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Ethnobotanical and anti-diabetic properties of *Rydingia persica* (Burm.f.) Scheen & V.A.Albert: A comprehensive review

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Abstract

Rydingia persica (Burm.f.) Scheen & V.A.Albert is an endemic plant known for its use in Iranian folk medicine. The decoction made from the roots and aerial parts of *R. persica* has been traditionally utilized for its anti-diabetic properties in Iran. This study aims to highlight the ethnomedicinal, pharmacological, and anti-diabetic activities of *R. persica*. The review encompasses clinical, *in vivo*, and *in vitro* studies related to diabetes and its complications. A comprehensive literature search was conducted across various scientific databases, including PubMed, Scopus, ISI-Web of Science, and the local Iranian database IRANDOC. Relevant articles were identified using keywords "*Rydingia persica*," "*Otostegia persica*," "ShekarShafa," "Goldar/Golder," and "Gol-Khaarou," covering studies published from the inception up to 2024. Pharmacological studies on *R. persica* indicate significant anti-diabetic potential. Various extracts from the plant, especially its aerial parts, have demonstrated anti-hyperglycemic, anti-hyperlipidemic, and antioxidant effects in both *in vitro* and *in vivo* studies. Key phytochemicals, including quercetin, caffeic acid, and isorhamnetin have been identified as major contributors to these effects. The extracts of the plant have shown promising results in lowering blood glucose levels, improving insulin sensitivity, and reducing oxidative stress. Furthermore, *R. persica* has demonstrated protective effects on vital organs, including the liver and kidneys, in animal models. Despite these encouraging findings, clinical studies involving human participants remain limited. Only one trial has reported insignificant effects from a methanol extract of the leaves. Therefore, further research, particularly clinical trials, is needed to validate the therapeutic potential of *R. persica* for managing diabetes.

Keywords: Diabetes, Ethnopharmacology, Anti-diabetic, *Rydingia persica*

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1. Introduction

Diabetes mellitus, which is a metabolic disorder, occurs due to insufficient insulin or factors that obstruct insulin's effects (1). Diabetes drug classes used to manage blood glucose levels include insulin therapy and oral antidiabetic agents such as metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and thiazolidinediones. For example, biguanides (e.g., metformin) reduces hepatic glucose production and enhances insulin sensitivity. Sulfonylureas (e.g., Glibenclamide, Glipizide) stimulate pancreatic β-cells to release insulin. DPP-4 Inhibitors (e.g., Sitagliptin, Saxagliptin) inhibit the DPP-4 enzyme, prolonging incretin action to enhance insulin release and suppress glu-

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Figure 1. *Rydingia persica* (Burm.f.) Scheen & V.A.Albert.

cagon. GLP-1 Receptor Agonists (e.g., Exenatide, Liraglutide) mimic incretin to enhance insulin secretion, suppress glucagon, and slow gastric emptying. SGLT2 inhibitors (e.g., Empagliflozin) inhibit renal glucose reabsorption, promoting glucosuria. Thiazolidinediones (e.g., Pioglitazone, Rosiglitazone) improve insulin sensitivity by acting on PPAR-γ receptors in adipose and muscle tissue (2).

There exists a considerable demand for research and the development of new treatments that exhibit minimal adverse effects. Traditional medicine may provide a cost-effective approach by addressing multiple health issues while reducing side effects (3). In Persia, the plant commonly referred to as Golder is scientifically identified as *Rydingia persica* (Burm.f.) Boiss. [Syn.: *Ballota persica* (Burm.f.) Benth]. This species belongs to the Lamiaceae family, which encompasses approximately 180 genera and more than 3,500 species. The Rydingia genus comprises roughly 20 species, primarily distributed throughout Asia, particularly in Iran, Afghanistan, and Pakistan, with additional populations located in the mountainous regions of East Africa. The shrub typically attains heights of 1-2 meters, featuring stems densely coated with short glandular indumentums (4).

The leaves exhibit a suborbicular to obovate and cuneate shape, and are characterized by a prominent glandular hair indumentum containing numerous sessile oil globules. The leaf margins present crenate to dentate features with spines measuring 0.5-1 mm. The petiole may extend up to 10 mm in length, while spines, reaching lengths of up to 20 mm, are found in the axils of both lower and upper leaves. The inflorescences are composed of few-flowered and remote verticillasters. The bracts are spiny and horizontally spreading, measuring 10 mm in length. The densely pilose calyx is distinctly 10-nerved or ribbed, featuring an 8 mm tube; the limb expands to a diameter of 10 mm and possesses a straw-colored, membranous, irregularly lobed, and toothed structure. The white corolla attains a length of 20 mm, with the tube corresponding to the length of the calyx tube; the upper lip is 10 mm long, falcate, and densely villous. The stamens may either be included or exerted. The nutlets are obovoid, measuring 2-5 mm and rounded at the apex, and typically contain a single maturing oil globule (Figure 1). The plant is known to harbor a diverse array of bioactive compounds, primarily flavonoids, terpenoids, steroids, and tannins. Significant flavonoids and phenolic compounds include quercetin, kaempferol, and maureen, alongside other isolated compounds such as β-sitosterol, and caffeic acid. The essential oil of its flowers is rich in alpha-pinene and cubenol, whereas the essential oil derived from the fruit comprises hexadecanoic acid. Notably, the essential oil from the aerial parts features dillapiole and trans-verbenol as key constituents (4, 5).

This study aims to investigate the pharmacological effects of *R. persica*, particularly its traditional use in folk medicine for diabetes and related metabolic disorders. By exploring

its active compounds and their mechanisms of action, we seek to understand the potential benefits of this plant for managing blood glucose levels and improving insulin sensitivity. Our research endeavors to provide scientific validation for the traditional use of *R. persica* in treating diabetes, offering a possible alternative with minimal adverse effects.

2. Material and Methods

The clinical, *in vivo*, and *in vitro* studies on diabetes and its relevant complications, including nephropathy, retinopathy, neuropathy, metabolic syndrome, cardiovascular disease, obesity, hypercholesterolemia, and hypertriglyceridemia, were included. The literature survey was conducted using scientific databases, including PubMed, Scopus, ISI-Web of Science, and the local Persian source of IRANDOC. The keywords of "*Rydingia persica*," "*Otostegia persica*," "ShekarShafa, "Goldar/Golder," and "Gol-Khaarou" were used to find the relevant articles from the inception up to 2024.

3. 3. Results and discussion

3.1. Ethnomedicinal and traditional uses

Rydingia persica, locally called ShekarShafa, Goldar/Golder, or Gol-Khaarou, is extensively distributed in the south and southeast of Iran (5, 6). Different parts of this plant have been used as medications for various ailments among ethnic people in Fars, Kerman, Hormozgan, and Sistan-Baluchestan provinces (Table 1). The flower is widely applied as an additive to buttermilk, meat, and yogurt (4,7). Furthermore, the aerial parts are used as analgesic remedies for arthritis and toothache (4, 7). The decoction and cataplasm of *R. persica* are traditionally indicated for cardiac distress, hypertension, hyperlipidemia, headache, gastric discomfort, and addiction treatment. Also, the decoction is used as an antispasmodic, antimalaria, antihistaminic, sedative, carminative, antipyretic, and laxative remedy (4, 8). On the other hand, *R. persica* has widespread antidiabetic effects among ethnic people in Iran, especially in Kerman and Sistan-Baluchestan provinces. Indeed, the Persian traditional name "ShekarShafa" is made up of two smaller parts including "Shekar" which means sugar in Persian, and Shafa which means curing. This traditional name represents the firm

Table 1. Ethnomedicinal importance of *R. persica.*

Part used	Dosage form	Local traditional indications	References
Aerial part	Powder	Analgesic in arthritis and toothache	(4, 7)
	Decoction	Antihistaminic, antispasmodic, antimalarial and anti-arthritis	(4, 9)
	Decoction and infusion	Diabetes, headache, stomachache, toothache, rheumatoid arthritis, hyperlipidemia, cardiac distress, regulating blood pressure, reducing palpitation, headache, gastric discomfort, cough, morphine withdrawal, parasite repellent and as an analgesic, antipyretic, laxative, and carminative	(5)
Flower and leaf	Decoction and cataplasm	Diabetes, cardiac distress, hypertension, reducing palpitation, hyperlipidemia, rheumatism, cold, headache, gastric discomfort, addiction treatment. antispasmodic, antimalarial, antihistaminic, sedative, carminative, antipyretic, and laxative	(8)
Flower	Powder	Additive to buttermilk, meat, and yoghurt	(4, 7, 11)
Fruit	Decoction	Diabetes	(12)
Root	Decoction	Diabetes, Jaundice	(13)

ethnic belief in the antidiabetic properties of this plant (4, 8-10).

3.2. Pharmacological activities

Several evidence-based studies confirm the ethnomedicinal use of *R. persica* for the management of diabetes among local people in Iran.

3.2.1. Anti-hyperglycemic effects

Hyperglycemia (FBS≥ 7.0 mmol/L, or BGL≥ 11.1 mmol/L) is a physiological abnormal characteristic in diabetic patients (14). Several studies have addressed the potential anti-hyperglycemic effects of *R. persica* (Table 2,3,4). The ethanol extract of its leaves has shown *in vitro* α–amylase and α-glucosidase inhibitory activities (15,16). Besides, the dichloromethane fraction of the hydro-alcoholic extract obtained from flowering aerial parts has shown antiglycation activity on bovine serum albumin (17). On the other hand, the phytochemicals of the herb can play an important role in hypoglycemic effects. So, *in vitro* studies have shown the ameliorating effects of quercetin on glucose uptake via the AMPK pathway and upregulation of insulin secretion (18, 19). Furthermore, docking analysis has recognized morin as a non-competitive inhibitor for PTP1B, which activates and sensitizes the insulin receptor (20).

According to *in vivo* studies, the aqueous extract of R. persica aerial part has lowering effects on FBS, mass, and also number of β- cells in pancreases of male Wistar rats (21). Hydro-alcoholic extract of the aerial part has shown strong antidiabetogenic effects via decreasing BGL, BIL, and hypertrophic changes in the remaining β-cells of pancreatic islets in STZ-induced diabetic rats (22). Methanol extract of aerial part decreased blood glucose, urea, and creatinine serum levels in STZ-Induced diabetic rats (23). Moreover, the ethanol extract of the aerial part exhibited decreasing effects on the serum glucose levels in STZ-induced diabetic rats (24, 25). Apigenin, one of the bioactive phytochemicals of R. persica, resulted in biochemical modulations improving diabetes and protecting effects against damage in the vital organs of STZ-Induced diabetic rats (26). On the other hand, caffeic acid has reactions with several regulating targets in the glucose metabolism pathways. It increases the AMPK level in the liver, skeletal muscles, and adipocytes, as well as GLUT4 expression and translocation in skeleton muscles in order to provoke glucose utilization. Furthermore, it suppresses the glucose output of the liver (27). Isorhamnetin has shown ameliorating effects on insulin resistance in diabetic rats (28). Besides, quercetin has attenuated endothelial dysfunction during elevating insulin resistance and asymmetrical dimethylarginine levels in STZ-induced diabetic rats (29). Also, it increased the normalization of glycemia levels and liver glycogen content, along with improving the activities of glucose-6-phosphatase and hexokinase in diabetic rats (30,31). In addition, quercetin has crucial roles in regulating insulin metabolism, islet protection, and improving intraperitoneal glucose tolerance (19, 32). Despite all the above-mentioned *in vitro*/ *in vivo* studies and the expanded ethnomedicinal application of *R. persica* for anti-diabetic properties, a double-blind clinical trial conducted on 56 diabetic patients showed no significant therapeutic effect of methanol extract obtained from the leaves after 3 months (33).

3.2.2. Antioxidant and anti-inflammatory effects

A relationship exists between oxidative stress and hyperglycemia. The onset of type 2 DM concerns the suppressive effects on antioxidant activity due to the increased Nrf2 expression. Free radical production associated with hyperglycemia damages the cell membrane, resulting in β- cell dysfunction. Therefore, antioxidants can protect the body against reactive oxygen, so they are important antidiabetic agents (14). In this context, the

hydroalcoholic extract, methanol extract, and essential oil obtained from the aerial parts of *R. persica* have shown antioxidant properties via in vitro studies (34-36). Also, the alcoholic extract and hydroalcoholic extract of aerial parts (37-39), as well as the phytochemicals such as caffeic acid (40), linalool (41), and quercetin have shown potential antioxidant properties (42). The methanol extract of the aerial part has shown a lowering effect on MDA while increasing GSH levels in the liver of diabetic rats (37, 43). In addition, apigenin has increased GSH and SOD activities and suppressed MDA, oxidative stress, and apoptotic cascade synthase pathways in STZ-induced diabetic rats (44). Both caffeic acid and quercetin have shown antioxidant properties via increasing GSH, catalase, and SOD activities in vivo (31,45). Quercetin reduced the level of advanced oxidation protein products in oxidative stress conditions (46). It attenuated the oxidative stress in the brains of STZ-induced diabetic rats (42). In addition, quercetin showed decreasing effects on plasma nitric oxide, liver SOD, and reduced-GSH activities in STZ-induced diabetic rats (29).

In vitro studies on quercetin administered to human umbilical vein endothelial cells showed its ability to decrease the release of pro-inflammatory factors (47). Quercetin decreased TNF-α and CRP and inhibited the aortic NF-κB in an in vivo study (48). It also showed alleviating effects in TNF-α and IL-6 levels in diabetic rats (32). Furthermore, the reducing effects of quercetin on eosinophil and IL-4 levels, its increasing effects on interferon-gamma in blood, and the inhibitory effects on inflammatory cell infiltration were observed in an *in vivo* study (49).

3.2.3. Other protective effects

Diabetes mellitus (DM) is associated with complications in carbohydrate metabolism. For instance, plasma lipid levels are higher in patients with DM than nondiabetics because insulin has regulatory effects on the intermediary lipid metabolism. Furthermore, hyperlipidemia, as a metabolic complica-

Table 2. *In vitro* anti-diabetic effects of different plant parts, extracts, and phytochemicals of R. persica

Plant part/ Extract or active component	Evaluated dose/ concentration	Model	Method and Assessment tool	Result	Ref
Aerial part/ Hydro-alcoholic extract	50-250 µg/mL	HUVECs	Intra and extra-cellular hydroperoxides concentration, FRAP	- Antioxidant	(34)
	5mg/mL	xanthine & enzyme solutions in phosphate buffer	Xanthine oxidase activity	- Xanthine oxidase inhibitory	(61)
	100,200,400 mg/kg	Chick chorioallantoic membrane	Number and length of vessels by using Image J. software.	-↑ VEGFR expression - Angiogenic effect	(59)
Aerial part/ Essential oil	10 µl/ml	In vitro assay	DPPH, ammonium thiocyanate method	- Antioxidant	(35)
Aerial part/ Methanol extracts	1000 µl /ml	In vitro assay	Ammonium thiocyanate method, ß-carotene bleaching method.	- Antioxidant	(36)
Flowering aerial part/ Different fractions of hydro-alcoholic extract	20 µl	BSA	Fluorescence spectrum based on AGEs with Spectrofluorimeter RF-1500	The CH2Cl2 fraction □ Anti-glycation activity	(17)

Continued Table 2.

Leaf/ Ethanol and aqueous extracts	5 mg/mL	In vitro assay	α -Amylase activity by spectrophotometer	- α–amylase Inhibitory (Ethanol extract showed more effectivity)	(15)
Leaf/ Ethanol extract and its fractions; chloroform, ethyl acetate & n-butanol solutions	0.15-40 mg/ml	In vitro assay	α-Glucosidase activity by chromogenic method	- α-Glucosidase inhibitory potential (IC50): chloroform fraction> butanol fraction> ethyl acetate fraction	(16)
Herb/ dichloromethane & methanol extracts	0.5 mg/ml	Carcinoma cell line of oral squamous cell	MTT test	- Anticancer effects	(62)
Quercetin	10, 100 µM	L6 myotubes	Mitochondrial membrane potential, intracellular calcium levels, quantitative Real Time PCR, Western Blotting & Immunofluorescence Assay	- Ameliorating glucose uptake via AMPK pathway	(18)
	2.5, 5, 10, 20 µM	HUVECs and Jurkat cells	Membrane fluidity and transmembrane potential	- Positive effects on cell membranes-↓Release of pro-inflammatory factors	(47)
	1 µM	PBMC	Membrane incorporated TMA-DPH fluorescence anisotropy & fluidity, by using fluorescence polarization	- ↑ Membrane fluidity	(63)
	0, 0.001, 0.01, 0.1, 1, 10, 100 µM	MIN-6 Cell line	Insulin secretion ERK1/2 & phospho-ERK1/2 as well as Activation of caspases & expression of Bcl-2 and BAX by using Western blot analysis, Intracellular Ca2+ by fluo-3 AM MTT assay, flow cytometry analysis, JC-1 probe	- ↑ Insulin secretion (quercetin level> 10 µM)- Involvement of Intracellular Ca2+ & ERK1/2 in the signaling pathway of quercetin-induced insulin secretion- ↓Palmitic acid-induced cell apoptosis by ↓activation of caspase-3, -9 & -12 □ ↑Bcl-2/BAX & reversing the impaired mitochondrial membrane potential	(19)
	25 µM	HepG2 cells	m-TOR and Nrf-2 expression by quantitative real-time PCR	- ↓ m-TOR & Nrf-2 expression - ↓ Oxidative stress caused by hyperglycemia□ It may modulate some carcinogenic signaling pathways	(64)

Bovine serum albumin (BSA); Extracellular regulated kinases (ERK); Ferric reducing antioxidant power (FRAP); Human umbilical vein endothelial cells (HUVECs); Peripheral blood mononuclear cells (PBMC); Thiazolyl blue tetrazolium bromide (MTT)

tion arising from DM, exacerbates metabolic anomalies and increases the risk of cardiovascular disorders (14). The lipid-lowering effects of methanol shoot extract, hydroalcoholic leaf extract, and aqueous root extract of *R. persica* have been demonstrated in several *in vivo* studies (13,37,50-52). Also, caffeic acid modulated the lipid profile of STZ-Induced gestational diabetes mellitus in pregnant rats (53). On the other hand, hydroalcoholic leaf extract has shown anti-sclerotic effects in hypercholesterolemic male Wistar rats (54).

According to epidemiologic studies, T2DM is associated with increased inflammatory biomarkers, and insulin resistance can occur by inflammatory response. There-

Table 3. *In vivo* anti-diabetic effects of different plant parts, extracts, and phytochemicals of *R. persica.*

Plant part / Extract	Evaluated dose (mg/ kg)	Model	Method and Assessment tool	Result	Ref.
Aerial part/ Aqueous extract	400	Male Wistar rat	FBS, insulin, TG, total cholesterol, HDL, light microscopy, histopathology effects	- ↓ FBS, TG - ↓ Mass & number of β- cells of pancreases	(21)
Aerial part/ Hydro-alcoholic extract	100, 200, 400	Male Wistar rat	The intra & extra-cellular hydroperoxides concentration, FRAP, tail-cuff method	- Antihypertensive & antioxidant effects -↓ Plasma H2O2 concentration -↑ Plasma FRAP levels - Preventing ↓ body weight related to dexamethasone administration	(39)
	500	STZ-Induced diabetic rat	BGL & BIL, Hypertrophic changes	-Strong antidiabetogenic effect -↓ Hypertrophic changes in the remaining beta cells in pancreatic islets -↓ BGL & BIL	(22)
Aerial part/ Methanol extract	100, 200, 300	STZ-Induced diabetic rat	BGL, urea, and creatinine serum levels using spectrophotometry technique	-↓ Glucose & creatinine, -↓ Urea & creatinine serum levels in various doses, after 3 days, but ↑urea at 200 mg/kg after 6 days - Improved renal function to some extent	(65)
			BGL & blood lipid levels	- ↓ BGL, cholesterol & TG	(50)
			BGL by spectrophotometry technique, Insulin secretion by ElISA, investigating dissected pancreas through H&E method	- ↓ Glucose - ↑ Insulin (100 mg/kg) - ↑ Number of Langerhans islets (100, 200, and 300 mg/kg) - ↑ Islet diameter (200, and 300 mg/kg)	(23)
			FBS, BGL, cholesterol & TG	- ↓ BGL, cholesterol & TG	(50)
	200, 300, 400	CCl4- induced acute hepatotoxicity in male rats	using biochemical parameters (plasma and liver tissue malondialdehyde (MDA), transaminase enzyme levels in plasma [aspartate transaminase (AST), alanine aminotransferase (ALT)] and liver glutathione (GSH) levels).	- Antioxidant & hepatoprotective activities (300 mg/Kg) - ↓ lipid peroxidation, MDA level - ↑ GSH	(37)
		STZ-Induced diabetic rat	BGL, BIL, MDA& GSH levels	- ↓ BGL (300 mg/kg) - ↓ MDA - ↑ BIL, glucose-induced insulin secretion in C187 β-cells, GSH levels in the liver	(43)
	100	Rat	Formalin test, carrageenan-induced paw edema assay	- Anti-nociceptive & anti-inflammatory	(66)
Aerial part/ Ethanol extract	300	Male Wistar rat	Catalase activity; Superoxide dismutase activity by Nitro blue tetrazolium; Non-protein sulfhydryl by the Ellman's reagent	- Antioxidant - Less declining trends in renal tissue catalase, superoxide dismutase activity & glutathione level	(38)

Continued Table 3.

	200, 300, and 450	STZ-induced diabetic rat	Serum glucose level, Histomorphometric study on left femoral & tibio-fibular bones, Ash weight of L4 vertebrate	- ↓Serum glucose levels (300 mg/kg) - Reversion of epiphyseal & metaphyseal trabecular thickness & epiphyseal bone area/ tissue (200 mg/kg) - ↓ Ash weight of L4 vertebrate (300, 450 mg/kg)	(24)
		Diabetic male Wistar rat	Fasting BGL, Histomorphometric study, Determination of ash weight	- Reversion of hyperglycemia (300 mg/kg) - ↑ Alkaline phosphatase activity - Reversion of epiphyseal & metaphyseal trabecular thickness & epiphyseal bone area/ tissue (200 mg/kg) - ↑ Marrow area (450 mg/kg) - ↓ Ash weight of L4 vertebrate (300, 450 mg/kg) - Ameliorating bone loss	(25)
	200, 350, 500	STZ-Induced Diabetic rat	BGL	- ↓BGL	(67), (68)
	40, 80, and 120	Adult male Wistar rat	AST, ALT, ALP, TB, ALB, TP, MDA, histomorphological changes	- ↓Enzyme markers, bilirubin levels& MDA - ↑TP and ALB - Hepatoprotective effect (80, 120 mg/kg)	(58)
Aerial part/ Powder	300	Male Wistar rats (diabetic or non-diabetic)	Renal functional and biochemical markers (MDA, MPO, NO, SOD, CAT)	- Ischemia/Reperfusion induced renal damage - Protecting the renal injury from ischemia-reperfusion	(56)
Flowering aerial part/ Aqueous infusion and its fractions	100–400 (i.p.)	STZ-Induced diabetic NMRI mice	BGL, DPPH	- Antidiabetic	(69)
Flowering aerial parts (methanol extract)	100, 200, 400, 800	Pentylenetetrazole-induced convulsion in Albino mice	Incidence of convulsion	- Anticonvulsant	(70)
Herb/ hydroalcoholic extract	250, 500	Male Wistar rats	Serum creatinine, urea & MDA, Histopathological study	- Attenuated elevation in the serum creatinine, urea & MDA (500 mg/kg) - Improved creatinine clearance & the proportion of weight kidneys to body weight - Ameliorating nephrotoxicity - Antioxidant	(57)
Leaf/ Hydroalcoholic extract	25	Hypercholesterolemic male Wistar rat	ABC A1 gene expression by Real-Time PCR in leukocytes, serum lipids by photometric method.	- Anti-sclerotic -↑ ABC A1 gene expression	(54)
		Male Wistar rats	LDL, TC, MDA & ROS	- Improvement of vascular structure & prevention from the plaque formation by antioxidant activity - ↑ HDL- ↓ LDL, TC, TG, MDA & ROS- ↓ Systolic, diastolic, mean arterial & pulse pressure	(54)

Continued Table 3.

Root/ Aqueous extract	200, 300, 400	Male Wistar rats (hyperlipidemic diabetic type I rats)	Serum total cholesterol, TG, LDL-C and HDL-C	- ↓ Serum total cholesterol, TG, LDL & HDL	(13)
		Alloxan-Induced diabetic rat	BGL, HDL, ALT, & TG	- ↓ BGL, HDL ALT & TG	(52)
Apigenin	10, 20, 40	STZ-Induced diabetic rat	Morris water maze test, MDA, SOD, GSH, cNOS, iNOS, caspase-3 & caspase-9	- ↑ Body weight, SOD activity & GSH - ↓ BGL, MDA- Improving the cognitive function - Exhibition of cNOS, iNOS & caspase-3/9 in the cerebral cortex and hippocampus - Suppression of oxidative stress, nitric oxide & apoptotic cascades synthase pathways	(44)
	Apigenin dissolved in water 0.1% v/v in Dimethyl Sulfoxide (i.p.)	STZ-Induced diabetic rat	GLUT4 & CD38 protein expression patterns, histopathological alterations in liver, kidneys & pancreas	- Biochemical modulation, improvement of diabetes & protecting damages of the vital organs	(26)
Caffeic acid	various concentration	STZ-Induced estational diabetes mellitus in female pregnant rat	The rats, fetus & placental weight, BGL, serum, lipids, antioxidant, cytokines and C-peptide	- Modulation of BGL, lipid profile & antioxidant parameters - ↑ BIL, hepatic glycogen, antioxidant enzymes in the liver & pancreas tissue	(53)
	50	Alloxan-Induced diabetic mice	Body weight & survival, FBS, serum lipids, atherogenic indice & oxidative damage in blood, liver & kidney tissue	- Antioxidant & protective effect on liver & kidney - Hypoglycemic & hypolipidemic effect - High protection against atherogenic outcomes	(40)
	25, 35	STZ-Induced diabetic rat	FBS. BIL using ELISA, lipid profile, determining the activities of SOD & catalase, and GSH levels, Histopathological analysis	- ↑ BIL, GSH & activities of CAT & SOD - ↓ BGL. Protective effects	(45)
Isorhamnetin	10, 20	STZ /high fat diet-induced type 2 diabetes using Wistar rat	Molecular analysis, immunofluorescence, histopathological examination	- Regulation of insulin signaling pathway - ↓ m-TOR, IGF1-R & LncRNA-RP11-773H22.4 - ↑ Expression of AKT2 mRNA, miR-1, & miR-3163 in skeletal muscle & adipose tissue - Ameliorating insulin resistance	(28)
Quercetin	15 (i.p.)	STZ-induced diabetic Male albino rat	SOD, GSH, plasma nitric oxide, asymmetrical dimethylarginine	- Atenuating endothelial dysfunction - ↑ Insulin resistance, asymmetrical dimethylarginine levels - ↓ plasma nitric oxide, liver SOD & reduced-GSH activities	(29)
		Diabetic rats	MDA, NADPH oxidase activity	- ↓ MDA & NADPH oxidase activity - ↑ Antioxidant activities - ↓ Sodium & water excretion via urine & plasma creatinine - Attenuation of renal dysfunction	(71)
	25 (i.p.)	STZ-induced diabetic rat	Histological assessment	- Protective effects against diabetic heart damage	(72)

Continued Table 3.

10	Alloxan-Induced diabetic rats	Determination of intestinal transit of semisolid barium sulphate meal & plasma levels of orally & intravenously administered pioglitazone, erythromycin N-demethylase assay	- Preventing the diabetes-induced GI dysfunction- No effect on the bioavailability of pioglitazone in diabetic rats	(60)
10, 30	Alloxan-Induced diabetic mice with allergic asthma	Nasal hyperresponsiveness, Bronchoalveolar lavage fluid,	- ↓ Eosinophils & interleukin-4 - ↑ Interferon-gamma in blood & BALF - ↓ Allergic airway inflammation by inhibiting inflammatory cell infiltration and mucous cell metaplasia - ↓ glucose reduction (30 mg/kg) - Immunomodulatory effect by modulating Th1/Th2 cytokine balance	(49)
10, 50	Alloxan-Induced diabetic rat	Level of glycemia & blood coagulation, liver glycogen content, serum lipids	- ↑ Normalization of glycemia level & blood coagulation, liver glycogen content - ↓ High blood serum concentrations of cholesterol & LDL	(30)
25, 50	Fructose-STZ induced diabetic rat	BGL, glycosylated hemoglobin, hepatic glycogen, plasma hemoglobin. glucose-6-phosphatase and hexokinase activities, pancreatic SOD, catalase & GSH, Molecular docking	- ↓ BGL, glycosylated hemoglobin & hepatic glycogen - ↑ Plasma hemoglobin concentration - Improving activities of glucose-6-phosphatase & hexokinase in diabetic rats - ↑ Antioxidant activity of SOD, catalase & GSH - ↓ Value for thiobarbituric acid reactive species, glycemia & damage in the liver and pancreas - A high affinity for hexokinase & catalase	(31)
30	STZ-induced diabetic rat	Biochemical parameters of oxidative & nitrosative stress, histopathological evaluations	- Attenuating the diabetic condition & restore sciatic nerves injuries: - Controlling hyperglycemia - ↓ Generation of free radicals - ↑ Antioxidant enzymes	(73)
30, 60	STZ-induced diabetic rat	Morris water maze, attentional set shifting tests, Body weight, serum glucose, serum nitrite/nitrate, vascular endothelial function, aortic superoxide anion, thiobarbituric acid reactive species, reduced GSH, SOD & CAT, mitochondrial enzyme complex, IL-6, 10, TNF-α, MPO & AChE	- Attenuating the ↓learning, memory, reversal learning, executive functioning, impairment in endothelial function & mitochondrial complex activity- Attenuating the ↑brain oxidative stress, inflammation & AChE activity.	(42)

Continued Table 3.

50	STZ-induced diabetic rat	Determination of thioredoxin-reductase, aconitase, succinate dehydrogenase activities & Insulin sensitivity	- ↑ Insulin sensitivity & activity of thioredoxin-reductase in heart mitochondria- ↓ Level of advanced oxidation protein products - Normalizing the functional state of cardiac mitochondria- Ameliorating oxidative stress- Inhibition of Ca2+-induced opening of the mitochondrial permeability transition pore - Protection against oxidative stress, mitochondrial permeability transition induction & mitochondrial dysfunction in cardiomyocytes	(46)
	STZ-induced diabetic rat & fructose-induced insulin resistance in rats	Tail blood pressure, concentration-response curves for phenylephrine, KCl in thoracic aorta rings, Non-fasting BGL, serum insulin level, insulin resistance index, TNF-α, serum CRP, (NF-κB & Histopathological examination	- Protection against diabetes-induced exaggerated vasoconstriction & reduced the elevated blood pressure- Inhibition of diabetes associated adventitial leukocyte infiltration, endothelial pyknosis & increased collagen deposition-↓ TNF-α & CRP - Inhibition of aortic NF-κB - Anti-inflammatory effect- No effect on glucose level	(48)
75	STZ-induced diabetic rat (female)	Biochemical & histopathological examination of Foetuses kidney tissue, MDA, CAT, SODGSH-peroxidase activities in the renal tissue	- Protective effect on Maternal diabetes complications including delayed fetal kidney development, renal tubular necrosis, reduced number of renal glomeruli, increased MDA level, decreased catalase, superoxide dismutase & glutathione peroxidase activities	(74)
100	STZ-induced diabetic rat	Serum MDA, GSH,TNF-α & IL-6	Effective role in regulating insulin metabolism-↓MDA levels - No significant difference in GSH levels -Alleviating TNF-α levels -↓IL-6 in diabetic rat	(32)
	STZ-induced diabetic rat	BGL, NF-κB, SIRT1 & MDA levels	-↓BGL, liver & kidney damage markers	(75)
	STZ-induced diabetic rat	BGL, BIL, blood glycated hemoglobin, maltase activity of the small intestine	- Attenuation of fasting & postprandial hyperglycemia- controlling fasting & postprandial blood glucose levels	(76)
500	Db/db mice with T2DM (BKS.Cg-m+/+Leprdb/J) and their lean wild-type control (C57BLKS/J db/+)	BGL, BIL, hepatic fat, hepatic glycogen content & histopathological studies	- Improvement of intraperitoneal glucose tolerance, BIL & hepatic TG- Excellent properties in islet protection	(19)
1500	STZ-induced diabetic mice	Biochemical parameters, Glucose-Stimulated Insulin Secretion, Western Blot Analysis, mRNA Analysis	- ↓ Iron level in the islet- ↓ GSH- Down-regulation of GPX4 & induced oxidative stress in pancreatic tissue	(77)

Acetylcholinesterase (AChE); Alanine aminotransferase (ALT); alkaline phosphatase (ALP); Albumin (ALB); Aspartate transaminase (AST); Blood glucose level (BGL); Blood insulin level (BIL); Catalase (CAT); Constitutive nitric oxide synthase (cNOS); Glutathione peroxidase 4 (GPX4); C-reactive protein (CRP); Fasting blood sugar (FBS); Ferric reducing antioxidant power (FRAP); Glutathione peroxidase 4 (GPX4); Inducible nitric oxide synthase (iNOS); Interleukin (IL); glutathione (GSH); Malondialdehyde (MDA); Myeloperoxidase-MPO; Nuclear factor kappa B (NF-κB); Streptozotocin (STZ); Superoxide dismutase (SOD); Triglycerides (TG); Total bilirubin (TB); Total protein (TP); Transforming growth factor-β 1 (TGF-β 1); Tumor necrosis factor alpha (TNF-α).

Table 4. Clinical evidences on anti-diabetic effects of different plant parts, extracts, and phytochemicals of *R. persica.*

Pharmacological Activity	Plant part / Extract	Evaluated dose/ concentration	Model/duration	Method and Assessment tool	Result	Ref.
Effect of on Blood Glucose	Leaf/ Methanol extract	300 mg capsule, three times a day	a double-blind clinical trial conducted on 56 patients with Type II Diabetes	BS test	- No significant differences were seen among the variables FBS, BS5, H1c, HDL, IDL, & TG before and after the study over 3 months	(33)
Assessments of glycemic parameters	Quercetin	Dietary intake by a validated 100-item food frequency questionnaire	14711 participants	Adjusted logistic regression models	- Protective effect in the development of Type II Diabetes	(78)
Systolic blood pressure, other cardiovascular risk factors & inflammatory biomarkers	Quercetin	500 mg capsule daily	double-blind randomized clinical trial/ 72 women	Systolic blood pressure, TNF-α, IL-6, LDL, TG, HDL, high-sensitivity CRP	- ↓ Systolic blood pressure, TNF-α & IL-6 -No changes in LDL, triglycerides TG & ratio of TG/ HDL and LDL/HDL, the mean changes in serum levels of IL-6, TNF-α, and high-sensitivity CRP	(79)

Blood sugar (BS); C-reactive protein (CRP); High-density lipoprotein (HDL); Interleukin (IL); Low-density lipoprotein (LDL); Glutathione (GSH); Triglycerides (TG); Tumor necrosis factor alpha (TNF-α).

fore, targeting the inflammatory pathways is beneficial to prevent and manage DM and the relevant complications (55). Quercetin, as an important bioactive phytochemical in *R. persica*, has shown decreasing effects on the levels of pro-inflammatory factors in human umbilical vein endothelial cells (47). Also, it has increased the activity of thioredoxin-reductase in heart mitochondria, which protects against mitochondrial dysfunction in cardiomyocytes and mitochondrial permeability transition induction in STZ-induced diabetic rats (46).

The alcoholic shoot extract of *R. persica* has improved renal function and triggered less declining trends in renal tissue catalase, glutathione, and superoxide dismutase activities in current *in vivo* studies (38). Aerial parts of the herb have shown protective effects against the renal injury associated with ischemia-reperfusion in male Wistar rats (56). Besides, the hydroalcoholic extract of the plant has demonstrated improving effects on creatinine clearance and ameliorating properties on nephrotoxicity in male Wistar rats (57). Furthermore, the plant has demonstrated hepatoprotective effects via lowering bilirubin levels and enzyme markers and increasing ALB and TP levels (58). The alcoholic shoot extract has shown hepatoprotective effects and ameliorating properties on bone loss in diabetic male Wistar rats (25, 37). Besides, the anti-apoptosis activities of the plant have been reported in recent studies (59). Moreover, apigenin has shown protective effects against vital organ damage and improving activities on cognitive function in STZ-Induced diabetic rats (26, 44). On the other hand, quercetin prevented diabetes-induced GI dysfunction in an in vivo study (60). Also, it has shown an immunomodulatory effect by modulating Th1/Th2 cytokine balance in alloxan-induced diabetic mice with allergic asthma (49). Besides, quercetin has attenuating effects on reduced learning and memory functions in STZ-induced diabetic rats (42).

4. Conclusion

Ethnic medicine offers a plethora of new candidates as alternatives to current synthetic drugs. It brings about new research opportunities in ethnopharmacology and natural medicine. This review described the in-

formation about botanical, ethnomedicinal, pharmacological, and anti-diabetic properties of *Rydingia persica* (Burm.f.) Scheen & V.A.Albert. According to Iranian folk medicine, the decoction made from aerial parts or the root has potent anti-diabetic activities. A great deal of research has been performed on the multiple biological activities of *R. persica* to discover the ethnopharmacological relevance of using this plant for the treatment and management of diabetes. Most of this research has been performed in Iran, where *R. persica* is an indigenous plant. Numerous studies reported anti-hyperglycemic, antioxidant, anti-inflammatory, and anti-hyperlipidemic effects of *R. persica*, underling the potential anti-diabetic effects of this important traditional plant. Besides, several *in vivo* and *in vitro* evidence support the anti-diabetic properties of different *R. persica* extracts. Although only a few numbers of relevant phytochemical investigations have yet been conducted, the presence of several bioactive phytochemicals (quercetin, apigenin, isorhamnetin, and caffeic acid) responsible for anti-diabetic properties have been reported in this plant. Based on the aforementioned data, there is an emergent need for complementary investigations on the chemical constituents and the anti-diabetic mechanism of action of *R. persica*. Furthermore, this review highlights the importance of scientific validation of the traditional anti-diabetic indication of *R. persica* to corroborate its potential effectivity in the clinics. Afterward, it may lead to the commercialization of potent traditional medications to treat diabetes in the future.

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Declaration of Generative AI in the Writing Process

The authors used Grammarly to assist in editing the text. They reviewed and modified the content as necessary, taking full responsibility for the final publication.

Authors' Contributions

- Author Gh.M: Conceptualization, Methodology, Data Curation, Writing - Review & Editing
- Author A.M: Conceptualization, Data Curation, Review & Editing
- Author S.Gh: Writing - Original Draft

Conflict of Interest

The authors declare that they have no conflict of interest.

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