



# Anti-diabetic Attributes of Desert Plant Retama: A Mini Review on its Traditional Uses and Potential Chemical Constituents

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## Abstract

**BACKGROUND:** Diabetes mellitus (DM) is a fast-growing metabolic disorder, which affect millions around the world mostly people from developing nations. The rise of diabetes is further set to rise more in the coming years in all inhabited continents of the world. DM mainly attributed for food and lifestyle changes, less or no physical activity, obese, overweight, and major socioeconomic changes. In recent years, herbal medicine is incredibly growing because many natural products exhibit less or no side effects. It is well-established that nature-derived products protect  $\beta$ -cells and decrease blood glucose.

**AIM:** We aimed to explain anti-diabetic attributes, traditional uses, and potential chemical constituents of desert plant retama.

**RESULTS:** Numerous previous studies support the use of plant derived bioactive substances for human and animal disease therapy and reinforce their importance as a potential source of novel drug candidates. In this line a flowering bush, belong to the genus "Retama" (Fabaceae) are in use of conventional remedy in the Mediterranean basin for various diseases including DM. This potential plant genus has a great medical and socioeconomic importance and provides crucial evidence for its anti-diabetic therapeutic potential. The present review collected various documented information using the following searching engines such as PubMed, Science direct, and Google scholar. We limit our search only to English written documents for the last few decades until date. For data mining, the following MeSH words used in the databases: Retama, diabetes, phytoconstituents, pharmacological potential, anti-diabetic, insulin, in vivo, and in vitro.

**CONCLUSION:** The outcome of this review may set new prospects for the DM patients, along with other standard medication and provide an overall insight to the well-being at the regional and global level.

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## Introduction

Diabetes mellitus (DM) is one of the extremely sensitive chronic metabolic epidemic disorder-affecting people with morbidity and mortality both in the developing as well as developed countries [1], [2], [3], [4]. DM not only affects quality and life expectancy of persons, as well as several countries health-care system [5], [6], [7]. Two characterized DM types such as Type 1, in which reduced production of insulin, whereas in Type 2 impairment of insulin secretion and/or action observed [8]. Both Type 1 and 2 diabetic persons experience various symptoms such as hyperglycemia, increased urination, and excessive thirsty, more fluid intake. In addition, blurry vision, no weight loss, tiredness, and dramatic variations in energy metabolism such as dyslipidemia [9], [10], [11], [12], [13] and dysregulation of adipokines [14], [15]. In addition, Type 2, three key defects also evident as more production of liver glucose, reduced insulin production, and weakened insulin action [16].

## Global incidence of Type 2 diabetes

Although two types of DM exist, Type 2 is prevalent more than 90%. According to American Diabetes Association estimation [7], approximately 285 million people currently affected, and the projection for the year 2030 is 438 million worldwide have diabetes [17], [18], [19]. In the previous decades, the position of Type 2 shifted from its previously measured mild syndrome of the ageing people, now affecting youth and middle-aged people to morbidity and mortality among them [20], [21].

It is projected the global incidence of DM may augment gradually from 4% in 1995 to 5.4% or more in the coming years [22] and the surge go beyond 642 million in the next two decade alarmed by the WHO. This major burden will emerge more in the developing countries (170%), whereas 42% increase in the developed countries [23], [24], [25]. The median age of diabetics is between 45 and 64 years old in the developing countries; however, it is above 65 for developed countries [6], [26]. Obesity and family

history considered as major factors for the progress of Type 2, which is evident from the global cartographic picture [14], [27]. Besides, many additional risk factors such as elevated cholesterol and peripheral insulin resistance [12], [13], [27], [28] affect various organs including small artery structure, function, and quality of life [29]. The present pharmacologic drugs existing for Type 2 are based either on accumulating insulin presence or to enhance the sensitivity for insulin or impede the distribution and absorption of sugar from the gastrointestinal tract or increasing urinary glucose elimination [30].



Figure 1: Branches with followers of Retem plant from Tabuk region, Saud Arabia (image courtesy/ref: [50], [51])

Numerous preventive approaches and other alternate therapeutics are currently existed for managing Type 2 DM [31], [32]. Improvements in traditional medicine exploration have considerably motivated the novel drug development for diabetes [33]. However, it is noteworthy that only a handful of herbs considered for their effectiveness in human being, and they remain completely inadequate. Yet, the quest for new therapeutics is still in progress due to its paramount importance and gaining attention. In recent years, herbal plant derived natural products (NPs) gained more attention for the intervention of several diseases [14], [33], [34], [35]. Besides, plant-derived drug candidates exploration is one of the fast-growing interesting field due to their no limited side effects or less toxic symptoms [36], [37].

NPs have extensive track and gained widespread recognition among common people and traditional medicine practitioners as well as herbal investigators due to their less or no toxic nature, cost effective, and high efficiency [14], [37], [38]. In recent years, more diabetic persons are attracted towards traditional plant based remedies as their primary healthcare choice and to manage hyperlipidemia condition [39]. In line with this, numerous herbal-derived natural active ingredients have demonstrated anti-diabetic potential by proven their multifaceted beneficial effects [17], [40], [41]. These herbal derived NPs not only involved in pancreatic  $\beta$ -cells regeneration, insulin releasing, and combat insulin resistance but also decrease blood glucose [42], [43], [44].

In line with this, the flowering herbal shrub "*Retama raetam* (Forssk) Webb" ("*Raetam*") fruits are

in the use of complementary and alternative medicine for treating diabetes [45]. Retama is spontaneous plant genus belongs to the family of "*Fabaceae*" (Table 1) which is comprised four species such as *Retama monosperma* (L.) Boiss., *R. raetam* (Forsk.) Webb; *Retama dasycarpa* Coss and *Retama sphaerocarpa* Boiss., spread in northeastern Mediterranean region as well as in the sparsely populated desert Sinai province [46] and various other countries including Saudi Arabia, Libya, Italy, Morocco, Egypt, Algeria, Spain, and Lebanon [47].

Table 1: Taxonomy of Retem plant

Number	Classification	Plant
1	Kingdom:	Plantae Plants
2	Subkingdom:	Vascular plants
3	Super division:	Seed Plants; Flowering plants
4	Class:	Dicotyledons
5	Subclass:	Rosidae
6	Order:	Fabales
7	Family:	<i>Fabaceae</i> Leguminosae
8	Genus:	<i>Retama</i> Raf

## Retem Plant Description

According to the manual for medicinal plants in North Africa reported by IUCN [48], Retem described as leguminous green plant, slender, and weeping multi-stemmed shrubs belongs to the family *Fabaceae* [49], [50]. Retem plant has green stems which accountable for photosynthesis, especially during the summer season (Figure 1). The shrub normally grows about 3 meters tall but may reach up to 6 m. Plant branches from the base, while the young stems covered with hairs become hairless with age. Besides, leaves are small, narrow, and alternate and drop very quickly. Flowering season starts from February up to May [51].

This desert shrub also found in Libya and North and Sahara, common to several countries of North-Africa (GRIN) employed as complementary medication by common name "*Retama*" or white broom or the white weeping broom more specific to combat skin infection and reduce blood glucose [49]. However, some Mediterranean countries use this herb for skin inflammation and joint aches [52], [53]. In addition, this green-barked bush employed as an emetic and abortifacient, hepatic protective, cytotoxic, and hypoglycemic properties [45], [54], [55], [56], [57], [58], [59], [60]. To support, numerous *in vitro* and *in vivo* investigations have demonstrated that the *Raetam* extract act on rat-isolated intestine by significantly inhibiting glucose absorption [31], [58].

In addition, *Retama* usage in folk medicine recommended by various traditional medicine practitioners for the control of diabetic disorder in the Mediterranean as well as many gulf nations including Saudi Arabia [45], [46], [61]. Several *Retama* herbs are engaged to treat numerous human diseases, which

include DM, hepatitis, skin rashes, jaundice, joint pain, throat infection, rheumatoid arthritis, common cold and fever, and inflammatory illnesses [62]. In addition, numerous investigations have revealed various potentials of *Retama* such as anti-diuretic [54], lipid lowering [63], and antioxidant [57], [64], anti-microbial [56], anti-hypertensive [55], and reduction of blood glucose activity [45], [54].

Despite latest investigational data authorizes the numerous pharmaceutical importance of this genus, yet, additional exploration of this plant species detailed molecular mechanisms underlying the anti-diabetic activity remain elusive and are necessary. Thus, this persistent problem prompted us to review the potential anti-diabetic mechanisms of the *Retama* especially on dyslipidemia and hypoglycemia. Besides, this mini review also focused on photochemistry. This mini comprehensive review deals with the updated evidence on the distribution, botanical characteristics, ethno-pharmacology, phytochemistry, anti-diabetic curative potentials, and toxicity of the *Retama* species to substantiate for future exploration of novel drug leads. Our review will enlighten scientific basis of secondary metabolites and detailed anti-diabetic actions to provide novel therapeutic prospects of this herb species. We have adopted various scientific search engines such as PubMed, Scopus, and Web of Science and used various search keywords and approach to compile chemical composition, essential oil, and pharmacological potential and mechanism of action.

## Phytoactive Constituents of *Retama* Plants

The previous investigations have reported that *Retama* spp. leaf crude extracts enriched with nearly 50 potential compounds, measured by qualitative phytochemical screening using Gas chromatography–mass spectrometry (GC/MS) and Liquid chromatography (MS), which represent different classes of secondary metabolites. The compounds include carbohydrates (galactomannans) [65], alkaloids (retamine, lupanine, quinolizidine, and biperidyl) [66], [67], [68], [69], [70], flavonoids/isoflavones [71], [72], [73], [74], [75], [76], and steroids. In addition, substances such as alkanes [77], terpene [77], ketones [77], fatty acids [69], [66], and sterol [69] are present. Besides, long chain alcohol Tetracosan-1-ol [69], cyclitol [73], polyols (cyclitol pinitol) [73], and phenolic compounds (genistein and daidzein) are reported. Besides, the quantitative screening indicated highest concentrations of saponins with 10%, flavonoids with 9%, and alkaloids with 8%.

## Discussion

Despite the existence of present diabetic medications in the pharmaceutical market, the traditional practice of diabetes with herbs is often fruition [78]. Recent years witnessed numerous plants with anti-diabetic, hypoglycemic, and anti-hyperglycemic actions with  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibition [31]. Approximately 509 plant species belong to 140 genera, among them, nearly 10 or more species exhibiting anti-diabetic effects [22], [31], [79] as many plant derivatives/NPs are available and do not involve strenuous pharmacological synthesis, appears extremely warranted. Herbal drug leads and NPs have no/less toxicity with no significant side effects/ramifications are notable therapeutic options for the treatment of diabetes worldwide [80], [81]. Most of these anti-diabetic actions attributed to the combination of bioactive phytochemicals present either as single entity or in combination found in their extracts evident using various extraction techniques to determine various phytochemical composition and their mechanisms verified using numerous animal investigations [82], [83]. Many of these studies are very beneficial to unearthing wide array of natural anti-diabetic drugs, which could be abundant significance [44], [82], [84]. Yet still, there are concerns emanating for their low or minimal efficacy and safety for couple of million diabetic persons seeking better medication, in this list, top priority is traditional curative herbs for ideal management of diabetes [44]. To support the above in this mini review, we attempted to discuss the therapeutic potential of *Retama* spp. on DM.

Numerous experimental evidence indicates that “*Retama*” plant parts contain several prominent secondary metabolites, which are mainly responsible for anti-diabetic actions. Substances, which include alkaloids, flavonoids, phenolic acids, glycosides, polysaccharides, saponins, stilbenes, and tannins, considered as potential pharmaceutical drug leads/candidates [85], [86], [87], [88], [89], [90], [91], [92]. Most of these NPs exhibit various biological as well as therapeutic activities such as anti-glycation, antioxidant, [93], anti-microbial [94], pain-relieving [95], cytotoxic [96], anti-hyperglycemic [58], reduce inflammation [73], [95], hemostatic, and promote diuresis [54], [96]. The saponin steroids also described to have, pain relieving and anti-inflammatory, immunomodulator, and immune-adjuvant and anti-tumor roles [59], [64], [70]. Moreover, powdered leaf extract was employed to heal circumcision and antiseptic wounds, pruritus, skin rashes, and in the supervisory control of microbial infections by traditional drug practitioners [93]. In line with this, the compound Pinitol obtained from aqueous extracts considered a mediator for the reduction of inflammation and blood glucose/hypoglycemic effect based on their potency [73].

The previous studies have also demonstrated that secondary metabolites such as quinolizidine alkaloid [97], flavonoid [98], [99], [100], [101], and soluble fiber [102] isolated from *Retama* are responsible for anti-diabetic effects. GC-MS analyses have revealed various quinolizidine alkaloids such as sparteine, N-methylcytisine, and lupanine are responsible for hypoglycemic effects due to insulin-releasing properties [103].

Additional diverse mechanisms also been proposed for the beneficial effects of phytochemicals. One such mechanism is the alkaloid-induced obstruction of ATP-sensitive K (KATP) channels exist in the  $\beta$ -cells with the subsequent release of insulin have been suggested as a mechanism [71] and the observed result may be due to the preservation of  $\beta$ -cells. This mechanism can be associated with the antioxidant property of *Retama* [57], [64]. The other suggested potential mechanisms of *Retama* are regulation of lipid metabolism [45], [104], insulin secretion [105], stimulating  $\beta$  cells [58], nuclear factor-kappa B signaling pathway [95], inhibition of gluconeogenic enzymes [106], reactive oxygen species protective action [107], and glucose-lowering effect, reduction of glucose area under the curve and inhibition of renal reabsorption of glucose [104] as evidenced by increased glycosuria [58].

Besides, numerous medicinal herbs have been demonstrated to improve glucose homeostasis through alterations in various molecular mechanisms such as glycolysis, Krebs cycle, gluconeogenesis, hexose monophosphate shunt pathway, glycogen synthesis and their degradation, cholesterol synthesis, metabolism and absorption of carbohydrates, or synthesis and release of insulin as reviewed by Prabhakar and Doble, 2008 [84]. In line with this, high concentration (500 mg) of *Retama* extract have significantly increased serum insulin levels in Streptozotocin induced diabetic rats [104], which might be due to the presence and/or concentration of the active metabolic constituents.

To substantiate further the anti-diabetic potential of *Retama* extract, *in vitro* experiment by employing an isolated rat intestinal segments has revealed that the glucose concentration/absorption was inhibited in a time and dose-dependent manner with the reduction of skeletal muscle glucose uptake [108]. The outcome suggests that the observed glucose decline by *Retama* may partially be due to the reduced glucose absorption in the small intestine since active transfer of glucose occurs throughout the intestinal membrane [47], [109]. Since liver serves as a fuel for other tissues and is capable of releasing glucose into circulation by two metabolic pathways like gluconeogenesis and glycogenolysis by an enzyme, G-6-Pase, catalyze [110], [111]. It is a well-known hypothesis that augmented hepatic glucose release is a main reason for the hyperglycemia that explains diabetes [112].

## Conclusion

The present comprehensive mini review summarizes the geographical distribution, ethnobotanical use, bioactive secondary metabolites composition, and anti-diabetic and other molecular mechanisms of *Retama* species, which provides new insights into further investigations and pharmacological applications. For longer period, these medicinal plants have employed in traditional medicine by generations in the Mediterranean region until the present day to treat various diseases such as diabetes, rheumatism, hyperlipidemia, and hypertension. In conclusion, numerous experimental as well as ethnomedicine indicated that different classes of secondary phytoconstituents obtained from this plant extract such as galactomannans, retamine, lupanine, quinolizidine and bipiperidyl, polyphenols, flavonoids/isoflavones, terpene, ketones and steroids improved diabetic symptoms, hyperglycemia, and hyperlipidemia. We expect that this plant species attributed at least partly, to stimulating pancreatic insulin release and reducing intestinal glucose absorption. The outcome obtained from this important potential herb may set new prospects for the Type 2 diabetic patients, along with other standard medication and provide an overall insight to the well-being at the regional and global level.

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