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ANTI-DIABETIC ACTIVITY OF REPORTED MEDICAL AND AROMATIC PLANTS: A REVIEW

Venugopala Reddy Mekala*

A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-03.

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***Corresponding Author**
Venugopala Reddy Mekala
A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-03.

ABSTRACT

Most of the medicinal plants are available as wild source and they are not explored scientifically for the utilization of mankind. Hence, there is a need to evaluate the biological activity of huge number of medicinal plants by using modern high throughput screening techniques. The use of herbs is common among diabetics. The aim of this review is to demonstrate the reported anti-diabetic medical and aromatic plants in animal induction models along with duration of study followed by authors. All the plants were studied and reported in Elsevier. Type 2 diabetes has become a global epidemic. Modern medicines, despite offering a variety of effective treatment options, can have several adverse effects. Ayurveda, a science that uses herbal medicines extensively, originated in India. It is considerable interest is the adoption of Ayurveda by the main stream medical system in some European countries (e.g., Hungary), emphasizing this modality is increasing worldwide recognition. The herbal drugs with anti-diabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine. By considering the public interest and importance of herbal drugs, it is necessary to search for the development of herbal medicine in the treatment of diabetic.

KEYWORDS: Diabetic, Anti-diabetic activity, Herbal plants.

1. INTRODUCTION

Diabetes mellitus, more simply called diabetes, is a chronic condition that occurs when there are raised levels of glucose in the blood because the body cannot produce any or enough of the hormone insulin or use insulin effectively.[1] As per estimates from the International

Diabetes Federation, the global prevalence of diabetes was 382 million and it has been predicted to reach 592 million by 2035.[2] As per the WHO diabetes mellitus represents a major public health threat worldwide with an estimated prevalence in 2014 of 422 million patients.[3] Diabetes is divided into two major categories: Type 1 also known as Insulin dependent diabetes mellitus (IDDM) and type 2 known as non- insulin dependent diabetes mellitus (NIDDM). Type 1 (IDDM) is an autoimmune disorder caused by auto aggressive T lymphocytes that infiltrate the pancreas and destroy insulin producing β-cells leading to hypoinsulinaemia and thus hyperglycemic condition.[4-5] This develops over a period of time to diabetic complications such as nephropathy, retinopathy, neuropathy, and cardiomyopathy.[5, 6] Associated metabolic complications of type-I diabetes are due to insulin deficiency and related glucose under-utilization of the insulin-dependent tissue, such as liver, and glucose over utilization in insulin-independent tissue, such as kidney.[5, 7] Type 2 diabetes (NIDDM) is known to have a strong genetic component with contributing environmental determinants. Though the disease is genetically heterogeneous, there appears to be a fairly consistent phenotype once the disease is fully manifested.[8] Whatever the pathogenic causes, the early stage of type 2 diabetes is characterized by insulin resistance in insulin-targeting tissues, mainly the liver, skeletal muscle, and adipocytes. Insulin resistance in these tissues is associated with excessive glucose production by the liver and impaired glucose utilization by peripheral tissues.[9-10]

During the last few years an increase in the use of medicinal plants in curing various health problems has been observed as they are from natural origin and have less side-effect.[11] Plants have been the primary source of medication since ancient times and many drugs have been directly or indirectly derived from different plants.[12] At least 12 000 plants in the world are used for medicinal purposes, but less than 10% of them are investigated from pharmacological point of view.[13] Plants have been the primary source of drugs, and many of the currently available drugs have been directly or indirectly derived from plants.

Traditional medicine (herbal) is used for treatment of diabetes in developing countries where the cost of conventional medicines is a burden to the population.[4] Despite the introduction of hypoglycemic agents from natural and synthetic sources, diabetes and its secondary complications continue to be a major medical problem. Many indigenous medicinal plants have been found to be useful to successfully manage diabetes throughout the worldwide. One of the great advantages of medicinal plants is that these are readily available and have very low side effects. Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them.

2. Role of herbal drugs in prevention and cure of Diabetics

Diabetic is a serious of metabolic disorder and plenty of medicinal plants are used in traditional medicines to treat diabetes. These plants have no side effects and many existing medicines are derived from the plants. Diabetic is mainly due to oxidative stress and an increase in reactive oxygen species that can have major effects. Many plants contain different natural antioxidents, in particular tannins, flavonoids, vitamins C and E that have the ability to maintain β-cells performance and decrease glucose levels in the blood. Nowadays, different treatments, such as insulin therapy, pharmacotherapy and diet therapy are available to control diabetes. There are several types of glucose lowering drugs that exert anti-diabetic effects through different mechanisms. These mechanisms includes stimulation of insulin secretion by sulfonylurea and meglitinides drugs, increasing of peripheral absorption of glucose by biguanides and thiazolidinediones[15], delay in the absorption of carbohydrates from the intestine by alpha-glucosidase and reduction of hepatic gluconeogenesis by biguanides.[16] In the past three decades, despite the significant process made in the treatment of diabetes, the results of treatment in patients is still far from perfect. These treatments have some disadvantages, including drug resistance (reduction of efficiency), side effects are even toxicity. For example, Sulfonylureas lose their effectiveness after 6 years of treatments in 44% of patients. It is also said that the glucose-lowering drugs are not able to control hyperlipidemia.[17] In addition, the side effects of medicines and their interactions with each other *in-vitro* must be considered by the medical stuff. Today, many treatments that involve the use of medical plants are recommended.[18] Most plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and can often have anti-diabetic effects.[19]

All herbal plants having specific active constitutes that gives a therapeutic action. Medicinal plants containing many active chemical constitute, and it is likely that they work together to produce the desired synergetic medicinal effect. The type of environment (climate, bugs, soil quality) in which a plant grew will affect its active components, as will how and when it was harvested and processed that also important for action of herbal medicine.

2.1. Herbal medicine since ancient time: In ancient literature more than 800 plant species have been reported to have potent antidiabetic activity.[20] The ancient or Ayurvedic literature survey is demonstrating that the in India diabetes was practically well known and well-conceived since ancient time. The knowledge of the system of diabetes mellitus, as the history reveals, existed with the Indians since prehistoric age.[21, 22]

Ayurvedic antidiabetic medicinal plant increases Rasas (gastric secretions) and improves digestive power, being Laghu, being Ruksha and gets easily digested in the body decrease output of overall body fluids e.g. sweat, urine etc. Food substances, which are 'madhumehaghna' (antidote), are an important essential principle of therapy for the prameha (diabetes) patient.

Food substance which correct the metabolic imbalance by their action e.g. foods exhibiting 'rasa', 'katu', 'laghu', 'medaghna', properties are old cereals, milk, roasted cereals, horsegram, jawar, barley, raw papaya, jamun, mung dal, tur dal, ragi, drumstick leaves, bittergourd, amla, fig, meat of animals that live in dry region, etc. The original diet modification useful in controlling blood sugar to the same extent as insulin and other hypoglycaemic agents do. But it has some other influences, which may be useful for the management of the disease and its complications.[23] Indian Materia Medica has mentioned many dravyas, which have been reported effective in Madhumeha (diabetes).[24] Its earliest reference (1000 BC in the Ayurvedic literature) is found in mythological form where it is said to have originated by eating Havisha,[25] a special food, which used to be offered at the times of yagna organized by Dakshaprajapati.

2.2. Different pharmacological action of herbal antidiabetic remedies: Mechanism of action of herbal antidiabetic is depending on presence of active chemical component in plant material. Different mechanism of action of herbal medicine is given below.

- Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2nd messenger) stimulation.[26]
- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes.
- Prevention of pathological conversion of starch to glucose.[27]
- Stimulation of insulin secretion.[28]
- Preventing oxidative stress that is possibly involved in pancreatic ß-cell dysfunction found in diabetes.[29]

- Reduction in insulin resistance.[30]
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells, Regenerating and/or repairing pancreatic beta cells, Increasing the size and number of cells in the islets of Langerhans.[31]
- Inhibition in renal glucose reabsorption.[32]
- Protective effect on the destruction of the betacells.[33]
- Inhibition of β -galactocidase and α-glucocidase.[34]
- Improvement in digestion along with reduction in blood sugar and urea.[35]
- Cortisol lowering activities.[36]
- Stimulation of glycogenesis and hepatic glycolysis.[37]
- Inhibition of alpha-amylase.[38]

3. Different types of induction of diabetics in animal models:

3.1. Alloxan

Diabetogenic action of alloxan is mediated by reactive oxygen species. Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide. Thereafter highly reactive hydroxyl radicals are formed by the fenton reaction. the action of reactive oxygen species with simultaneous massive increases in cytosolic calcium concentration causes rapid destruction of β cells. The action of alloxan in the pancreas is preceded by its rapid uptake by the β cells.[39]

3.2. Streptozotocin

Streptozotocin2-deoxy-2-[3-[methyl-3- nitrosoureidp]-d-glucopyranose]] is synthesized by steptomycetes achromogenes and is used to induce both type-1 and type-2. Streptozotocin induces diabetes in almost all the species. diabetes dose varies with the species and the optimal dose required to produce diabetes in rat was found to be [50-60mg/kg i.p. or i.v], in mice 9175-200mg/kg i.p. or i.v] and in the dogs [`15 mg/kg for 3 days]. Due to its low solubility the rapid i.v; injection appears to be best route of administration.[40]

3.3. Ferric nitrilotriacetate induction of diabetes mellitus

This rarely used procedure. Rats and rabbit`s parentrally treated with à large daily dose of ferric nitriloacetate manifestated diabetic symotoms such as hyperglycemia glycosuria ketonemia and ketourea after approximately 60 days of treatment the blood insulin response to oral glucose loading poor.[40]

3.4. Non insulin dependent diabetes mellitus [NIDD] resembling animal models

By altering the dose and the dose of the STZ injection, the n-stz models exhibit various stages of type-2 diabetes mellitus, such as impaired glucose tolerance, mild, moderate and severe hyperglycemias neonatal stz-induced rat model of type 2 diabetes mellitus model is generated by injecting Wister rats on the day of their birth intravenously[40] [saphenous vein] or intraperitoneal with 100mg/kg of stz.

3.5. Harmone induced diabetes

Growth harmone induced diabetes; in intact adult dogs and cats repeated administration of growth harmone induces an intensively diabetic condition with all symptoms of diabetes including severe ketonemia and ketonuria, corticosteroid induced diabetes: hyperglycemia, glycosuria, are observed in forced fed rats treated with cortisone, in guinea pig and rabbit <experimental corticoid diabetes could be obtained without forced feeding.[40]

3.6. Insulin deficiency due to insulin antibodies

Bovine insulin [1mg] is injected subcutaneously to guinea pig at monthly intervals and is bleed by cardiac puncture two weeks after the second and subsequent doses of antigen. Intravenously injection [0.25-1.0ml] of guinea pig anti insulin serum to rats induces aldose of dependent increase of blood glucose. This effect is due to neutralization by insulin antibodies secreted by the injected animal.

3.7. Virus induced diabetes

Type-1 diabetes may due to virus infection and β- cell specific autoimmunity. The d-variant of the encephalamycarditis virus [emc-d] selectively infects and destroys the β cells in the male ICR Swiss mice similar to the human insulin dependent diabetic.[40]

3.8. Genetically diabetic animals

Several animal species, mostly rodents have been described to exhibit spontaneous diabetes mellitus on a hereditary basis E.g.; spontaneously diabetic rats like BB rat WBN/KOB rat etc.[40]

3.9. Models of diabetes accelerated atherosclerosis

Accelerated cardiovascular disease is leading cause of both morbidly and mortality in diabetic patients. Aggressive therapy of dyslipidemia is necessary since the risk of myocardial infarction is the same as in non diabetic patients with previous myocardial infarction. Currently rats and mice are the most widely used models to study diabetes and atherosclerosis.

3.10. Genetic models of diabetes

A) Spontaneously develop diabetic rats

These models permit the evaluation of the effect of the natural product on an animal without an interference of the side effects induced by the chemical drugs like alloxan and STZ reported above. Several recent publications summarized the major advances in this field (ex; spontaneously diabetic Gotokakizakhi rat which is a genetic model of type-2 diabetes originating from selective breeding over many generations of glucose-intolerant non diabetic wister rats.

B) Genetically engineered diabetic mice

In this case, rodents may be produced to over or under express proteins thought to play an keyrole in the glucose metabolisms although significant advances in this field have arisen in recent years, especially with the advent of transgenic mice, there have been no studies carried out involving natural products on this models.[40]

4. List of Medicinal plants with Anti-diabetic activity

The traditional medicine all over the world is nowadays revalued by an extensive activity of research on different plant species and their therapeutic principles. Experimental evidence suggests that free radicals (FR) and reactive oxygen species (ROS) can be involved in a high number of diseases.

A large number of antidiabetic medicines are available in the pharmaceutical market for diabetes and its related complications; however, currently no effective therapy is available to cure the disease. However, due to unwanted side effects the efficacies of these compounds are debatable and there is a demand for new compounds for the treatment of diabetes.[41, 42] In the last few years, there has been a growing interest in the herbal medicine in care and management of diabetes both in developing and developed countries, due to their natural origin and less side effects.[43, 44, 45]

S.No	Herbal plants	Part used	Activities Induction	Dose (mg/kg of Body weight)	Duration of Study	Reference
1.	Achillea millefollium	Aerial Parts	Streptozotocin	120	20 Days	FabiolaChavez-Silva [2018]-[46]
2.	Acorus calamus L.	Radix	Streptozotocin	150	4 Weeks	Yun-XiLiu [2015]-[47]
3.	Ajuga iva	Whole Plant	Alloxan Monohydrate	60	15 Days	Amit K.Kesharia [2016]-[48]
4.	Alchemilla mollis	Aerial Part And Root	Alloxan Monohydrate	150	4 Hours	HanefiOzbek [2017]-[49]
5.	Algerian Pistachia lentiscus L.	Leaves	Alloxan Monohydrate	150	14 Days	A.Cherbal [2017]-[50]
6.	Allium tuberosum	Whole Plant	Alloxan Monohydrate	150	30 Days	XingliTang [2017]-[51]
7.	Amaranthus spinosus L	Leaves	Streptozotocin	70	21 Days	Girija K [2011]-[52]
8.	Anacardium occidentale Linn.	Leaves	Streptozotocin	100	30 Days	Y.S.Jaiswal [2017]-[53]
9.	Annona muricata	Leaves	Streptozotocin	55	28 Days	Ngueguim Tsofack Florence [2014]-[54]
10.	Anoectochilus roxburghii and Anoectochilus formosanus	Roots And Leaves	Streptozotocin	47	30 Days	Tingting Tanga [2018]-[55]
11.	Artemisia indica linn	Aeriel Parts	Streptozotocin	50	15 Days	Waqar Ahmad [2014]-[56]
12.	Atriplex halimus L	Leaf	Streptozotocin	50	30 Days	Ilyas Chikhi [2014]-[57]
13.	Callicarpa arborea	Stem Bark	Streptozotocin	55	21 Days	Julfikar Ali Junejo [2017]-[58]
14.	Callistemon lanceolatus DC,	Aerial Parts	Streptozotocin	60	15 Days	Syed Nazreen [2014]-[59]
15.	Centratherum anthelminticum	Seeds	Streptozotocin	65	4 Weeks	Aditya Arya [2012]-[60]
16.	Chaenomeles sinensis (Thouin) Koehne	Fruits	Streptozotocin	45	14 Days	Sandesh Sancheti [2013]-[61]
17.	Chloroxylon swietenia	Bark	Streptozotocin	50	45 Days	B.Jayaprasad [2016]-[62]
18.	Cichorium intybus L	Root	Streptozotocin	65	7 Days	Karine Ferrare [2017]-[63]
19.	Cissampelos pareira	Leaf	Streptozotocin	200	14 Days	Kuldeep Singh Yadav [2013]-[64]
20.	Coccinia grandis	Leaf	Streptozotocin	50	21 Days	Shahid Iqbal Mohammed [2016]-[65]
21.	Corn silk	Skin	Streptozotocin	160	4 Weeks	Wenzhu Zhao [2012]-[66]
22.	Cucurbita maxima	Seed	Streptozotocin	50	28 Days	Devesh Kumar Kushawaha [2017]-[67]
23.	Cuscuta reflexa Roxb.	Aerial	Streptozotocin	40	30 Days	Diptirani Rath [2016]-[68]

		Parts				
24.	Cynodon dactylon Pers	Aerial Parts	Alloxan Monohydrate	100	24 Hours	Md. Saidur Rahman [2015]-[69]
25.	Decalepis hamiltonii	Root	Alloxan Monohydrate	150	11 Days	Devi Manickam [2013]-[70]
26.	Dillenia indica L.	Leaves	Streptozotocin	50	28 Days	Navpreet Kaur [2016]-[71]
27.	Dioscoreophyllum cumminsii (Stapf),	Leaf	Alloxan Monohydrate	150	21 Days	H.O.B.Oloyede [2015]-[72]
28.	Diospyros melanoxylon	Leaves	Streptozotocin	45	28 Days	Kalpana Rathore [2014]-[73]
29.	Eugenia jambolana	Seeds	Streptozotocin	40	35 Days	Kishalay Jana [2015]-[74]
30.	Ficus racemosa	Stem Bark	Streptozotocin	50	7 Days	Pichaya Chowtivannakul [2016]-[75]
31.	Ficus talboti	Bark	Streptozotocin	55	21 Days	Karuppusamy Arunachalam [2014]-[76]
32.	Forsythia suspensa (Thunb.) Vahl	Fruit	Streptozotocin	180	4 Weeks	Yanyan Zhang [2016]-[77]
33.	Gymnema sylvestre (R. Br)	Leaves	Streptozotocin	150	28 Days	Srinivasan Prabhu [2014]-[78]
34.	Gypsophila trichotoma	Whole Plant	Streptozotocin	40	3 Weeks	Rumyana Simeonova [2016]-[79]
35.	Heracleum dissectum Ledeb	Aerial Parts	Streptozotocin	60	14 Days	Hailong Zhang [2017]-[80]
36.	Hyoscyamus albus L.	Seeds	Streptozotocin	130	20 Days	Lynda Bourebaba [2016]-[81]
37.	Lagerstroemia speciosa	Whole Plant	Streptozotocin	60	15 Days	Vipin Kumar Agarwal [2017]-[82]
38.	Icacina trichantha (I. trichantha) tuber	Root	Alloxan Monohydrate	160	21 Days	Onakpa Michael [2013]-[83]
39.	Indian Bauhinia vahlii	Stembark	Streptozotocin)	60	1 Week	Das Surya Narayan [2012]-[84]
40.	Kigelia pinnata	Flowers	Streptozotocin	60	21 Days	S. Kumar [2012]-[85]
41.	Leucaena leucocephala (Lam.) de Wit	Seed	Streptozotocin	65	6 Weeks	Jorge Alberto García-Díaza [2016]-[86]
42.	Malus toringoides (Rehd.) Hughes	Leaves	Streptozotocin And Alloxan Monohydrate	STZ (150) and ALX (200)	4 Days	Dan Li [2014]-[87]
43.	Marrubium vulgare L	Leaf	Alloxan Monohydrate	150	15 Days	Amel Boudjelal [2012]-[88]
44.	Melastoma malabathricum Linn.	Leaf	Alloxan Monohydrate	150	14 Days	Karuppasamy Balamurugan [2014]-[89]
45.	Mentha arvensis L	Leaves	Soluble Potato Starch 2 G/Kg B.W.	2000	120 Min	Sachin B.Agawane [2018]-[90]
46.	Merremia tridentata (L.)	Root	Streptozotocin	55	21 Days	Karuppusamy Arunachalam [2012]-[91]
47.	Musa paradisiaca	Bark	Streptozotocin	50	30 Days	Shanmuga Sundaram

	tepal					[2014]-[92]
48.	Pandanus fascicularis Lam	Root	Streptozotocin	60	24 Hours	Jothimni Rajeswari [2012]-[93]
49.	Persea americana Mill.	Leaf	Streptozotocin	50	4 Weeks	C.R. Lima [2012]-[94]
50.	Pistacia lentiscus	Leaf And Fruit	Streptozotocin	60	24 Hours	Chafiaâ Mehenni [2016]-[95]
51.	Polygonatum kingianum	Rhizome	Streptozotocin	30	8 Weeks	Jian-mei Lu [2015]-[96]
52.	Psidium guajava (L.) Bat.	Leaves	Alloxan Monohydrate	100	24 Hours	Santosh Mazumdar [2015]-[97]
53.	Quercus brantii Lindl.	Whole Plant	Streptozotocin	50	21 Days	Abdulahad Dogan [2015]-[98]
54.	Sarcococca saligna	Whole Plant	Streptozotocin	40	4 Weeks	Naeem Ullah Jan [2018]-[99]
55.	Selaginella tamariscina (Beauv.)	Whole Plant	Streptozotocin	35	8 Weeks	Xiao-ke Zheng [2011]-[100]
56.	Soymida febrifuga A. Juss	Bark	Alloxan Monohydrate	150	21 Days	Varicola Karunasree [2012]-[101]
57.	Synsepalum dulcificum	Leaf	Streptozotocin	40	21 Days	T.O.Obafemi [2017]-[102]
58.	Syzygium calophyllifolium	Bark	Streptozotocin	60	28 Days	Rahul Chandrana [2016]-[103]
59.	Trigonella foenum graecum	Bark	Streptozotocin	35	30 Days	Sorimuthu Pillai Subramanian [2014]-[104]
60.	Trigonella foenum graecum	Seed	Streptozotocin	60	4 Weeks	Mohammed R.Haeri [2012]-[105]
61.	Vatairea macrocarpa	Stem-Bark	Streptozotocin	47	22 Days	Helder C. Oliveira [2008]-[106]
62.	Vernonia amygdalina	Leaves	Streptozotocin	65	28 Days	Khang Wei Ong [2011]-[107]
63.	Zanthoxylum armatum DC	Spiny Shrub	Alloxan Monohydrate	80	24 Hours	Carey Vana Rynjah [2018]-[108]
64.	Zizyphus spina-christi (L.)	Leaf	Streptozotocin	50	24 Weeks	Camilia George Michel [2011]-[109]

5. DISCUSSION

Diabetes mellitus is spreading in an alarming way throughout the world and three fourth of the world populations and considered as a major cause of high economic loss which can in turn impede the development of nations. Moreover, uncontrolled diabetes leads to many chronic complications such as blindness, heart disease, and renal failure, etc. For this, therapies developed along the principles of western medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. Therefore, treating diabetes mellitus with plant derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. The study revealed that 64 plant species were generally used for treatment of diabetes. The majority of the experiments confirmed the benefits of medicinal plants with antidiabetic effect in the management of diabetes mellitus. The detailed natural plants not only used for the treatment of diabetes, but also treated for other ailments also. The fruits were most commonly used plant parts and other parts (leaf, root, stem, bark, flower, and whole plant) were also useful for curing. However, the diabetic model that was most commonly used was the streptozotocin and alloxan-induced diabetic mouse or rat as diabetic models. In this study, most commonly used animal model was STZ rat. The most commonly involved active constituents are Flavonoid, Tannin, Phenolics, and Alkaloid. Numerous mechanisms of actions have been proposed for these plant extracts. Some hypotheses relate to their effects on the activity of pancreatic ß cells (synthesis, release) or the increase of the insulin sensitivity or the insulin-like activity of the plant extracts. All of these actions may be responsible for the reduction or abolition of diabetic complications.

6. CONCLUSION

The present review has presented comprehensive details of antidiabetic plants used in the treatment of diabetes mellitus. Some of these plant derived medicines, however, offer potential for cost effective management of diabetes through dietary interventions, nutrient supplementation, and combination therapies with synthetic drugs in the short term, and as the sole medication from natural sources over the long term. The presences of bioactive chemicals are mainly responsible for this antidiabetic action. However, many other active agents obtained from plants have not been well characterized. More investigations must be carried out to evaluate the mechanism of action of medicinal plants with antidiabetic effect.

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