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The Influence of *Securigera securidaca* on Diabetes Management in Animal Models: A Systematic Review

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ABSTRACT

Background & Objective: It has been reported that allopathic drugs do not have significant effects on diabetes treatment. In contemporary literature, much attention has been given to the potential use of traditional medicines, including medicinal plants, in the treatment of metabolic abnormalities. Indeed, the effect of *Securigera securidaca*, as a medicinal agent, in alleviating the complications of diabetes has received marked attention, particularly in animal models. The aim of this review is to clarify the *S.securidaca* therapeutic effects in diabetes mellitus treatment based on animal research.

Materials & Methods: PubMed, Google Scholar, and the Web of Science were searched, from inception to January 2020 to investigate the effects of *S.securidaca* on diabetes in animal models. Each article was critically rewired for its methodological quality using the CAMARADE tool.

Results: Thirteen articles were reviewed and some positive effects of *S.securidaca* were observed in alloxan and Streptozotocin-induced diabetic animals. With a closer look at the mechanisms, *S.securidaca* is comparable with current antidiabetic drugs. The results of animal trials indicated hypoglycemic effects of *S.securidaca* in animal models.

Conclusion: Remedies like *S.securidaca* could count as a treatment option for diabetic patients, alongside current antidiabetic medications, yet with fewer side-effects.

Keywords: Securidaca, Diabetes Mellitus, Hypoglycemic Agents, Herbal Medicine

Introduction

Diabetes is one of the most prevalent chronic diseases in the world. Based on the reports, about 425 million diabetic patients, between 20 -79 years of old, were identified in 2017. It has been predicted that millions of new patients will be added to this number by 2045. There are reports that about 46.1% of diabetes patients under 60 years died because of diabetes complications (1). Considering the rise in the number of patients, the increment in diabetics' mortality rate is predictable, and represents a global challenge for human health (2).

Hyperglycemia is one of the preponderant complications of diabetes that results in a number of other complications including heart attack, stroke, kidney disease, limb amputations, poor vision, and nerve damage(3). Diabetes may be treated through lifestyle adaptations (such as diet therapy and physical activity), oral medication (such as biguanides, sulfonylureas, and a-glucoside drugs inhibitors), injected drugs (such as insulin and glucagon-like peptide-1amide [GLP-1] agonists), surgical treatment, and complementary and alternative medicines (4). Currently, one of the most effective treatments for diabetes is injecting insulin and taking oral hypoglycemic medications which most probably would leave a lot of side effects(5). There is a huge dating back to herbal medicine. Also, the curiosity about their functional details raises more than before; mainly because they are most efficient, have the least side effects, and cost lower than chemical and synthetic drugs. It has been investigated that herbal medicine is the first option for the treatment of various diseases, for almost 80% of the developing countries population (6, 7).

Securigera securidaca (L.), colloquially termed, goat pea, hatchet vetch, scorpion vetch, ax, or weed seed, is a type of herb part of the Leguminosae family. It is native to Western Asia, Europe, Australia, and Iran, especially in Tehran and Khuzestan provinces (8). *Securigera*

securidaca (L.) is an annual, glabrous, 10–40 cm long herb, with wide branches in an upright form or occasionally dispersed on the ground. It has four to six slightly thick, full, and fleshy leaflet pairs. Morphologically, *Securigera securidaca* (L.) is similar to the chickpea and has light brown fruits and each of them has several red-brownish square flat seeds. Having the ability to grow in any kind of climate is one of its advantageous properties. Although this plant is usually growing near rivers, gardens, and wheat farms **(9)**.

Flavonoids, steroidal and pentacyclic triterpenoid-type saponins, cardenolides, and tannins have been found in *S. securidaca* extract through its phytochemical analysis **(10)**. Securidaca seeds have been recommended as a traditional herbal medicine for treating multiple complications by specialists in traditional medicine such as hypertension, hypercholesterolemia, hyperglycemia, wound healing, gastric reflux, malaria, and inflammation **(11, 12)**. Besides, some other advantages of it are under discussion including positive effects on seizure **(13)**, hypoglycemia, ulcers **(14)**, and also, its antioxidative, antiviral, antitumor, and anti-parasite effects are considerable **(15, 16)**.

Various studies have worked on the hypoglycemic effects of S. securidaca seeds, but some of them have not demonstrated significant impacts on the blood glucose level. This study aims to make a comprehensive review of the articles that investigated Securigera securidaca usage in the treatment of hyperglycemia in animal models.

Materials and Methods

Search strategy

We performed the present systematic review based on the "Cochrane Handbook for Systematic Reviews of Interventions" guidelines. The present study aims to review the characteristics and traits of Securigera securidaca to find out if this plant is effective for the treatment of hyperglycemia. Databases searched were PubMed, Google Scholar, and the Web of Science; from the inception until January 2020. For the systematic search, "Securigera securidaca", "diabetes", and "hyperglycemia" have been used as keywords. Only animal studies were included. Detailed characteristics of the used search strategy are presented in Table 1.

Table 1. Number of publications involving "*Securigera securidaca*" and hyperglycemia

Database	Keyword	Number of publications
PubMed	"hyperglycemia" OR hyperglycemia* OR hyperglycemic OR antihyperglycemic OR blood sugar OR blood glucose OR diabetes*OR diabetic OR antidiabetic OR diabetes mellitus OR hypoglycemia*OR hypoglycemic	798,482
	securigera securidaca OR hatchet vetch OR goa pea	22
	"hyperglycemia" OR hyperglycemia* OR hyperglycemic OR antihyperglycemic OR blood sugar OR blood glucose OR diabetes*OR diabetic OR antidiabetic OR diabetes mellitus OR hypoglycemia*OR hypoglycemic AND securigera securidaca OR hatchet vetch OR goat pea	8
Google Scholar	"blood sugar" OR "blood glucose" OR hypoglycemia OR hypoglycemic OR hyperglycemia OR diabetes OR hyperglycemic OR diabetic OR antihyperglycemic OR antidiabetic	3,390,000
	"securigera securidaca"	968
	"blood sugar" OR "blood glucose" OR hypoglycemia OR hypoglycemic OR hyperglycemia OR diabetes OR hyperglycemic OR diabetic OR antihyperglycemic OR antidiabetic AND "securigera securidaca"	431
Web of Science	"securigera securidaca"	48

Eligibility criteria and data extraction:

Inclusion criteria were pre-specified as follows: Biological function: Securigera securidaca's blood sugar reduction effects, intervention: extract from Securigera securidaca, Study design: in vivo clinical trials (with Securigera securidaca and diabetic animals), and all articles written in English and Persian. Plus, non-randomized controlled trials, human clinical trials, and studies with inappropriate design or reported data were excluded. The information we collected from the articles include the name of authors, publication date, intervention details (such as plant source, extraction procedure, sorts and number of animals, their age and weight), and eventually the main findings of the studies.

Assessment of methodological quality and data analyses

The methodological quality of the included studies was evaluated based on the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADE) checklist and the assessment tool of other systematic reviews in animal models **(17)**. The ten items consisted of: **(1)** Publication in a peer-reviewed journal; **(2)** Statement of control of temperature; **(3)** Randomization of treatment or control; **(4)** Allocation concealment; **(5)** Blinded assessment of outcome; **(6)** Avoidance of anesthetics with marked intrinsic properties; **(7)** Use of animals with diabetes; **(8)** Sample size calculation; **(9)** Statement of compliance with regulatory requirements; and **(10)** Statement regarding possible conflict of interest. Each study was given a quality scores out of a possible total of 10 points; subsequently, the group median was calculated.

Results

Study selection

Results of the primary search on 3 databases have indicated 487 related articles. 455 of them left after the elimination of duplicated studies. Screening titles and abstracts helped to remove 323 irrelevant articles. After reviewing the full text of remaining articles and eliminating 53 of them because of being a review (n=6); not meeting inclusion criteria (n=28); duplicate publication (n=19), eventually 13 studies included in the systematic review. Finally, 13 eligible studies were identified, in which ten studies were in English (10, 18-26) and 3 remaining studies were in Persian **(27-29)**. The screening process is summarized in Figure 1.

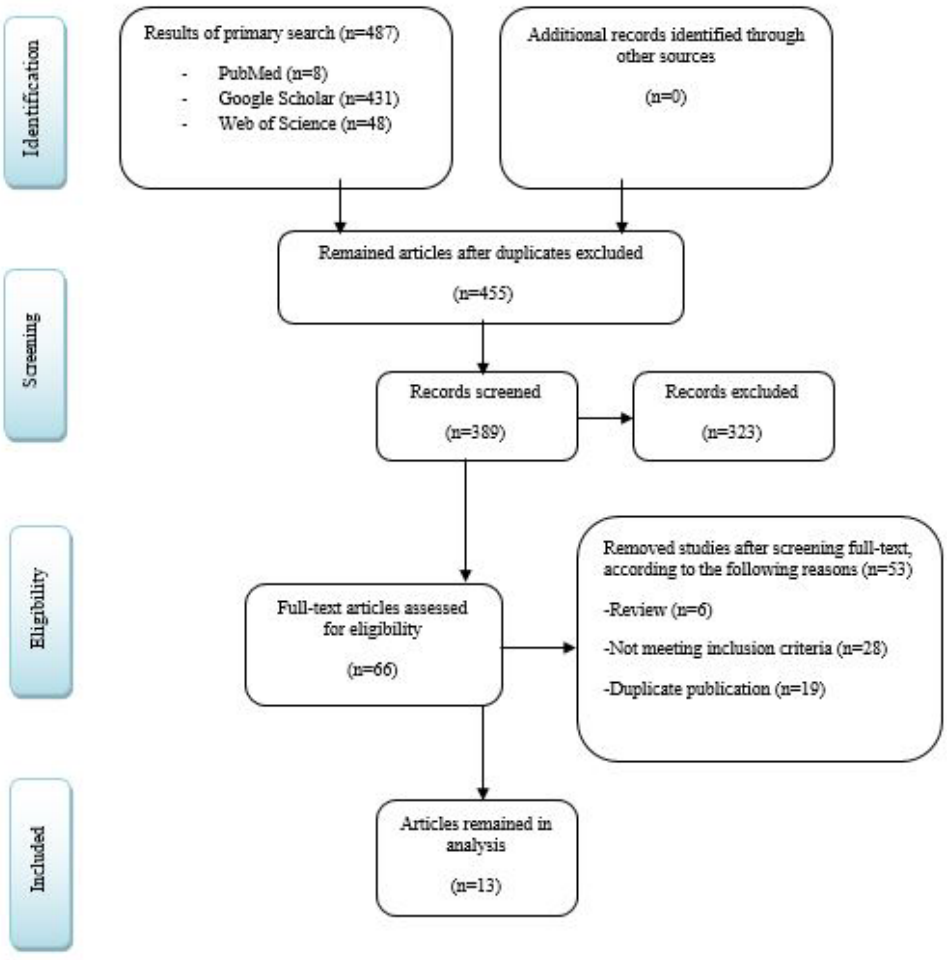

Figure 1. Flow diagram of selection of studies

Quality of included studies

CAMARADES 10-item checklist statement is the tool used in the assessment of included articles methodological quality (Table 2). Included articles quality score, ranged from 2 to 6, out of a total of 10 points, and the median was 5. Among these 13 studies, 2 studies (15.4%) scored 2 points **(22, 29)**; 3 studies (23.1%) scored 3 points **(21, 23, 25)**; 4 studies (30.8%) scored 5 points(10, 24, 26, 28) and 4 studies (30.8%) scored 6 points(18-20, 27) (Table 2). The below items give more information:

(I) All of the articles (100%) were published in peer-reviewed journals **(10, 18-29)**;

(II) Ten studies (76.9%) described control of the temperature **(10, 18-20, 24-29)**;

(III) Seven studies (53.8%) investigated random allocation to the intervention group **(10, 18-20, 24, 26, 27)**;

(IV) None of the studies described masked induction of diabetic model;

(V) None of the studies reported blinded assessment of outcome;

(VI) Three studies (23.1%) used anesthetic without significant intrinsic properties **(20, 27, 28)**;

(VII) Twelve studies (92.3%) used appropriate animal model **(10, 18-28)**;

(VIII) None of the studies declared the sample size calculation;

(IX) Ten studies (76.9%) mentioned compliance with animal welfare regulations **(10, 18-21, 23, 24, 26-28)**;

(X) Two studies (15.4%) contained statements of potential conflict of interests **(18, 19)**.

Table 2. The methodological quality according to CAMARADES 10-item checklist

Study year	A	B	C	D	E	F	G	H	I	J
Ahmadi et al. 2015	√	√	√				√		√	√
Ahmadi et al. 2016	√	√	√				√		√	√
Alizadeh et al. 2019	√	√	√			√	√		√	
Hosseinzadeh et al. 2002	√						√		√	
Ibrahim et al. 2015	√						√			
Minayan et al. 2006	√	√	√				√		√	
Porchezian et al. 2008	√	√					√			
Pouramir et al. 2011	√						√		√	
Rajaei et al. 2014	√	√	√				√		√	
Tofighi et al. 2016	√	√	√				√		√	
Tofighi et al. 2016	√	√				√	√		√	
Zahediasl et al. 2005	√	√								
Gheitasi et al. 2007	√	√	√			√	√		√	

Studies fulfilling the criteria of A: Publication in a peer-reviewed journal; B: Statement of control of temperature; C: Randomization of treatment or control; D: Allocation concealment; E: Blinded assessment of outcome; F: Avoidance of anesthetics with marked intrinsic properties; G: Use of animals with diabetes; H: Sample size calculation; I: Statement of compliance with regulatory requirements; J: Statement regarding possible conflict of interest.

Characteristics of the included studies

Highlighted in Table 3, the majority of trials utilized rats. About 24 up to 285 animals were included in these trials, and their body weight varied between 150-350 g in rats and 20-30 g in mice. Information regarding the age of the animals was not mentioned in any of the studies, except for one reporting four weeks of age **(20)**. Furthermore, all of the works used naturally-sourced *Securigera securidaca*. Table 4 shows the details of the experimental model, outcomes, and conclusion of included trials. There are generally 4 methods for inducing diabetes in animals: the first option is injecting Streptozotocin (STZ) to their intraperitoneal (i.p), the second option is perfusing a single dose of STZ into their tail vein, the third choice is injecting Alloxan monohydrate to their i.p, and the final choice is a single subcutaneous (s.c) injection of Alloxan monohydrate. About 61.5% of included studies have used STZ for inducing diabetes **(10, 18-20, 24, 26-28)**, the rest of them used alloxan **(21-23, 25)**. Nine of the thirteen studies applied current antidiabetic medications such as tolbutamide, gliclazide or glibenclamide as a positive control **(18-22, 24-26, 28)**. Other articles have not

included any positive control as a part of their experimental model (10, 23, 27, 29). Twelve of the thirteen studies reported significant affirmative response of Securigera securidaca hypoglycemic effect, whereas Minayan et al. (24) reported the ineffectiveness of Securigera securidaca seed extract in reducing blood glucose level. Four studies reported an improvement in blood lipid profile (10, 18, 19, 22). Pouramir et al. (23) indicated that animals treated with Securigera securidaca had an improvement in their insulin secretion. In another included study, a decrease in glucose and insulin resistance was observed after supplementation with hydroalcoholic extract of *Securigera securidaca* seeds (20).

Table 3. Information about the animals and plant material used in the selected studies.

	Animal				*Securigera securidaca* (SS)		
Study year	**Animal used**	**Number**	**Weight**	**Age**	**Source**	**Preparation of the extract**	**Reference**
Ahmadi et al. 2015	Rats	40	180-200g	N/I	In natura	A solvent combination of Carbon tetrachloride, 70 % ethanol-water, and dichloromethane was used to prepare extract.	(19)
Ahmadi et al. 2016	Rats	40	180-200g	N/I	In natura	A solvent combination of Carbon tetrachloride, 70 % ethanol-water, and dichloromethane was used to prepare extract.	(18)
Alizadeh et al. 2019	Rats	40	270±7g	4 weeks	In natura	SS seeds powder were drenched in 70% ethanol and concentrated under a vacuum.	(20)
Hosseinzadeh et al. 2002	Mice	352	25-30g	N/I	In natura	The powdered plants were macerated using ethanol (80%, v/v) and concentrated in a rota evaporator.	(21)
Ibrahim et al. 2015	Rats	60	180-250g	N/I	In natura	SS flowers were extracted by cold maceration accompanied by 90% ethanol.	(22)
Minayan et al. 2006	Rats	64	200-250g	N/I	In natura	Seed powder was drenched in 80% ethanol, Concentrated and evaporated under reduced pressure.	(24)
Porchezian et al. 2008	Rats	24	150-180g	N/I	In natura	Powdered seeds of SS were macerated in distilled water and dried by vacuum rotary evaporation.	(25)
Pouramir et al. 2011	Rats	30	180-220g	N/I	In natura	The seeds were powdered and macerated in distilled water.	(23)
Rajaei et al. 2014	Rats	36	200-230g	N/I	In natura	Hydroalcoholic extract was obtained using 70% ethanol/H2O that was subsequently concentrated in an oven.	(10)
Tofighi et al. 2016	Mice	78	20-25g	N/I	In natura	The SS seeds powder were drenched in 80% methanol. Then chloroform was used to give chloroform fraction, and the residue named methanol fraction.	(26)
Tofighi et al. 2016	Rats & Mice	66	Rats: 250-300g Mice: 25-30g	N/I	In natura	SS seeds powder were macerated with 80% methanol and condensed in a vacuum rotary evaporator.	(28)

	Animal			*Securigera securidaca* (SS)			
Zahediasl et al. 2005	Mice	285	25-30g	N/I	In natura	The powdered seeds were macerated in chloroform/ ethanol.	(29)
Gheitasi et al. 2007	Rats	70	250-350g	N/I	In natura	The powdered seeds were macerated with 96% ethanol /water.	(27)

N/I- Non informed, SS- *Securigera securidaca*

Table 4. Diabetes induction procedure, protocol experimental, outcomes, and conclusion.

Experimental model	Outcomes	Conclusion	Ref.
Control **Streptozotocin(100 mg/kg)** **STZ + glibenclamide** **STZ + carbon tetrachloride(200 mg/kg)** **STZ + ethanol-water: 70 %(200 mg/kg)** **STZ + Dichloromethane** **(200 mg/kg)**	Hypoglycemic effects of extracts were noticeable compared to the glibenclamide group for carbon tetrachloride and dichloromethane extracts 16 days after STZ injection.	The most effective hypolipidemic and hypoglycemic properties were attributed to SS seeds Carbon tetrachloride extract.	(19)
Control **Streptozotocin(100 mg/kg)** **STZ + glibenclamide** **STZ + carbon tetrachloride(200 mg/kg)** **STZ + ethanol-water: 70 %(200 mg/kg)** **STZ + Dichloromethane (200 mg/kg)**	Hypoglycemic effects of extracts were noticeable compared to the glibenclamide group for carbon tetrachloride and dichloromethane extracts 16 days after STZ injection.	The outcomes of the carbon tetrachloride extract analysis have indicated a significant hypoglycemic effect and antihyperlipidemic effect of this extract.	(18)
Control **Diabetic control (55mg/kg)** **STZ + SS seed extract (100mg/kg)** **STZ + SS seed extract (200mg/kg)** **STZ + SS seed extract (400mg/kg)** **STZ + glibenclamide (5 mg/kg)** **STZ + SS seed extract(200 & 400mg/kg) and glibenclamide(5 mg/kg)**	Hypoglycemia, enhancement in body weight and insulin sensitivity, and reduction in insulin resistance are reported to be glibenclamide and the HESS effects.	Antioxidative effects and anti-inflammatory effects of the current medication were boosted by the usage of extract.	(20)
Control (saline) **Diabetic and normal rats** **Interperitoneal and oral administration** **-Saline(20ml/kg)** **-Glibenclamide (10mg/kg)** **-Insulin(0.6 iu/kg)** **Alloxan-induced diabetes (90mg/kg)** **Interperitoneal and oral administration** **-SS aqueous extract of seeds (50,200,350,500 mg/kg)** **-SS ethanol extract of seeds (20,80,140,200 mg/kg)**	It has indicated both oral and intraperitoneal consumption of the hydro extract and ethanolic extract could have hypoglycemic effects on alloxan-induced diabetic mice. Interestingly, blood glucose level wasn't decreased by glibenclamide administer in alloxan-induced mice, however, it indicated blood glucose reduction effects on normoglycemic samples.	This study reported that SS seed extract can suppress gluconeogenesis, shows zero insulin-like effects, and stimulating glycolysis.	(21)

Experimental model	Outcomes	Conclusion	Ref.
Glucose-induced hyperglycaemic mice (5g/kg glucose) Interperitoneal and oral administration -SS aqueous extract of seeds (50,200,350,500 mg/kg) -SS ethanol extract of seeds (20,80,140,200 mg/kg)			
Normal Diabetic control (150mg/kg) Alloxan + alcoholic extract of SS flowers 100mg/kg) Alloxan + alcoholic extract of SS flowers (200mg/kg) Alloxan + alcoholic extract of SS flowers (400mg/kg) Alloxan + Gliclazide (5mg/kg)	Significant reduction in blood glucose level has been observed in all doses of SS flower extract at 100, 200, and 400 mg/kg.	This investigation suggested the high phenolic content of the SS flowers as the reason behind its antidiabetic and antihyperlipidemic roles.	(22)
Control Streptozotocin(60mg/kg) STZ+ hydroalcoholic extract of SS seeds (200 mg/kg p.o.) STZ+ hydroalcoholic extract of SS seeds (400 mg/kg p.o.) STZ+ hydroalcoholic extract of SS seeds (800 mg/kg p.o.) STZ+ hydroalcoholic extract of SS seeds (400 mg/kg i.p.) Glibenclamide (10 mg/kg, p.o.)	The hydroalcoholic SS extract wasn't effective in reducing blood glucose neither in normal nor in diabetic animals.	The evidence of SS seeds role in blood glucose reduction in diabetic rats was unreliable.	(24)
-Control (vehicle) Diabetic and normal rats -Aqueous extract of SS seeds (400mg/kg) Diabetic and normal rats -Tolbutamide (500mg/kg) Diabetic and normal rats	SS extract administration has a significant reducing effect on blood glucose in both normal and Alloxan-induced diabetic rats.	The antihyperglycemic effect of SS extract was reliable.	(25)
Pretreatment: Group I (10 ml/kg/day distilled water) Group II (2 g/kg/day SS suspension) Group III (4 g/kg/day SS suspension) Alloxan induction post-four-day treatment (70mg/kg)	This study has demonstrated SS seeds suspension could have antioxidative, antihyperglycemic, and serum insulin upregulating effects in Alloxan-induced hyperglycemic animals at 24, 48, and 72h after injection.	SS suspension has shown antioxidative and antihyperglycemic effects on alloxan-induced rats.	(23)
Control Diabetic control (55 mg/kg) STZ+ SS extract (100 mg/kg) STZ+ SS extract (200 mg/kg)	4 weeks of treatment with 200 mg/kg of SS seeds extract resulted in blood glucose reduction, plus lowering total cholesterol and LDL cholesterol, and enhancing HDL cholesterol in diabetic rats.	SS extract has indicated significant antihyperglycemic and antihyperlipidemic effects on STZ-induced diabetic rats.	(10)
STZ (200mg/kg)	The lowering blood effect of MF at 100 mg/kg and CF at 400 mg/kg was	It seems the reason for SS anti-diabetic properties is three	(26)

Experimental model	Outcomes	Conclusion	Ref.
Methanol fraction(MF) of SS seed extract (100,200,300,400,500 mg/kg) **Chloroform fraction(CF) of SS seed extract (300,400,600 mg/kg)** **Securigenin glycosides 1-3 (10 mg/kg)** **Glibenclamide(3 mg/kg)** **NPH insulin (12.5 IU/kg)** **Normal saline**	comparable with glibenclamide (3mg/kg). Compared to 3 mg/kg glibenclamide, Securigenin glycosides have almost equal hypoglycemic effects in diabetic animals (P>0.05).	isolated cardenolide glycosides in SS seed extract and their hypoglycemic effects are because of up-regulation in insulin level.	
Acute study: **-Saline** **Normal and diabetic control (200 mg/kg)** **-Whole SS seed extract (250,500 & 1000 mg/kg)** **-Chloroform fraction of SS seed extract (250 & 500 mg/kg)** **-Methanol fraction of SS seed extract (250 & 500 mg/kg)** **-Mixture of chloroform and methanol fraction (30:70, 500 mg/kg)** **-Glibenclamide (10 mg/kg)** **Sub-acute study:** **-Saline** **Normal and diabetic control (200 mg/kg)** **-Mixture of chloroform and methanol fraction (30:70, 500 mg/kg)** **-Glibenclamide (10 mg/kg)** **-Regular and NPH insulin (30:70, 12 IU/kg)**	This acute study has indicated hypoglycemic effects of chloroform fraction happen after 1 hour. On the other hand, 4 hours is the period needed for methanol fraction and mixture of fractions to bring glucose level back to normal.	It has been suggested mechanism of hypoglycemic action of SS seed is the same as the insulin mechanism.	(28)
Normal saline **Hydroalcoholic extract of SS seeds (1,2,3,4,5,10 mg/kg)** **Chloroformic extract of SS seeds (1,2,3,4,5,10 mg/kg)** **Mixture of** **hydroalcoholic and chloroformic extract (50:50, 1,2,3,4,5,10 mg/kg)**	It seems that chloroformic extract has a dose-dependent hypoglycemic effect which has the highest response in 3 mg/kg doses.	SS seed chloroformic extract hypoglycemic effect mechanism is due to the increase in insulin secretion and induction of insulin-like effects.	(29)
Normal **Control + distilled water** **Control + hydroalcoholic SS seed extract (1 g/kg)** **Diabetic control (45 mg/kg)** **STZ + hydroalcoholic SS seed extract (500 mg/kg)** **STZ + hydroalcoholic SS seed extract (1000 mg/kg)** **STZ + hydroalcoholic SS seed extract (2000 mg/kg)**	After 2 weeks administration of 500 and 1000 mg/kg SS extract, no significant change was observed in STZ-induced animals. Whereas 2000 mg/kg has a significant hypoglycemic effect.	The results of this study approved the dose-dependent hypoglycemic effect of SS extract on STZ-induced diabetic rats.	(27)

Discussion

Even in the era of highly advanced biomedicine, herbal medicines remain of contemporary interest for researchers around the world for their ability to complement modern drugs and as sources for the development of novel drugs. The mechanism of most of the named plants has not been approved yet; however, various herbs and their derived bioactive compounds are currently consumed for their advantage on diabetic patients. This may be attributed to the efficacy of new plant-based remedies and increased attention to natural products, concomitant to the presence of deleterious side effects, high-cost, and lack of access to modern antidiabetic drugs for people who live in the countryside, specifically in developing countries **(30)**.

The findings of this review are consistent with the results of studies conducted on *Securigera securidaca* across many regions with different experimental animals. The information about serum glucose levels collected from these critically reviewed articles obviously indicates that the various *Securigera securidaca* significantly reduced hyperglycemia in alloxan and STZ-induced diabetic animals through various possible mechanisms. Indeed, their hypoglycemic effect was comparable with that of the usual hypoglycemic drugs: gliclazide, tolbutamide, insulin, and glibenclamide.

Most included studies demonstrated that SS seed hydroalcoholic extract can significantly reduce serum glucose levels in diabetic animals **(10, 18-22, 27-30)**. GC-MS analysis showed that, in SS seeds hydroethanolic extract, most bioactive components are fatty acids with antidiabetic and antioxidative effects with a total of 43.1 % content. Also, phenol, polyol, and sterol compounds (total content: 34.86 %) in this extract may represent another reason for the greater hypoglycemic activities of the extract **(19)**. Ahmadi et al. **(18, 19)** reported a significant blood glucose lowering effect of the intervention compared to the control group, at all time-points. Another article by Tofighi et al. **(26)** further confirmed the antidiabetic activity of SS seed extract's chloroformic and methanolic fractions. Following isolation of three cardenolide glycosides as active compounds, the authors were able to indicate that blood glucose lowering effects of these cardiac glycosides are related to increasing insulin level in blood.

Two of the included studies in this review assessed the anti-hyperglycemic activity of S.securidaca flowers, and reported a marked decrease in blood glucose level, advocating considering SS flowers as an anti-diabetic treatment, which could be based on the noticeable phenolic content **(18, 22)**.

In contrast, in Minaiyan et al. study **(24)**, S. securidaca has been shown as a non-effective agent in decreasing blood glucose of STZ-induced diabetic samples. It seems that the presence of phenolic components, fatty acids, flavonoids, and sterols in S. securidaca is the reason for the antihyperglycemic and antioxidative effects of this plant. Investigations suggested that the blood glucose lowering effect of SS seeds is probably distinct from sulfonylurea and insulin-like factors, and has no effect on gastrointestinal absorption of glucose. Nevertheless, some properties related to biguanides such as gluconeogenesis suppression, glycolysis stimulation, serum glucose depletion, or enhancing insulin functions may be involved in SS seeds mechanisms of actions **(19)**. Phenolic and flavonoid compounds take part in blood glucose regulation similar to α- 12 amylase and α-glucosidase suppressors in diabetes, along with synthetic analogs. Moreover, there are multiple other possibilities for phenolic and flavonoid compounds anti-diabetic mechanisms including suppressing gastrointestinal glucose absorption because of suppression of Na+-dependent resorption, stimulating β-cell to increase insulin secretion, increasing the number of insulin receptors which leads to more glucose uptake, inhibition in fatty acid synthesis, and anti-gluconeogenesis activity. Aside from antidiabetic effects of the phenolic and flavonoid compounds, they have shown significant antioxidative effects. The protective effect of these metabolites against oxidative damage depends on the redox potential of phenolic hydroxyl groups that allow them to act as hydrogen donators and reducing agents, singlet oxygen scavengers, and metal chelators **(20)**. Previous investigations suggested fatty acids as a basis for glucose-stimulated insulin release from pancreatic β-cells. In addition, β-cells glucose-induced apoptosis regulated by fatty acids, plus, they adjust β-cell proliferation and reduce insulin resistance, which could be connected to mitochondrial, endoplasmic reticulum (ER) stress, and Fas signal pathways, respectively. The sterols have a variety of pharmacological functions that regulate plasma cholesterol and increase antioxidant capacity by activating an estrogen receptor/PI3-kinase-dependent pathway with an ROS scavenger role.

Furthermore, reductions in glucose, nitric oxide (NO), and HbA1c generally occur after an increase in insulin level and improvement in insulin sensitivity, and show protective effects on the pancreas due to its antioxidant activity, which means protecting beta-cells from free radical-induced damage, resulting in the prevention and improvement of diabetes **(19)**.

Limitations and strengths

There are multiple limitations in this study that must be considered in the conclusion. It is suggested that caution be taken in generalizing these consequences, based on the evidence that the analyzed publications have methodological variations about the species of the animals, the kind of extract of *Securigera securidaca*, and the type of the protocols. Moreover, although we

tried to retrieve the articles following the selected keywords, it is plausible that articles may have been missed if they were not published in English or Persian and published in journals that were not indexed in the PubMed, Google scholar or Scopus database. Despite the aforementioned limitations, the study has multiple strengths points: Firstly, to the authors' knowledge, the present study represents the first study to comprehensively review the use of *Securigera securidaca* in the treatment of hyperglycemia in animal models. Furthermore, we followed stringent guidelines, and we conducted a detailed methodological quality assessment.

Conclusion

In this systematic review, we found that various extracts of *Securigera securidaca* elicit antidiabetic effects in animal models. Although current chemical drugs are significantly successful in diabetes treatment, recently, herbal medicines have gotten noticeable attention as diabetes treatments because of their desired efficiency and fewer side effects. Given the prevalence, importance, and efficacy of *Securigera securidaca* for treating and managing diabetes in animal models, a detailed assessment of the general toxic profile and formulation for eventual use in humans is advisable.

Acknowledgments

None.

Conflict of Interest

The authors declare that they have no conflict of interests.

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