Oral*	3	-	Normalizes glucose and insulin levels in mice and promotes GPR119 activation and cAMP levels in INS-1 cells, and GLP-1 level in GLUTag cells.	Park et al. 2016
Aralia elata	-	-	*In vivo* (Mice)	20 and 100 mg/kg/day	*Oral*	8	-	Prevents retinal injuries associated with diabetic retinopathy.	Kim et al. 2017
Aster koraiensis	Flowers, leaves, and stems	Maceration (ethanol)	*In vivo* (Rats)	50 and 100 mg/kg/day	*Oral*	16	-	Prevents blood-retinal barrier breakdown and the loss of occluding.	Kim et al. 2021
Aronia melanocarpa	Whole plant	Decoction (ethanol)	*In vivo* (Mice) *In vitro* (RINm5F cell)	10 and 100 mg/kg/day	*Oral*	1	-	Decreases the hyperglycemia in mice and protects the pancreas β cells.	Jeon et al. 2018
Aster koraiensis	Aerial parts	Maceration (ethanol)	*In vivo* (Rats)	100 and 200 mg/kg/day	*Oral*	13	-	Decreases proteinuria and albuminuria	Sohn et al. 2010
Auricularia cornea	Roots	Maceration (water)	*In vivo* (mice)	100 and 400 mg/kg/day	*Oral*	4	Metformin (100 mg/kg)	Decreases TC, TG, LDL-C, and FBG levels.	Fu et al. 2022
Camellia sinensis	Leaves	Maceration (water)	*In vivo* (Mice)	-	*Oral*	4	-	The extract has no effect on BW and glucose level, but its coadministration with polymer polyethylene glycol improves these parameters.	Park et al. 2013
Cirsium setidens	-	Maceration (methanol)	*In vivo* (Mice)	(35 mg/kg/day	*Oral*	3	Metformin	Increases glucose uptake.	Shin et al. 2022
Codonopsis lanceolata	-	Maceration (water)	*In vivo* (Rats)	0.3-3% diet	*Oral*	17	Rosiglitazone (20 mg/kg bw/day)	Enhances liver insulin sensitivity and insulin signaling.	Jeong et al. 2017
Daphniphyllum macropodum	Fruit	Maceration (ethanol)	*In vivo* (mice)	50 mg/kg/day	*Oral*	-	-	Decreases serum glucose, TC and TG levels.	Koo et al. 2014
Dendrobii Herba	-	Maceration (ethanol)	*In vivo* (Mice)	200 and 300 mg/kg/day	-	4	Metformin (200 mg/kg)	Elevates insulin secretion in RINm5F cells, and glucose intake in L6 cells.	Myung-ji and Yeoung-Ju 2019
Dendropanax morbifera	Leaves and stems	Maceration (water and ethanol)	*In vivo* (Mice)	100 and 200 mg/kg/day	*Oral*	2	-	Prevents BW loss and normalizes blood glucose and insulin levels.	An et al. 2014
Dendropanax morbifera	Leaves	Maceration (methanol)	*In vivo* (Mice)	50, 100 and 200 mg/kg/day	*Oral*	6	Metformin (200 mg/kg)	Stimulates AMP-activated protein kinase and prevents retinal damage.	Heo et al. 2018

Table 1 continued

Ecklonia cava	Whole plant	Maceration (methanol)	*In vivo* (Rats) *In vitro* (C2C1 cells)	300 mg/kg/day	-	3	-	Improves glycemia and insulinemia in rats. Activates AMP-activated protein kinase/ACC and PI-3 kinase/Akt signal pathways in C2C1 cells.	Kang et al. 2010
Euonymus alatus	Arrowroo t	Maceration (water and ethanol)	*In vivo* (Mice) *In vitro* (INS-1 cells)	500 mg/kg/day	-	4	Metformin (200 mg/kg)	Decreases water intake and plasmatic TG concentration, and increases the pancreatic insulin level.	Kim et al. 2022
Glycyrrhiza uralensis	-	Maceration (water)	*In silico* and *in vitro*	-	-	-	-	Strong binding affinity with DPP-4.	Shaikh et al. 2022
Gryllus bimaculatus	-	Powder	*In vivo* (Rats)	1.63, 3.25, and 6.5 g/kg twice a day	*Oral*	2	-	Improves FBG level, insulin sensitivity and the expression of Bcl2 and Bax.	Park et al. 2019
Gryllus bimaculatus	-	Powder	*In vivo* (Mice)	5 and 10 mg/kg	*Intraperitoneal*	4	Glycosaminoglyc an	Prevents hyperglycemia and modulates ALT, AST, ALP, LDL-cholesterol and BUN levels.	Ahn et al. 2020
Gryllus bimaculatus	-	Maceration (water)	*In vivo* (Mice)	100 mg/kg	*Oral*	4	-	Prevents insulin resistance and hepatic lipid accumulation	Kim et al. 2022b
Gymnema sylvestre	Leaves	Maceration (water/etha nol)	*In vivo* (Rats)	100 mg/kg/ day	*Oral*	4	-	Prevents lipid peroxidation in the liver and normalizes blood glucose level.	Kang et al. 2012
Helianthus tuberosus	-	Maceration (Ethyl Acetate)	*In vivo*	-	-	-	Acarbose	Anti-α-amylase and anti-α-glucosidase.	Mariadoss et al. 2021
Hordeum vulgare	-	Maceration (hexane)	*In vivo* (Mice	200 mg/kg/day	*Oral*	6	-	Decreases FBG level, lipid profile, and gluconeogenic (PPARγ) and hepatic inflammatory genes (NFκB, TNFα, and IL-6), and increases insulin expression and hepatic glycogen content.	Ham et al. 2021
Houttuynia cordata	-	Maceration (ethanol)	*In vivo* (Mice)	200 and 400 mg/kg/day	*Oral*	14	Metformin (50 mg/kg/)	Reduces BW, liver and kidney weights, fat ratio, liver markers, blood glucose level, and proinflammatory cytokines.	Wang et al. 2018
Houttuynia cordata	-	Maceration (ethanol)	*In vitro*	-	-	-	-	Potent antioxidant, antithrombotic and antidiabetic action.	Lee et al. 2023
Ixeris dentata	Whole plant	Maceration (methanol)	*In vitro* (HSG cells)	0.005 to 0.08 mg/ml	-	-	-	Increases p-IRE-1α, PDI and ERO-1α expression.	Lee et al. 2013
Jerusalem artichoke	-	Decoction (water)	*In vivo* (Mice	10 g/kg diet	*Oral*	6	-	No changes in FBG levels. Has a high toxicity rate.	Kim et al. 2021
Jerusalem artichoke	-	-	*In vivo* (Rats)	4 mL/kg	*Oral*	4	-	Improves liver markers, lipid profile and normalizes glycemia.	Kim et al. 2015a
Liriope platyphylla	Roots	Maceration (water)	*In vivo* (Rats)	5 and 10 mg/kg	*Oral*	2	-	Improves insulin secretion, Akt phosphorylation, and Glut-1 genes.	Kim et al. 2012b
Momordica charantia	Fruits	Maceration (ethanol)	*In vivo* (Mice)	-	*Oral*	12	-	Reduces insulin resistance caused by high-fat diet.	Yoon et al. 2017
Momordica charantia	Fruits	-	*In vivo* (Rats)	-	*Oral*	6	-	Improvement of glucose and insulin levels, and proinflammatory cytokines.	Yang et al. 2015
Morus alba	Branch	Maceration (ethanol)	*In vivo* (Mice)	0.5 or 1 g/kg/day	*Oral*	3	-	Regulates FBG, HGT2 and glycogen content.	Ahn et al. 2017

Table 1 continued

Morus alba	Branch	Maceration (water)	*In vivo* (Mice)	5 g/kg/day	*Oral*	2	-	Decreases elevated FBG, TC, HDL-C, TG, and liver glycogen content, and reduces the activities of lactase and sucrase in the small intestine.	Ahn et al. 2023
Morus alba	Leaves	Maceration (water)	*In vivo* (Mice) *In vitro* (C2C1, 3 T3-L1 and HIT-T15 cells)	300 and 600 mg/kg/day	*Oral*	7	Metformin (300 mg/kg)	Decreases glycemia and HbA1C level in mice. Elevates the glucose uptake in C2C12 and 3 T3-L1 cells, and promotes insulin secretion in HIT-T15 cells.	Jung et al. 2019b
Nardostachys jatamansi	Whole plant	Decoction (water)	*In vivo* (Mice)	125 mg/kg/day	*Oral* and *intraperitoneal*	-	-	Normalizes insulin secretion and prevents cytokine-induced NF-kappaB activation.	Song et al. 2010
Nepeta angustifolia	Areal parts	Maceration (ethanol)	*In vivo* (Rats) *In vitro* (HBZY-1 cells)	60, 120 and 240 mg/kg/day 50, 100 and 200 μg/mL	-	8	Metformin (250 mg/kg)	Maintains BW, blood glucose level, and kidney biomarkers. Protects the HBZY-1 cells against H2O2-induced cytotoxicity.	Huang et al. 2020
Osteomeles schwerinae	Leaves and twigs	Maceration (ethanol)	*In vitro* (GMCs cells)	1, 10 and 100 μg/ml	-	-	-	Improves the AGE/RAGE binding and TGF-β1 protein expression.	Kim et al. 2016
Paeonia japonica	Roots	Maceration (methanol)	*In vitro* RAW 264.7 and 3T3-L1 cells	10-50 μg/mL	-	-	Insulin	Inhibits glucose uptake and upregulates GLUT4 genes in 3T3-L1 cells.	Yang et al. 2024
Panax ginseng	Roots	Maceration (water)	*In vivo* (Rats)	25, 50, and 100 mg/kg/day	*Oral*	6	-	Prevents diabetes-induced blood-retinal barrier breakdown.	Jung et al. 2019a
Panax ginseng	Roots	Maceration (water)	*In vivo* (mice)	25 mg/kg/day	*Oral*	6	-	Improves glycemia, ameliorates pancreatic ultrastructure, and restores insulin secretion.	Hong et al. 2012
Panax ginseng	Roots	Maceration (ethanol)	*In vivo* (Mice)	300 and 900 mg/kg diet	*Oral*	4	-	Decreases FBG, HbA1c, TG, and TC levels.	Kang et al. 2017
Panax ginseng	-	-	*In vivo* (zebrafish)	50 and 100 mg/mL	-	-	-	Prevents sensorineural damage and improves cell cilia in diabetic zebrafish.	Nam et al. 2019
Panax quinquefolius	Roots	Maceration (methanol)	*In vivo* (Mice)	150 mg/kg/day	ip	-	-	Decreases blood glucose, TC and LDL-C levels, and increases glycogen and HDL-C concentrations.	Yoo et al. 2012
Perilla frutescens	Seeds	Maceration (water and ethanol)	*In vitro*	-	-	-	Acarbose	Anti α-glucosidase and anti α-amylase activity.	Choi et al. 2023
Perilla frutescens	Seeds	Maceration (water)	*In vivo* (Mice) *In vitro* (HepG2 cells)	100, 300, and 1,000 mg/day	*Oral*	4	-	Improvement in FBG, insulin, TG and TC levels in mice, and AMPK phosphorylation and glucose G6P level in HepG2 cells.	Kim et al. 2018
Phellinus linteus	-	Maceration (methanol)	*In silico*	-	-	-	-	Activation of AMPK signaling pathway and insulin receptor phosphorylation.	Oh et al. 2021

Table 1 continued

Pinus densiflora	Inner Barks	Maceration (ethyl acetate)	*In vitro* (HIT-T15 cells)	-	-	-	Insulin (1 µM) and metformin (2 mM)	Regulates insulin secretion.	Min et al. 2019
Portulaca oleracea	-	-	*In vivo* (Mice)	0.4 g/100 g diet	*Oral*	6	-	Decreases BG and HbA1c levels, and improves homeostatic index of insulin resistance and insulin sensitivity check index	Lee et al. 2020
Portulaca oleracea	Roots	Maceration (water and ethanol)	*In vitro* (3T3-L1 cells) *In vivo* (Mice)	300 mg/kg	*Oral*	-	Acarbose (100 mg/kg)	α-glucosidase and α-amylase inhibitory action. Decrease PPG in mice.	Park and Han 2018
Rhus verniciflua	Stem	Maceration (Water, ethanol and methanol)	*In vitro*	2, 4 and 8 µg/ml	-	-	Acarbose (100 mg/kg/day)	A strong anti-α-glucosidase effect.	Kim et al. 2011
Sasa borealis	Leaves	Maceration (methanol)	*In vitro* (C2C12 and HepG2 cells) *In vivo* (Mice)	40 µg/mL/24h 300 and 500 mg/kg/day	*Oral*	- 2	-	Inhibits AMPK activation, and improves insulin signaling in C2C12 cells, and PPARα genes in HepG2 cells. Reduces BGL and TG in diabetic mice.	Nam et al. 2013
Sasa Borealis	Leaves	Maceration (methanol)	*In vitro* (HUVECs cells)	0-100 µg/mL	-	-	-	Prevents LP and oxidative stress in HUVECs cells exposed to high glucose.	Hwang et al. 2010
Sasa Borealis	Leaves	Decoction (ethanol)	*In vivo* (Mice)	5% diet	*Oral*	12	-	Decreases glucose and insulin levels, and improves leptin, TNF-α, and IL-6 concentrations.	Yang et al. 2010
Smallanthus sonchifolius	-	Decoction (water)	*In vivo* (Rats)	125, 250 and 500 mg/kg	*Oral*	5	-	Improves BGL, insulin metabolism.	Oh et al. 2012
Smallanthus sonchifolius	Roots and Leaves	Maceration (ethanol)	*In vivo* (Rats)	1,000mg/kg/day	*Oral*	1	-	Reduces BGL, TC and TG levels, and increases glycogen, glucokinase and glucose-6-phoshatase(G-6-Pase) levels.	Kim and Lee 2013
Smallanthus sonchifolius	Leaves	Maceration (water)	*In vivo* (Mice)	0.16 and 0.8% diet	*Oral*	6	-	Improves glycemia, liver transaminases, insulin, leptin and liver glucokinase.	Kim et al. 2010
Sorghum bicolor	-	-	*In vivo* (Mice)	0.5 and 1%diet	*Oral*	7		Decreases TC, TG, LDL-C and glucose levels.	Park et al. 2012
Vaccinium uliginosum	-	-	*In vivo* (Rats)	1% diet	*Oral*	-	-	Improvement in TC, TG, LDL-C, FBG, and SOD levels.	Han et al. 2012
Vaccinium myrtillus	-	-	*In vivo* (Rats)	100 mg/kg/day	*Oral*	6	-	Downregulation of diabetic retinopathy markers retinal such as VEGF.	Kim et al. 2015b
Vigna nakashimae	Seeds	Maceration (ethanol)	*In vivo* (Mice) *In vitro* (HepG2 cells)	100 and 500 mg/kg/day	*Oral*	2	Acarbose (50 mg/kg)	Decreases glycemia and plasmatic TG in mice, and ER stress in HepG2 cells.	Yeo et al. 2011
Viscum album	Whole plant	Maceration (water)	*In vivo* (Rats)	0.6% diet	*Oral*	8	-	Reduces TC, LDL-C, TG, IR, and improves HDL-C level and mTOR phosphorylation.	Huang et al. 2020

Table 1 continued

Viscum album	Whole plant	Maceration (water)	*In vivo* (Mice) *In vitro* (C2C12 cells)	50 and 100 mg/kg/day	*Oral*	1	-	Decreases BGL, OGTT, TC and TG levels in mice. Increases glucose uptake and upregulates PGC-1α, GLUT4, ERR-α, NRF-1, and TmfA genes in C2C12 cells.	Jung et al. 2015
Vitis vinifera	Seeds	Maceration (water/acetone)	*In vivo* (mice)	100 and 250 mg/kg/day	*Oral*	12	-	Prevents nerve fiber loss in HFD-induced prediabetic mice.	Jin et al. 2013
Zingiber mioga	Leaves	Maceration (water/ethanol)	*In vivo* (Rats)	100 µg/mL	*Oral*	-	Acarbose (5 mg/kg)	Potent sucrase, maltase and α-amylase inhibitory activity. Prevents postprandial increase of glycemia.	Jo et al. 2016
Zingiber mioga	Flower buds	Maceration (water)	*In vivo* (mice) *In vitro* 3T3-L1 cells	0.25 or 0.5% diet	*Oral*	8	-	Decreases BW, TC, TG, IR, and downregulates hepatic gluconeogenic genes.	Lee et al. 2016

Abbreviations. BGL: blood glucose level; CAT: catalase; ERR-α: estrogen-related receptor-α; FBG: fasting blood glucose; G6P: glucose 6-phosphate; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GSH-Px: glutathione peroxidase; GSSG: oxidized glutathione; HbA1c: glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HGT2: hepatic glucose transporter 2; ip: intraperitoneally; LDH: locate dehydronase; LDL-C: low-density lipoprotein cholesterol; NF-κB: nuclear factor-Kb; NRF-1: nuclear respiratory factor-1; OGTT: oral glucose tolerance test; PPG: postprandial glycemia; PTP1B: protein-tyrosine phosphatase 1B; SOD: superoxide dismutase; STZ: streptozotocin; TBARS: thiobarbituric acid reactive substances; TC: total cholesterol; TG: triglyceride; TmfA: mitochondrial transcription factor A; VEGF: vascular endothelial growth factor.

Discussion

Traditional Korean medicine (TKM) was founded on the principles of ancient medical science, with its origins traced back to 11 oriental books that document ancient remedies. Among these books, Dong-Eu-Bo-Gam is the most significant, and is regarded as the bible of TKM up to the present in Korea. South Korea is recognized as one of the leaders in the integration of traditional medicine with conventional medical practices, aiming to enhance care and promote health and well-being. In fact, students who choose to pursue a major in conventional medicine are required to take courses in traditional medicine and vice versa. This ensures that healthcare professionals are able to apply both medical systems. Students have the opportunity to enroll in 13 medical universities situated at both central and provincial levels, as well as one university specializing in Koryo traditional medicine. Each medical university has faculty dedicated to Koryo traditional medicine, where this discipline is taught. The fundamental principles of Koryo medicine, including acupuncture, herbal prescriptions, surgery, gynecology, pediatrics, and others, are taught with modern medical subjects such as anatomy, physiology, pathology, and internal medicine. TKM clinics acquire herbal medicines through one of three ways. The first is through the procurement of approved herbal medicines supplied by the Korea's Ministry of Food and Drug Safety (MFDS), available in powder, soft extracts, and tablet forms (Sung et al. 2020). The second method is through the procurement of herbal medicines prepared at TKM institutions, mainly in the form of decoctions. The third approach involves receiving herbal medicines prepared at the External Herbal Dispensaries (EHDs) based on prescriptions from TKM clinics. EHDs provide tablets, powders, and medicines that are difficult to produce in the TKM institutions. The Korean Ministry of Health and Welfare (MoHW) has announced the establishment of an accreditation system for the EHDs associated with TKM clinics to ensure compliance with established norms and standards (Sung 2024). This initiative is designed to guarantee the efficacy and safety of herbal products. The use of plant extracts in the management of DM in South Korea dates back centuries, but experimental and clinical studies are more recent. This review aims to provide valuable insights for scholars, scientists, and healthcare professionals engaged in pharmacology and therapeutics focused on the development of antidiabetic medications.

Overall, we compiled 134 studies (116 preclinical and 18 clinical) conducted on antidiabetic plants across different regions of South Korea. From the results obtained, the leaves were the most frequently used plant part, which could be justified by their ease of harvesting, as well as their role as the primary site of photosynthesis. Additionally, leaves may serve as reservoirs for secondary metabolites that contribute to the biological characteristics of the plant (Noureddine et al. 2022). The predominance of aqueous extract could be assimilated to the recommendations of traditional healers and its ease (low costs). The oral administration was the main route. This route of administration is usually safe, easy, economical, and facilitates a swift physiological response, thereby enhancing the efficacy of the herbal formulation. Moreover, antidiabetic herbs acting as α-glucosidase inhibitors, when administered orally, may easily inhibit the activity of α-glucosidase enzymes, leading to a delay in the absorption of ingested carbohydrates, ultimately resulting in a decrease in blood glucose level (Dirir et al. 2021).

In the present study, the possible mechanism of action of South Korean antidiabetic plants was also studied. It was categorized into: (1) inhibition of α-glucosidase, α-amylase and aldose reductase, leading to reduced carbohydrate absorption, (2) enhancement of glucose consumption in muscle and adipose tissues,

(3) upregulation of PPAR, (4) promotion of insulin receptors, (5) enhancement of antioxidant status and inhibition of β-cell apoptosis, (6) enhanced insulin secretion, (7) facilitation of glycogenesis or inhibition of glycogenolysis in the liver, (8) promotion of glucagon degradation via incretins, and (9) inhibition of renal fibrosis (Figure 4 and Table S5).

Since each extract may contain various active molecules, each plant may have multiple mechanisms of action. For instance, *Angelica dahurica* could exhibit an antidiabetic potential by stimulating peripheral glucose uptake, upregulating insulin receptors, and increasing insulin sensitivity, while *Brassica rapa* may act by promoting peripheral glucose uptake, insulin receptor sensitivity, glucagon degradation, glycogenesis, and inhibiting hepatic glycogenolysis (Jung et al., 2008; Park et al. 2016). *Panax ginseng* may increase peripheral glucose uptake, augment insulin receptor sensitivity and insulin secretion, and inhibit lipid peroxidation, apoptosis of β-cells and glucagon generation (Hong et al. 2012; Kang et al. 2017). The exploitation of the mechanism of action could serve as a basis for further research in humans in order to develop new plant-based antidiabetic drugs.

South Korean antidiabetic plants have been studied, but several limitations can be noted. For instance, the lack of reference antidiabetic drugs in some studies (Kwon et al. 2016; Vu et al. 2020), a single dose of plant extract (Kang et al. 2010; Koo et al. 2014; Park et al. 2016), high doses of plant extracts (Kim and Lee 2013), the type of extract selected, which was not always in accordance with the recommendations of traditional healers (Min et al. 2019; Ham et al. 2021), and the low number of animals per group, or the inappropriate duration of treatment (Kang et al. 2012). Few clinical investigations have been published, but several challenges in the development of new antidiabetic plant-based products persist. *-Patentability:* The active ingredients isolated from plant extracts cannot be patented as new substances. Additionally, patenting their applications poses challenges due to the extensive information already available in the literature. However, it is feasible to patent a novel herbal formulation based on preclinical and clinical findings. - *Product standardization:* Achieving this objective necessitates rigorous monitoring of raw materials, extraction processes, and final composition. In the absence of robust quality control measures, the uniformity of the herbal formulation may be compromised. In the majority of studies reported here, no standardization processes were documented. - *Placebo-controlled, randomized clinical trials:* Many herbal formulations are used in South Korean folk medicine in the management of DM, based on ancestral knowledge, but without updated experimental and/or clinical investigations (for instance: Odootang, Ojeubockcheonwhan, Omeamogwatang, Palmisingiwhan, Seokjajenitang, and Soongisan). - *Toxicity studies:* Plant extracts are commonly perceived as safe and associated with few or no side effects. Nevertheless, their effects are typically less powerful compared to modern drugs. Therefore, high doses are often necessary to attain the desired therapeutic outcomes. The majority of clinical studies reported in this work lack information on their safety. Further toxicological and efficacy studies in human subjects are of great interest for the development of new effective plant-based antidiabetic drugs.

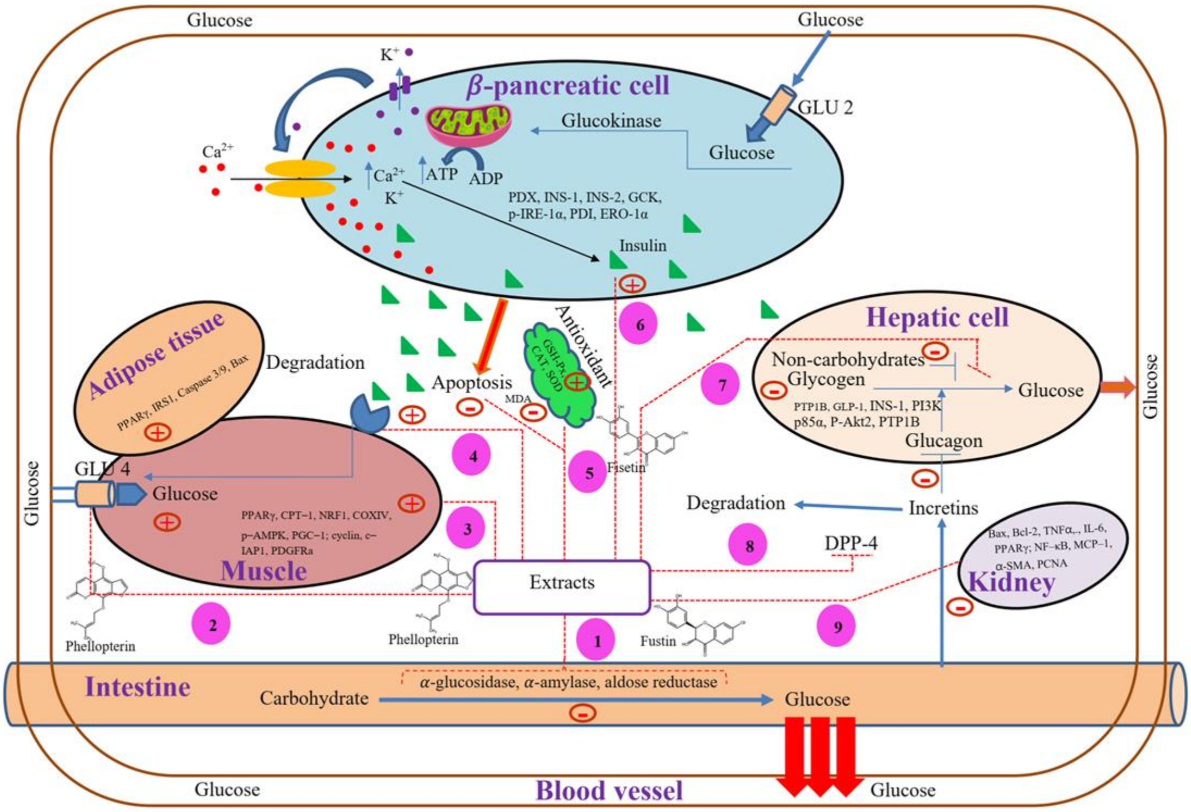

Figure 4. Mechanisms of action of selected South Korean antidiabetic plants and plant-derived molecules. (1): Inhibition of α-glucosidase, α-amylase, and aldose reductase, leading to the reduction of carbohydrate absorption; (2): Increased glucose consumption in muscle; (3): Stimulation of PPAR; (4): Upregulation of insulin receptors; (5): Inhibition of β-cell apoptosis; (6): Increased insulin secretion; (7): Inhibition of gluconeogenesis in the liver; (8): Blocks incretins from degradation of glucagon; (9): Inhibition of renal fibrosis. +: activation; -: inhibition. Further information is shown in Table S4. Abbreviations: ADP: adenosine diphosphate; ATP: adenosine triphosphate; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; c–IAP1: cellular inhibitor of apoptosis protein-1; COXIV: C oxidase subunit IV; CPT–1: carnitine palmitoyltransferase-1; ERO-1α: endoplasmic reticulum disulphide oxidase 1α; GCK: glucokinase; GLP-1: glucagon-like peptide-1; IL-6: interleukin–6; INS-1: preproinsulin 1; INS-2: preproinsulin 2; IRS1: insulin receptor substrate 1; MCP–1: monocyte chemotactic protein-1; MDA: malondialdehyde; NF–κB: nuclear factor kappa–B; NRF1: nuclear respiratory factor-1, p-IRE-1α: inositol-requiring enzyme 1α.

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Conflicts of interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

PBDD, Validation, Data curation, Methodology, Investigation, Formal analysis, Software, Writing – original draft. KH, Data curation, Methodology, Investigation, Manuscript writing. HYK, Data curation, Methodology, Investigation, Manuscript writing. MHW, Supervision, Data curation, Methodology, Project administration, Writing – final draft, Funding acquisition.

Abbreviation:

AMPK: 5' adenosine monophosphate-activated protein kinase; AST: aspartate amino transferase; ATP: adenosine triphosphate; BGL: blood glucose level; BMI: body mass index; CAT catalase; CAT: catalase; EHDs: external herbal dispensaries; ERR-α: estrogen-related receptor-α; FBG: fasting blood glucose; FoxO: forkhead box O; FPG: fasting plasma glucose; GC-MS: gas chromatography–mass spectrometry; G6P: glucose 6-phosphate; GIP: glucose-dependent insulinotropic polypeptide; GLP1: glucagon-like peptide-1; GLUT2: glucose transporter type 2; GLUT4: glucose transporter type 4; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GSH-Px: glutathione peroxidase; GSSG: oxidized glutathione; HbA1c: glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HGT2: hepatic glucose transporter 2; HIF-1: hypoxia-inducible factor 1; IL–1β: interleukin–1β; IL–6: interleukin–6; ip: intraperitoneally; LC-MS: liquid chromatography–mass spectrometry; LDH: locate dehydronase; LDL-C: low-density lipoprotein cholesterol; MDA: malondialdehyde; NF–Kb: nuclear factor kappa–B; MFDS: ministry of food and drug safety; MoHW: Korean ministry of health and welfare; NRF-1: nuclear respiratory factor-1; NSS: non-sulfonylurea secretagogues; OGTT: oral glucose tolerance test; PDB: protein data bank; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-α; PI3K: phosphatidylinositol–3 kinase; PPAR: peroxisome proliferator–activated receptor; PPARγ: peroxisome proliferator-activated receptor γ; PPG: postprandial glucose; PTP1B: protein-tyrosine phosphatase 1B; Rap1: repressor activator protein 1; Ras: reticular activating system; SOD: superoxide dismutase; STZ: streptozotocin; SUR1: sulfonylurea receptor 1; TKM: traditional Korean medicine; T2DM: type 2 diabetes mellitus; TBARS: thiobarbituric acid reactive substances.

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Supplementary

Supplementary Table 1. South Korean empirical formulas for the treatment of DM (Vuksan et al. 2008; Shin et al. 2012; Shishtar et al. 2014; Park et al. 2020).

Name	Composition
Backhogainsamtang	*Panax ginseng*, *Anemarrhena asphodeloides*, Gypsum, Licorice, Oryzae semen, Lactose hydrate
Bosinjihwangwon	*Phellodendron amurense* Rupr, *Rehmannia glutinosa* Libosch, *Poria cocos* F.A. Wolf, *Rehmannia glutinosa* Libosch, *Asparagus cochinchinensis* Merr, *Panax ginseng* C. A. Meyer, *Chrysanthemum indicum* L, *Scutellaria baicalensis* Georgi, *Angelica gigas* Nakai, *Citrus aurantium* L, *Liriope latyphylla* Wang et Tang, *Scutellaria baicalensis* Georgi
Cheongsimyeonjaeum	*Lycii radicis*, *Nelumbo nucifera*, *Scutellaria baicalensis*, *Astragalus membranaceus*, *Glycyrrhiza uralensis*, *Poria cocos*, Plantaginis Semen, *Panax ginseng*, and *Liriope platyphylla*
Cheongsinbogitang	*Cimicifuga heracleifolia* Kom, *Bupleurum falcatum* L, *Angelica gigas* Nakai, *Schizonepeta tenuifolia* Briq, *Sinomenium acutum* Rehder et E. H. Wilson, *Prunus persica* (L.) Batsch, *Phellodendron amurense* Rupr, *Coptis japonica* Makino, *Anemarrhena asphodeloides* Bunge, *Glycyrrhiza uralensis* Fisch, *Gypsum*, *Rehmannia glutinosa* Libosch, Asarum heterotropoides F. *Maekawa*, *Prunus armeniaca* L. var. ansu Maxim, *Zanthoxylum bungeanum*, *Carthamus tinctorius* L
Cheonwhasan	*Trichosanthes kirilowii* Maxim, *Rehmannia glutinosa* Libosch., *Pueraria lobata* (Willd.) Ohwi, *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch
Dahwanggamchoeumja	*Rheum undulatum* L., *Glycyrrhiza uralensis* Fisch, *Glycine semen*
Eegwonsan	*Talcum*, *Glycyrrhiza uralensis* Fisch
Gagambackchulsan	*Pueraria lobata* (Willd.) Ohwi, *Panax ginseng* C. A. Meyer, *Atractylodes japonika* Koidz., *Poria cocos* Wolf, *Aucklandia lappa* Decne, *Anemarrhena asphodeloides* Bunge, *Phellodendron amurense* Rupr, *Glycyrrhiza uralensis* Fisch, *Schizandra chinensis* Bailon
Gagambackhotang	*Gypsum*, *Anemarrhena asphodeloides* Bunge, *Panax ginseng* C. A. Meyer, *Phellodendron amurense* Rupr, *Scrophularia buergeriana* Miq, *Glycyrrhiza uralensis* Fisch, *Schizandra chinensis* Bailon, *Oryza sativa* L.
Gagamsingihwan	*Rehmannia glutinosa* Libosch, *Paeonia suffruticosa* Andr, *Poria cocos* Wolf, *Cornus officinalis* S. et Z, *Schizandra chinensis* Bailon, *Alisma orientale* Juz, *Cervus nippon* hortulorum, *Dioscorea batatas* Decne, *Cinnamomum cassia* Blume, *Aquilaria agallocha* Roxb.
Gamijeonssibackchoolsan	*Pueraria lobata* (Willd.) Ohwi, *Panax ginseng* C. A. Meyer, *Atractylodes japonika* Koidz, *Poria cocos* Wolf, *Agastache rugosa* (Fisc.r et Mey.) Kuntze, *Glycyrrhiza uralensis* Fisch, *Aucklandia lappa* Decne, *Bupleurum falcatum* L, *Citrus aurantium* L, *Schizandra chinensis* Bailon
Gangsimtang	*Trichosanthes kirilowii* Maxim, *Panax ginseng* C. A. Meyer, *Polygala tenuifolia* Willd, *Angelica gigas* Nakai, *Rehmannia glutinosa* Libosch., *Poria cocos* Wolf, *Astragalus membranaceus Bunge*, *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch, *Zizyphus jujuba* var. inermis
Goryuntang	*Melia azedarach*, *Moschus moschiferus*
Hwahyulikgitang	*Phellodendron amurense* Rupr, *Cimicifuga heracleifolia* Kom, *Rehmannia glutinosa* Libosch, *Coptis japonica* Makino, Gypsum, *Prunus armeniaca* L. var. ansu Maxim, *Prunus persica* (L.) Batsch, *Anemarrhena asphodeloides* Bunge, *Sinomenium acutum* Rehder et E. H. Wilson, *Ostericum koreana* Kitagawa, *Angelica gigas* Nakai, *Bupleurum falcatum* L, *Ephedra sinica*, *Glycyrrhiza uralensis* Fisch, *Carthamus tinctorius* L.
Hwalhyeolyunjosaengjineum	*Trichosanthes kirilowii*, *Angelica gigas*, *Asparagus cochinchinensis*, *Rehmannia glutinosa*, *Liriope platyphylla*, Cannabis Semen, *Rehmanniae Radix*, *Schizandra chinensis*, and Trichosanthis Semen
Hyuntodan	*Cuscuta chinensis* Lamark, *Schizandra chinensis* Bailon, *Poria cocos* Wolf, *Nelumbo nucifera* Gaertn, *Dioscorea batatas* Decne.

Supplementary Table 1. continued

Insambockreyngsan	*Talcum, Gypsum rubrum, Glycyrrhiza uralensis* Fisch, *Poria cocos* Wolf, *Pueraria lobata* (Willd.) Ohwi, *Scutellaria baicalensis* Georgi, *Mentha arvensis* var. piperascens MALINV, *Rheum undulatum* L., *Forsythia viridissima* Lindley, *Panax ginseng* C. A. Meyer, *Atractylodes japonika* Koidz, *Alisma orientale* Juz, *Platycodon grandiflorum* A. DC, *Gardenia jasminoides* Ellis, *Trichosanthes kirilowii* Maxim, *Amomum villosum* Lour.
Insamsan	*Talcum, Gypsum rubrum, Glycyrrhiza uralensis* Fisch, Gypsum, *Panax ginseng* C. A. Meyer
Insamseokgotang	*Gypsum, Anemarrhena asphodeloides* Bunge, *Panax ginseng* C. A. Meyer, *Glycyrrhiza uralensis* Fisch
Jaeumyangyoungtang	*Angelica gigas* Nakai, *Panax ginseng* C. A. Meyer, *Rehmannia glutinosa* Libosch, *Liriope platyphylla* Wang. et Tang, *Paeonia japonica* (Makino) Miyabe, *Anemarrhena asphodeloides* Bunge, *Phellodendron amurense* Rupr., *Glycyrrhiza uralensis* Fisch, *Schizandra chinensis* Bailon
Joosahwangreonwon	*Coptis japonica* Makino, *Rehmannia glutinosa* Libosch, *Cinnabaris*
Macmoondongeumja	*Liriope platyphylla* Wang. et Tang, *Anemarrhena asphodeloides* Bunge, *Trichosanthes kirilowii* Maxim, *Panax ginseng* C. A. Meyer, *Schizandra chinensis* Bailon, *Pueraria lobata* (Willd.) Ohwi, *Poria cocos* Wolf, *Rehmannia glutinosa* Libosch., *Glycyrrhiza uralensis* Fisch, *Sasa japonica Makino var. purpurascens* Nakai
Maekmundongeumja	*Pueraria lobata*, *Panax ginseng*, *Rehmannia glutinosa*, *Liriope platyphylla*, *Trichosanthes kirilowii*, *Anemarrhena asphodeloides*, *Poria cocos*, *Schizandra chinensis*, and *Glycyrrhiza uralensis*
Meahwatang	*Oraza sativa* L. *var. glutinosa,* Matsumura, *Morus alba* Linne
Moondongeumja	*Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Panax ginseng* C. A. Meyer, *Lycium chinense* Mill., *Poria cocos* Wolf, *Glycyrrhiza uralensis* Fisch
Mundongeumja	*Glycyrrhiza uralensis*, *Lycii radicis*, *Panax ginseng*, *Liriope platyphylla*, *Poria cocos*, *Schizandra chinensis*
Nahaeumja	*Gypsum, Anemarrhena asphodeloides* Bunge, *Glycyrrhiza uralensis* Fisch, *Ledebouriella seseloides* (Hoffm.) Wolff, *Panax ginseng* C. A. Meyer., *Forsythia viridissima* Lindley, *Amomum cardamomum* L., Platycodon grandiflorum A. DC, *Cimicifuga heracleifolia* Kom., *Pinellia ternata* Breitenbach, *Zingiber officinale* Roscoe
Nockyounghwan	*Liriope platyphylla* Wang. et Tang, *Cervus nippon hortulorum, Rehmannia glutinosa* Libosch., *Astragalus membranaceus* Bunge, *Schizandra chinensis* Bailon. *Gallus gallus* var. domesticus, *Cistanche deserticola* Y.C. Ma, *Cornus officinalis* S. et Z., *Psoralea corylifolia* L., *Achyranthes bidentata* Blume, *Panax ginseng* C. A. Meyer, *Poria cocos* Wolf, *Lycium chinense* Mill., *Scrophularia buergeriana* Miq
Ockcheonsan	*Trichosanthes kirilowii* Maxim, *Pueraria lobata* (Willd.) Ohwi, *Liriope platyphylla* Wang. et Tang, *Rehmannia glutinosa* Libosch, *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch, *Oraza sativa* L. var. glutinosa Matsumura
Ockcheonwhan	*Trichosanthes kirilowii* Maxim, *Pueraria lobata* (Willd.) Ohwi, *Liriope platyphylla* Wang. et Tang, *Panax ginseng* C. A. Meyer, *Poria cocos* Wolf, *Astragalus membranaceus* Bunge, *Prunus mume* Siebold et Zucc, *Glycyrrhiza uralensis* Fisch
Odootang	*Pueraria lobata* (Willd.) Ohwi, *Dryopteris crassirhizoma* NAKAI, *Glycyrrhiza uralensis* Fisch, *Glycine semen, Glycine max* Merrill, *Vigna radiata* (L.) R. Wilczek., *Phaseolus angularis* W. F. WIGHT.
Ojeubockcheonwhan	*Coptis japonica* Makino, *Pueraria lobata* (Willd.) Ohwi, *Trichosanthes kirilowii* Maxim, *Anemarrhena asphodeloides* Bunge, *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Panax ginseng* C. A. Meyer, *Rehmannia glutinosa* Libosch, *Prunus mume* Siebold et Zucc, *Nelumbo nucifera* Gaertn, *Angelica gigas* Nakai, *Glycyrrhiza uralensis* Fisch.
Omeamogwatang	*Prunus mume* Siebold et Zucc, *Chaenomeles sinensis* Koehne, *Hordeum vulgare* L, *Amomum tsao-ko* Crevost et Lemarie, *Glycyrrhiza uralensis* Fisch
Palmisingiwhan	*Rehmannia glutinosa* Libosch, *Dioscorea batatas* Decne, *Cornus officinalis* S. et Z, *Alisma orientale* Juz, *Paeonia suffruticosa* Andr, *Poria cocos* Wolf, *Schizandra chinensis* Bailon, *Cinnamomum cassia* Blume
Saengjingamrotang	*Gypsum, Gentiana scabra* Bunge, *Phellodendron amurense* Rupr, *Bupleurum falcatum* L, *Ostericum koreana* Kitagawa, *Astragalus membranaceus* Bunge, *Anemarrhena asphodeloides* Bunge, *Scutellaria baicalensis* Georgi, *Angelica gigas* Nakai, *Cimicifuga heracleifolia* Kom, *Ledebouriella seseloides* (Hoffm.) Wolff, *Sinomenium acutum* Rehder et E. H. Wilson, *Rehmannia glutinosa* Libosch, *Glycyrrhiza uralensis* Fisch, *Prunus armeniaca* L. var. ansu Maxim, *Prunus persica* (L.) Batsch, *Carthamus tinctorius* L.

Supplementary Table 1. continued

Saengjinyanghyeltang	*Angelica gigas* Nakai, *Paeonia japonica* (Makino) Miyabe, *Rehmannia glutinosa* Libosch, *Liriope platyphylla* Wang. et Tang, *Cnidium officinale* Makino, *Coptis japonica* Makino, *Trichosanthes kirilowii* Maxim, *Anemarrhena asphodeloides* Bunge, *Phellodendron amurense* Rupr, *Nelumbo nucifera* Gaertn, *Prunus mume* Siebold et Zucc, *Mentha arvensis* var. piperascens MALINV, *Glycyrrhiza uralensis* Fisch
Samooltang	*Rehmannia glutinosa* Libosch, *Paeonia japonica* (Makino) Miyabe, *Cnidium officinale* Makino, *Angelica gigas* Nakai
Samsohwan	*Coptis japonica* Makino, *Liriope platyphylla* Wang. et Tang, *Pueraria lobata* (Willd.) Ohwi
Sangbaekpitang	*Morus alba* Linne, *Poria cocos* Wolf, *Panax ginseng* C. A. Meyer, *Liriope platyphylla* Wang. et Tang, *Pueraria lobata* (Willd.) Ohwi, *Dioscorea batatas* Decne, *Cinnamomum cassia* Blume, *Glycyrrhiza uralensis* Fisch
Seangjihwangeuja	*Panax ginseng* C. A. Meyer, *Rehmannia glutinosa* Libosch, *Astragalus membranaceus* Bunge, *Asparagus cochinchinensis* Merr, *Liriope platyphylla* Wang. et Tang, *Citrus aurantium* L, *Dendrobium nobile* Lindl, *Eriobotrya japonica* (Thunb.) Lindley, *Alisma orientale* Juz.
Seangjihwanggo	*Rehmannia glutinosa* Libosch, *pis Indira Radoszkowski*, *Poria cocos* Wolf, *Panax ginseng* C. A. Meyer
Seokjajenitang	*Japanese lady bell*, Gypsum, *Panax ginseng* C. A. Meyer, *Poria cocos* Wolf, *Trichosanthes kirilowii* Maxim, Magenetitum, *Anemarrhena asphodeloides* Bunge, *Pueraria lobata* (Willd.) Ohwi, *Scutellaria baicalensis* Georgi, *Glycyrrhiza uralensis* Fisch, *Sus scrofa* var. domesticus, Glycine semen
Singihwan	*Rehmannia glutinosa* Libosch, *Dioscorea batatas* Decne, *Cornus officinalis* S. et Z, *Alisma orientale* Juz, *Paeonia suffruticosa* Andr, *Poria cocos* Wolf, *Schizandra chinensis* Bailon
Soongisan	*Magnolia officinalis* Rehder et Wilson, *Rheum undulatum* L, *Poncirus trifoliata* Rafinesqul
Wesangcheonwhawon	*Coptis japonica* Makino, *Dolichos lablab* L, *Aloe vera* L, Cinnabaris, *Poria cocos* Wolf, *Ostrea gigas* Thunb, *Anemarrhena asphodeloides* Bunge, *Sophora flavescens* Ait, *Trichosanthes kirilowii* Maxim
Whalhyulyunjosangjineum	*Asparagus cochinchinensis* Merr, *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Trichosanthes kirilowii* Maxim, *Cannabis sativa*, *Angelica gigas* Nakai, *Rehmannia glutinosa* Libosch, *Trichosanthes kirilowii* Maxim, *Glycyrrhiza uralensis* Fisch
Whanggeumtang	*Scutellaria baicalensis* Georgi, *Gardenia jasminoides* Ellis, *Platycodon grandiflorum* A. DC, *Liriope platyphylla* Wang. et Tang, *Angelica gigas* Nakai, *Rehmannia glutinosa* Libosch., *Trichosanthes kirilowii* Maxim, *Pueraria lobata* (Willd.) Ohwi, *Panax ginseng* C. A. Meyer, *Paeonia japonica* (Makino) Miyabe, *Prunus mume* Siebold et Zucc.
Whanggitang	*Rehmannia glutinosa* Libosch, *Astragalus membranaceus* Bunge, *Poria cocos* Wolf, *Trichosanthes kirilowii* Maxim, *Liriope platyphylla* Wang. et Tang, *Schizandra chinensis* Bailon, *Glycyrrhiza uralensis* Fisch
Whangryonjiwhangtang	*Coptis japonica* Makino, *Rehmannia glutinosa* Libosch, *Trichosanthes kirilowii* Maxim, *Schizandra chinensis* Bailon, *Angelica gigas* Nakai, *Panax ginseng* C. A. Meyer, *Pueraria lobata* (Willd.) Ohwi, *Poria cocos* Wolf, *Liriope platyphylla* Wang. et Tang, *Glycyrrhiza uralensis* Fisch, *Zingiber officinale* Roscoe, *Zizyphus jujuba* var. inermis, *Sasa japonica Makino var.* purpurascens Nakai
Whangryunjeodoowhan	*Sus scrofa var.* domesticus, *Coptis japonica* Makino, *Triticum aestivum* L, *Trichosanthes kirilowii* Maxim, *Poria cocos* Wolf, *Liriope platyphylla* Wang. et Tang
Whangryunjeodoowhan	*Sus scrofa* var, *Coptis japonica* Makino, *Liriope platyphylla* Wang. et Tang, *Anemarrhena asphodeloides* Bunge, *Trichosanthes kirilowii* Maxim
Whanhgiyuckiltang	*Astragalus membranaceus* Bunge, *Glycyrrhiza uralensis* Fisch
Woozeumgo	*Rehmannia glutinosa* Libosch, *Bos taurus coreannae*, *Coptis japonica* Makino, *Trichosanthes kirilowii* Maxim, *Zingiber officinale* Roscoe, *Apis Indira* Radoszkowski
Yeojigo	*Bos taurus var. domesticus* Gmelin, *Apis indira* Radoszkowski, *Prunus mume* Siebold et Zucc., *Zingiber officinale* Roscoe, *Moschus moschiferus*
Yindongwon	*Lonicera japonica* Thunb.
Yongbongwon	*Dioscorea batatas* Decne, *Cuscuta chinensis* Lamark, *Cervus nippon* hortulorum
Yukmigeehwanghwan	*Rehmannia glutinosa* Libosch, *Dioscorea batatas* Decne, *Cornus officinalis* S. et Z, *Alisma orientale* Juz, *Paeonia suffruticosa* Andr, *Poria cocos* Wolf

Supplementary Table 2. Preclinical evidence of some South Korean antidiabetic formulations

Scientific Name	Plant part	Extract tested	Model(s)	Dose range	Administration	Duration	Positive control	Pharmacological activity	Reference
Panax ginseng, Pueraria lobata, Dioscorea batatas Decaisne, Rehmannia glutinosa, Amomum cadamomum Linné, Poncirus fructus and *Evodia officinalis*	-	Maceration (water)	*In vivo* (Mice) *In vitro* (C2C12 and HepG2 cells)	-	-	-	-	Regulates glycemia, insulinemia, cholesterol profile, and HbA1c levels in mice. Activates PPARγ-dependent luciferase activity and AMPK in C2C12 cells. Inhibits TNF-α-stimulated IKKβ/NF-κB signaling and prevents ER stress in HepG2 cells.	Yeo et al. 2011
Phellodendron cortex and *Aralia cortex*	-	Maceration (water)	*In vivo* (Rats)	250 mg/kg, 3 times/week for 8 weeks	ip	8 weeks	-	Increases renal TBARS and carbonylated protein levels, and normalises GSH/GSSG ratio.	Lee et al. 2000
Coptidis Rhizoma, Salviae Miltiorrhizae Radix, and *Cinnamomi Cortex*	-	Maceration (water)	*In vivo* (Mice)	500 mg/kg/day	*Oral*	4 weeks	Metformin (500 mg/kg)	Reduces the calorie intakes in HFD mice and normalises glycemia, insulinemia, lipid profile and liver markers.	Jung et al. 2021
Ligularia fischeri and *Momordica charantia*	Leaves, and fruits, respectively	Maceration (ethanol)	*In vivo* (Mice) *In vitro* (3T3-L1 and C2C12 cells)	50-200 mg/kg/day 6.25-100 g/ml	*Oral*	4 weeks	Acarbose (6.25-100 g/ml)	The co-administration of both plants promotes adipocyte differentiation in 3T3-L1 cells, improves glucose uptake and insulin metabolism in C2C12 cells, and shows an antidiabetic effect in mice.	Baek et al. 2018
Chrysanthemum coronarium, *Dioscorea batatas*, *Morus alba* and *Citrus unshiu*	Leaves, roots, leaves and Pericarpium, respectively	Decoction (water)	*In vivo* (Rats)	100 mg/kg/ day	*Oral*	7 days	Glibenclamide (0.2 g/kg)	Reduction in blood glucose, GOT, GPT, and LDH levels.	Kim et al. 2006
Angelica gigas, Cnidium officinale, and *Paeonia japonica*	Roots, rhizomes and roots, respectively	Decoction (water)	*In vivo* (Mice)	100 mg/kg/ day	*Oral*	4 weeks	-	Improves blood glucose and plasma insulin levels.	Kim et al. 2014
Oat, sorghum, adzuki bean, finger millet, and proso millet	-	-	*In vivo* (Rats)	500 mg/kg/day	*Oral*	6 weeks	Metformin (200 mg/kg)	Improvement in fasting blood glucose level and insulin immunoreactivities.	Yang et al. 2023
Aralia elata, Acanthopanacis cortex and *Ulmus davidiana*	-	Maceration (water)	*In vivo* (Rats)	11.42 g/kg diet	*Oral*	7 weeks	-	Improvement in liver markers, blood glucose and insulin levels	Kyong-Hee et al. 2004
Alnus hirsuta, *Rosa davurica*, *Acanthopanax senticosus* and *Panax schinseng*	-	-	*In vivo* (Rats)	-	*Oral*	6 weeks	-	Decreases BGL and TG levels, and improves the pancreas ultrastructure of diabetic rats.	Hu et al. 2013
Sasa borealis and white lotus roots and leaves	Roots and leaves	Maceration (ethanol)	*In vitro* (3T3-L1 and Min6 cells)	-	-	-	-	Promotes glucose uptake and insulin sensitivity, and prevents TG synthesis.	Byoung-Seob et al. 2006

Abbreviations. AMPK: adenosine 5'-monophosphate (AMP)-activated protein kinase; BGL: blood glucose level; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GSH-Px: glutathione peroxidase; GSSG: oxidized glutathione; HbA1c: glycosylated hemoglobin; HFD: high fat diet; IKKβ: inhibitory kappa B kinase beta; LDH: locate dehydronase; NF-κB: nuclear factor-Kb; PPARγ: peroxisome proliferator activated receptor gamma; TBARS: thiobarbituric acid reactive substances; TG: triglyceride; TNF-α: tumor necrosis factor alpha.

Supplementary Table 3. Preclinical evidence of some antidiabetic phytocompounds isolated from South Korean plants

Bioactive compounds	Source	Experimental model	Therapeutic doses	Results	References
Phellopterin, Imperatorin, Bergapten	*Angelica dahurica*	*In vivo* (Mice) *In vitro* (3T3-L1 cells)	0.5, 1 and 2 mg/kg 12.5, 25, 50 and 100 mg/ml	Normalizes glycemia, TC and TG levels in rats. Regulates the mRNA expression of PPARγ in 3T3-L1 cells.	Han et al. 2018a
Protopanaxadiol and Protopanaxatriol	*Panax ginseng*	*In vivo* (Mice)	50 and 100 mg/kg/day	Decreases FBG and improves insulin resistance, lipid profile, antioxidant markers, and proinflammatory cytokines	Deng et al. 2017
GS-E3D	*Panax ginseng*	*In vivo* (Rats)	25, 50 and 100 mg/kg/day	Decreases the symptoms of diabetic nephropathy such as the reduction of urinary levels of albumin, 8-OHdG, and AGEs.	Kim et al. 2017c
Cucurbitane Triterpenoids (C1-C4)	*Momordica Charantia*	*In vitro* (C_2C_{12} cells) *In vivo* (Mice)	-	Regulates IRS-1 in C_2C_{12} cells. Normalizes blood glucose level and improves glycogen storage in diabetic mice.	Han et al. 2018b
Curcumin	*Curcuma longa*	*In vivo* (Mice)	0.02% of diet	Improves insulin resistance and upregulates IGF-1R, p-Akt, p-S6K expressions.	Kim et al. 2018b
Erianin	*Dendrobium chrysotoxum*	*In vitro* (RF/6A cells)	0-50 nM	Prevents retinopathy and peripheral neuropathy.	Yu, et al. 2016
Hwanggeumchal sorghum, Chal sorghum, and Heuin sorghum	*Sorghum bicolor*	*In vivo* (Rats)	100 and 250 mg/kg	Hwanggeumchal sorghum improves the serum insulin level, exhibits the highest hypoglycemic effect, and significantly reduces blood glucose, TC, TG, urea, uric acid, creatinine, AST, and ALT levels.	Chung et al. 2011
Fisetin	*Cotinus coggygria*	*In vivo* (Rats)	10 mg/kg	Improves glucose consumption, regulates insulin metabolism and inhibits gluconeogenesis.	Maher et al. 2011; Kim et al. 2012b; Prasath et al. 2014
Fustin, gallic acid, and 3′,4′,7-trihydroxyflavone	*Rhus verniciflua*	*In vitro*	10 and 50 µg/ml	Potent antioxidant and α-glucosidase inhibitory activities.	Kim et al. 2010

Abbreviations. 8-OHdG: 8-hydroxy-2'-deoxyguanosine; AGEs: advanced glycation end-products; ALT: alanine amino transferase; AST: aspartate amino transferase; FBG: fasting blood glucose; PPARγ: peroxisome proliferator-activated receptors γ; TC: total cholesterol; TG: triglyceride.

Supplementary Table 4. Clinical studies of some South Korean antidiabetic plants.

Scientific Name	Form	Dose	Duration of follow-up	Participants	Age (Years)	Primary purpose	Outcomes	Reference
Aloe vera	Capsules	700 mg/cap (2 after breakfast and 2 after dinner)	8 weeks	136	-	Investigation of the therapeutic effects of Aloe QDM complex on obese patients with early DM.	Reduction in BW and body fat mass.	Choi et al. 2013
Diospyros kaki	Tablets	500 mg/tab (2 g/day)	8 weeks	68	20-75	Discovery of molecular mechanisms that could justify the effectiveness of *D. kaki* against diabetes.	Improves the salivary proteomic profile in prediabetic patients.	Khan et al. 2017
Momordica charantia	-	-	12 weeks	76	18-80	Effects on diabetes-related parameters in prediabetic patients.	Significant reduction in postprandial glycemia and glucagon level of prediabetic patients.	Kim et al. 2022b
Momordica charantia	Capsules	Twice a day (total 2380 mg daily)	12 weeks	96	20-70	Effects in type 2 diabetic patients.	Reduction in FBG and HbA1c levels.	Kim et al. 2020
Momordica charantia	Capsules	300 mg/cap (2cap/day)	12 weeks	41	-	Effects on patients with T2DM who do not respond to modern therapy.	Normalization of HbA1C, FPG, BMI and BW after 3 months of treatment.	Yang 2022

Supplementary Table 4 continued

Momordica charantia	Capsules	300 mg/cap (2cap/day)	3 months	142	>20	Antidiabetic effect with a specific sequence of 19 amino acids (mcIRBP-19) on diabetic subjects.	Regulation of FPG, HbA1C, insulin, and TG levels.	Hsu 2020
Momordica charantia	Tablets	1-1.5g tab	8 weeks	75	40-60	Antidiabetic effects in type 2 diabetic patients.	Regulation of FPG, PPG, HbA1c, insulin, TC, BMI and MDA levels.	Kumar 2018
Momordica charantia	Capsules	500 mg/cap (2cap/day)	3 months	24	35-60	Effects on insulin metabolism in type 2 diabetic patients.	No significant changes in BW, BMI, WC, and A1C levels, but a reduction in serum glucose level.	Cortez-Navarrete 2018
Momordica charantia	Capsules	1000 mg/cap and 4cap/day	10 weeks	95	30-70	Comparative effect with glibenclamide in type 2 diabetic patients.	No significant changes in A1C (%), but significant improvement in FPG, 2-hour OGTT, and plasma sialic acid.	Rahman 2015
Momordica charantia	Capsules	500 mg/cap and 4cap/day	4 weeks	129	35-70	Comparative effects with metformin in type 2 diabetic subjects.	Improvement in FPG, 2-hour OGTT.	Fuangchana et al. 2011
Momordica charantia	-	-	-	423	>18	Effects on glucose level and lipid profile in subjects with T2DM.	Reduction in FBG, PPG, HbA1c, and TC levels.	Zhang et al. 2024
Panax ginseng	-	1, 3, and 6 g (single dose)	4 days	30	18-75	Antidiabetic and cardioprotective effects in subjects with T2DM.	Nontoxic, and did not affect PPG and glycemic parameters.	Shishtar et al. 2014
Panax ginseng	Tablets	500 mg/tab (3 g/day)	24 weeks	61	19-75	Changes in current perception threshold (CPT), FBG and HbA1c levels.	Improvement in CPT.	Park et al. 2020
Panax ginseng and *Panax quinquefolius*	Capsules	2.25 g/day	12 weeks	80	-	Coadministration of ginsenoside-enriched Korean and American Ginseng with the standard drugs on cardiometabolic factors in patients with T2DM.	Decreases HbA1c, TC, TG, and LDL-C.	Jovanovski et al. 2021
Sasa borealis	Leaves	2000 mg/day	6 weeks	14	>20	Determine its α-glucosidase inhibitory activity and its action on PPG level in patients after meal.	Anti-α-glucosidase activity and decreases PPG.	Yun et al. 2010
Vigna nakashimae	Tablets	1 g (thrice daily)	12 weeks	18	20-70	Antidiabetic activities in diabetic subjects.	Improvement in HbA1c level.	Kim et al. 2018b
Vitis vinifera	-	150 mg/day	12 months	153	40-80	Its safety in subjects with non-proliferative diabetic retinopathy.	Improvement in total macular volume and hard exudate.	Moon et al. 2019
Daeshiho-tang, Bojungikgi-tang, Jowiseunggi-tang, and Hoechunyanggyeok-san	-	1 sachet, 3 times/day, 2 hours after meals	-	21	61-89	Action on FBG level and PPG.	Significant reduction in FBG and PP glucose levels.	Jeong et al. 2020

Abbreviations. LDL-C: low-density lipoprotein cholesterol; BMI: body mass index; CPT: current perception threshold; DM: diabetes mellitus; FBG: fasting blood glucose; FBS: fasting blood sugar; HbA1c: glycosylated hemoglobin; MDA: malondialdehyde; OGTT: oral glucose tolerance test; PPG: postprandial glucose; T2DM: Type 2 diabetes mellitus; TC: total cholesterol; TG: triglycerides.

Supplementary Table 5. Various mechanisms of action of antidiabetic plants and selected antidiabetic molecules from South Korean medicinal herbs. Numbers in parentheses correspond to the mechanisms illustrated in Figure 5. -: inhibition; +: stimulation.

Scientific Name	**-carbohydrate absorption (1)**	**+ peripheral glucose consumption (2)**	**+ PPAR (3)**	**+ insulin receptors (4)**	**+ insulin receptor sensitivity (4)**	**- oxidative stress, peroxidation or apoptosis of β-cells (5)**	**+ insulin secretion (6)**	**-gluconeogenesis /glycogenolysis (7)**	**- glucagon (8)**	**- renal fibrosis (9)**	**Not reported**	**Reference**
Acanthopanax senticosus		*			*							Soon-Dong et al. 2005; Hong et al. 2009; Kwon et al. 2016
Allium cepa	*	*					*	*				Bang et al. 2009; Vu et al. 2020
Allium sativum			*									Oh et al. 2022
Aloe vera				* *		*						Kim et al. 2009a
Anemarrhena asphodeloides					*			*				Shin et al. 2008
Angelica dahurica		*		* *								Park et al. 2016
Aralia elata				*								Kim et al. 2004; Kim et al. 2017a
Aronia melanocarpa				*	*							Jeon et al. 2018
Aster koraiensis					*					*		Sohn et al. 2010; Kim et al. 2017b
Auricularia auricula					*							Kim et al. 2007
Auricularia cornea				*	*							Fu et al. 2022
Brassica rapa		*		*			*	*				Jung et al. 2008
Camellia sinensis										*		Park et al. 2013
Capsicum frutescens						*						Islam et al. 2008
Codonopsis lanceolata				* *								Jeong et al. 2017
Cortex cinnamomi			*									Kwon et al. 2006
Daphniphyllum macropodum										*		Koo et al. 2014
Dendrobii Herba		*				*						Myung-ji and Yeoung-Ju 2019
Dendropanax morbifera		*		* *		*						An et al. 2014; Heo et al. 2018
Ecklonia cava					*	*						Kang et al. 2010

Supplementary Table 5. continued

Eucommia ulmoides						*	*				Lee et al. 2005
Euonymus alatus	*	*					*				Soo-Kyung et al. 2007; Kim et al. 2022a
Glycyrrhiza uralensis										*	Shaikh et al. 2022
Gryllus bimaculatus		*			*						Park et al. 2019
Gryllus bimaculatus		*		*	*						Ahn et al. 2020; Kim et al. 2022c
Gymnema sylvestre		*				*					Kang et al. 2012
Hordeum vulgare			*			*	*	*			Ham et al. 2021
Houttuynia cordata		*				*					Wang et al. 2018; Lee et al. 2023
Hydrangea dulcis		*					*				Kim et al. 2009b
Inonotus obliqua		*				*					Hong et al 2007; Yoo-Kyoung et al. 2009
Ixeris dentata						*					Lee et al. 2013
Jerusalem artichoke										*	Kim et al. 2021
Jerusalem artichoke		*				*					Kim et al. 2015a
Liriope platyphylla							*				Kim et al. 2012
Momordica charantia		*			*						Yang et al. 2015; Yoon et al. 2017
Morus alba	*	*					*	*			Ahn et al. 2017; Jung et al. 2019; Ahn et al. 2023
Nardostachys jatamansi							*				Song et al. 2010
Nepeta angustifolia		*				*					Huang et al. 2020a
Osteomeles schwerinae										*	Kim et al. 2016
Paeonia japonica	*	*									Yang et al. 2024
Panax ginseng		*			*	*	*		*		Jung et al. 2005; Hong et al. 2012; Kang et al. 2017; Jung et al. 2019a; Nam et al. 2019; Tran and Lee 2022

Supplementary Table 5. continued

Panax quinquefolius		*								Yoo et al. 2012
Perilla frutescens	*	*					*			Kim et al. 2018a; Choi et al. 2023
Phellinus linteus				*	*					Oh et al. 2021
Pinus densiflora							*			Min et al. 2019
Polygonum cuspidatum	*	*								Sohn et al. 2014; Zhao et al. 2017
Portulaca oleracea	*	*			*		*			Park and Han 2018; Lee et al. 2020
Psidium guajava		*				*				Oh et al. 2005
Rhus verniciflua	*	*								Jung et al. 2006; Kim et al. 2011a
Sasa borealis	*	*			*	*	*			Hwang and Han 2007; Hwang et al. 2010; Yang et al. 2010; Nam et al. 2013
Smallanthus sonchifolius		*			*		*	*		Kim et al. 2010; Oh et al. 2012; Kim and Lee 2013
Sorghum bicolor						*				Park et al. 2012
Taraxacium offinal		*				*				Cho et al. 2002
Tinospora cordifolia						*	*	*		Sharma et al. 2019
Vaccinium uliginosum		*				*				Han et al. 2012
Vaccinium myrtillus									*	Kim et al. 2015b
Vigna nakashimae	*	*				*				Yeo et al. 2011
Viscum album		*			*		*			Jung et al. 2015; Huang et al. 2020
Vitis vinifera		*								Hwang et al. 2009; Jin et al. 2013
Zingiber mioga	*	*			*	*	*			Jo et al. 2016; Lee et al. 2016
Phellopterin		*	*							Han et al. 2018a
Imperatorin		*	*							Han et al. 2018a
Bergapten		*	*							Han et al. 2018a
Protopanaxadiol		*		*	*	*				Deng et al. 2017
Protopanaxatriol		*		*	*	*				Deng et al. 2017

Supplementary Table 5. continued

Curcumin			*	*				You et al. 2013, Kim et al. 2016b; 2018b
Erianin							*	Yu, et al. 2016
GS-E3D							*	Kim et al. 2017c
Cucurbitane Triterpenoids		*		*		*		Han et al. 2018a
Hwanggeumchal sorghum		*						Chung et al. 2011
Fustin, gallic acid, 3′,4′,7-trihydroxyflavone, and fisetin	*				*			Kim et al. 2010