Review Article

Diabetes and related remedies in medieval Persian medicine

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ABSTRACT

Diabetes Mellitus is a common metabolic disorder presenting increased amounts of serum glucose and will cover 5.4% of population by year 2025. Accordingly, this review was performed to gather and discuss the stand points on diagnosis, pathophysiology, non-pharmacological therapy and drug management of diabetes this disorder as described in medieval Persian medicine. To this, reports on diabetes were collected and analyzed from selected medical and pharmaceutical textbooks of Traditional Persian Medicine. A search on databases as Pubmed, Sciencedirect, Scopus and Google scholar was also performed to reconfirm the Anti diabetic activities of reported herbs. The term, *Ziabites*, was used to describe what is now spoken as diabetes. It was reported that *Ziabites*, is highly associated with kidney function. Etiologically, *Ziabites* was characterized as kidney hot or cold dystemperament as well as diffusion of fluid from other organs such as liver and intestines into the kidneys. This disorder was categorized into main types as hot (*Ziabites-e-har*) and cold (*Ziabites-e-barid*) as well as sweet urine (*Bole-e-shirin*). Most medieval cite signs of *Ziabites* were remarked as unusual and excessive thirst, frequent urination and polydipsia. On the management, life style modification and observing the essential rules of prevention in Persian medicine as well as herbal therapy and special simple manipulations were recommended. Current investigation was done to clarify the knowledge of medieval scientists on diabetes and related interventions. Reported remedies which are based on centuries of experience might be of beneficial for- further studies to the management of diabetes.

Key words: Diabetes, herbal medicine, medieval persia, traditional medicine, *Ziabites*

Introduction

With reference to the findings of contemporary medicine, Diabetes Mellitus is a common metabolic disorder. This complication which is resulted from insulin insufficiency or dysfunction may cover over 5.4% of population or 57.2 million people by the year 2025.[1,2] Although the pathophysiology of diabetes is not yet well understood, evidences have suggested the impact of free radicals in the pathogenesis and development of diabetes.[3,4] Most common cited symptoms of diabetes Mellitus are increased serum glucose, unusual thirst, frequent urination, blurred vision, hyperphagia, nausea and vomiting as well as loss of weight.[5] On the treatment pathway, a number of medicaments are administered in addition to the insulin therapy.[6] Other than the current pharmacotherapy of diabetes, interventions concerned to the complementary and alternative medicine are also considerable. Accordingly, extensive information would be obtained from the beliefs of folk medicine and practices by local healers as well as remained manuscripts of traditional medical systems.[7] With respect to the findings of integrative medical systems, it is remarkable that Traditional Persian Medicine (TPM) plays a considerable role in the development of treatment approaches during the medieval era.[8] During the 8th to 12th century AD, Persian physicians and scholars such as Rhazes and Avicenna gathered the medical information of traditional remedies from China, Egypt,

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Greece and India and also supplemented it by their own findings and experiences.[9,10] In this regard, remained medical and pharmaceutical manuscripts authored by early Persian practitioners encompass large and remarkable information on various categories of ailment. Among those, considering the nutritional aspects and pharmacological of diabetes and related complications would be of beneficial. Accordingly, current study has been carried out to gather the most cited medieval Persian information on diabetes as well as those management approaches.

Materials and Methods

Medieval reports encompassing the profile of definition and terminology, classification and etiology, as well as sign and symptoms of diabetes were collected and analyzed from selected medical textbooks of TPM. The concerned collection was based on the analysis of remaining manuscripts of medieval Persia from 9th to 18th centuries AD involving medical and pharmaceutical textbooks of this period. In this regard, manuscripts namely *Canon of Medicine* (11th century), *Al- aghraz al- tebbieh va al- mabahes al-alayieh* (12th century), *Kholasat-ol-Tajarob* (16th century), *Tebb-e-Akbari* (18th century) and *Eksir-e-Aazam* (19th century) were considered for the medical points.[11-15] On the other hand, pharmacological treatment aspects of diabetes in medieval period were also gathered from main Persian pharmaceutical manuscripts containing The *Liber Continents* by Rhazes (9th and 10th centuries), The *Canon of Medicine* by Avicenna (11th centuries), *Alabnie an haghaegh-ol-advieh* by Aboo mansour Heravi (10th century), *Ikhtiyarat-e-Badiyee* by Zein al-Din Attar Ansari Shirazi (14th century), *Tohfat ol Moemenin* by Mohammad Tonkaboni (17th century) and *Makhzan ol Advieh* by Aghili-Shirazi (18th century).[16-20] These texts are considered as most important sources among medical and pharmaceutical manuscripts of Persian medicine.[21] Other textbooks such as "Matching the Old Medicinal Plant Names with Scientific Terminology",[22] "Dictionary of Medicinal Plants",[23] "Dictionary of Iranian Plant Names",[24] "Popular Medicinal Plants of Iran"[25] and "Indian Medicinal Plants"[26] were also used to check and reconfirm the plants scientific names. Table 1 represented brief information on employed manuscripts of medieval Persian medicine.

It is also considerable, that an extensive search on most popular databases as Pubmed, Sciencedirect, Scopus and Google scholar was performed to reconfirm the Anti diabetic activities of reported herbs as well as concerned pharmacological actions.

Results

Diabetes, current medicine

As a metabolic disorder, diabetes is characterized in that of unexpected serum glucose elevation. General manifestation of diabetes is known as polyuria, polydipsia and polyphagia as well as weight loss. Generally, diabetes is divided into two main types, 1 and 2. Type 1 is resulted from loss of insulin secretion and the most prevalent of type 2 is reported as obesity and unusual weight gain. In addition to these main groups, gestational diabetes mellitus (GDM) is also present as the commonest metabolic disorder during pregnancy. Other specific diabetes types also need to be mentioned. Of those, genetic defects of beta cell function, insulin genetic dysfunction, exocrine pancreatic disorders and endocrinopathies such as hyperthyroidism and glucagonoma may cause diabetes. Also a kind of diabetes namely diabetes insipidus is reported in medical textbooks which is related to impaired angiotensin-vasopressin secretion.[27] Main clinical approaches in diabetes mellitus include life style modification, drug therapy to control glycemia and prevention/management of associated complication.[27]

Ziabites, Medieval definition, etiology, categories and clinical manifestation

The term, *Ziabites*, or *Doolab* (water wheel) in Persian, was used by early Persian scholars to define and describe what is currently spoken as diabetes. Since, *Ziabites* is a Greek word; it was mentioned by Greek physicians well before the entrance to Persian manuscripts. Concerning the definition, it was remarked that the disorder of *Ziabites*, which in that patient suffers from excessive thirst, is highly associated with kidney function. It was said that retentive force of kidney is impaired and hence can be distinguished by excessive urine output. Furthermore, the diffusion of fluid from other organs such as liver and intestines into the kidneys was noted as another etiological symptom that Persian scholars believed in.[11,13,14]

Similar to the fundamental mechanisms of humoral medicine,[28] the disorder was said that may be resulted from an imbalance in the kidney temperament as well as whole body. Hence, treatment was based on the modification of temperament and humors to reach to an optimum or balanced state.[29]

Regarding the mentioned dystemperament, the disorder was categorized into two main types as hot (*Ziabites-e-har*) and cold (*Ziabites-e-barid*). The hot type was reported to be accompanied by unusual and excessive thirst, unusual colored urine and frequent urination as well as excessive augmentation of libido and weight loss or emaciation. On

Table 1: Medieval manuscripts which were reviewed for the survey

Manuscript	Author	Authoring date	Description
Alabnieh an haghaegh ol advieh (the book of remedies)	Aboo mansour Heravi	10th century A.D.	It is the oldest documented Persian text in the whole world that involves 547 monographs on simple herbal, animal and mineral medicines. An original manuscript with 400 pages is kept in Vienna museum.
Kitāb al-Qānūn fī al-ṭibb (The Canon of Medicine)	Avicenna	11th century A.D.	It is one of almost 450 treatises authored by Persian scientist and physician Avicenna. He has listed 800 medicaments, containing plant, animal and mineral substances, with descriptions on their administration and effectiveness.
Ikhtiyārāt-i Badīʿī (Selections for Badīʿī)	Ali ibn al-Husayn al-Ansari Shirazi	14th century A.D.	The text is a Persian pharmacopoeia of simple and compound natural medicines written in Persian in 1368 A.D in Shiraz. The treatise is in two sections encompassing 1005 natural medicaments in alphabetical order in 28 chapters.
Kitāb al-Ḥāwī fī al-ṭibb (The Comprehensive Book on Medicine or Liber Continens)	Rhazes	10th century A.D.	The book involves several chapters in medicine and pharmacy, 20th and 21st of which are on materia medica and contain 898 simple drugs.
Tuḥfat al-mu'minīn (The Present for the Faithful)	Muhammad Mumin Daylami Tonkaboni	17th century A.D.	The book is a Persian treatise and a comprehensive pharmacopoeia of simple and compound medications. Totally, 763 simple natural medicaments have been described in the book.
Makhzan al-adviyah (The Storehouse of Medicaments)	Mohammad Hossein Aghili Alavi Khorasani Shirazi	18th century A.D.	The book is often mentioned as the largest and one of the latest pharmacopoeias of Traditional Persian Pharmacy in 14 chapters on principals and 28 chapters on drugs in alphabetical order and containing 1698 monographs.
Eksir-e-Aazam (The Grand Exir)	Azam Khan Cheshti	19th century	It is one of the most detailed medical encyclopedias of traditional Persian medicine in 4 large volumes and involves diseases from head to toe, general ailments and concerned treatments. The author gathered all experiences of other scholars from Persia, India and Greece as well as his own finding and authored the text in 30 years.
Al- aghraz al- tebbieh va al- mabahes al-alayieh (medical objectives and excellent researches)	Seyyed Esmaeel Jorjani	12th century	The book is written in Persian and contains 26 chapters in two volumes. First volume discusses the principals of medicine and related topics. Diseases from head to toe are mentioned in following.
Kholasat-ol-Tajarob (Summery of experiences)	Baha-o-dowleh Razi	16th century	It is a medical Persian textbook and encompasses 28 chapters in 350000 words. The author discussed the diseases and remedies from his own experiences and also those of inventors from India.
Tebb-e-Akbari (Akbar's Medicine)	Akbarshah Arzani	18th century	It is a Persian medical textbook in 27 chapters (babs) and a conclusion (khatimah). Symptoms and treatment of diseases are mentioned in related chapters and compound remedies and medical terminology are discussed in conclusion part.

the other hand, in cold type, thirst but less than the above type, bright colored urine, loss or reduction in libido, loss of appetite and also weight loss and slimming. According to the medieval reports, the hot type of *Ziabites* was more prevalent.[11,13,14]

In a resulted version of *Ziabites*, Persian scholars remarked that ants and other insects may be attracted to the patient's urine. Also it was mentioned by Avicenna that by standing the urine of a diabetic patient under surrounding air, a residue is leaved with sticky and sweet tastes as honey.[30] *Ziabites*, in this case was named as *Bole-e-shirin* or sweet urine. This type was reported that may be occurred in case of chronicity of *Ziabites*. It was also assumed that the kidney function may be impaired in this condition. Therefore, all medications and management strategies which were considered for the impaired kidneys should also be applied for this disorder, as it was mentioned by early Persian practitioners.[11] Table 2 represented the classification of diabetes according to Persian medicine. Also a brief overview and comparison between modern aspects of diabetes and medieval description of *Ziabites* is represented in Table 3.

Clinical interventions

Concerning the management strategies as well as preventive approaches for *Ziabites*, there are lots of recommendations in reviewed manuscripts. The six essential schemes for health

Table 2: Medieval classification of *Ziabites*

***Ziabites* type**	**Etiology**	**Sign and symptoms**	**Treatment**
Hot (*Ziabites-e-har*)	Hot dystemperament of kidneys, Impairment of kidney retentive force.	Excessive thirst, unusual colored urine, frequent urination, excessive augmentation of libido, weight loss or emaciation.	Life style modification, food or medicines having cold temperament.
Cold (*Ziabites-e-Barid*)	Cold dystemperament of kidneys, Impairment of kidney retentive force.	Thirst (less than the above type), bright colored urine, frequent urination, loss or reduction in libido, loss of appetite, weight loss and slimming.	Life style modification, food or medicines having cold temperament.
Sweet urine (*Bole-shirin*)	Hot or cold, but chronic type of *Ziabites*, Impairment of kidney retentive force.	Thirst, frequent urination, sweet urine or honey urine.	Life style modification, food of medicines with opposite temperament regarding nature of the disease.

Table 3: Ziabites and Diabetes, the comparison

	Ziabites (Traditional term)	**Diabetes (Current medicine)**
Definition	A disease in which, patient suffers from excessive thirst and tries to compensate the situation. But the ingested water is excreted through urine.	It is a common metabolic disorder that is characterized by high blood sugar levels (hyperglycemia).
Signs/Symptoms	Unusual thirst, polydipsia, Weight loss, Polyuria.	Polydipsia, Weight loss, Polyuria.
Categorization	Cold and Hot Ziabites, Chronic type (Bole-shirin or sweet urine.	Types I, II, Gestational diabetes and specific types.
Etiology	Dystemperament or impairment of kidneys, Hot or Cold.	Lack or loss of insulin regarding impairment of pancreas, resistance to insulin secretion, hormonal variation, pancreatitis, hyperthyroidismand malignancies.
Diagnosis	From signs and symptoms which were mentioned in medieval texts.	Fasting blood sugar level between 100 and 125 mg/dL Random blood sugar of 200 mg/dL in addition to Polydipsia, Weight loss and Polyuria. The 2h post-challenge plasma glucose over 200 mg/dL.
Prevention	Observing the six essential parameters for the health maintenance or Setteh-e-Zarurieah (weather, food and beverage, retention and evacuation, repose and movement, sleep and wakefulness and sensual qualities).	Inhibition of immune system by increasing the resistance of pancreas islands beta cells to the destruction, Administration of certain antibodies (Type I diabetes). Life style modification and reducing the risk factors (Type II diabetes).
Interventions	Nutritional therapies (Tadbir ba Ghaza) and life style modification Herbal remedies (simple or compound medicines) special physical manipulations (A'mal-e-yadavi)	Insulin, Alpha-glucosidase inhibitors (such as Acarbose) in association with insulin (Type I diabetes) Stimulators of insulin secretion (such as gliclazide), Biguanides (such as Metformin), Thiazolidinedione (such as Pioglitazone)

maintenance which were called *Setteh-e-Zarurieah* (involving observation and optimization of six main parameters as weather, food and beverage, retention and release, repose and movement, sleep and wakefulness as well as sensual and mental states) were considered as main preventive approaches. These parameters were being observed prior medication and are considered as life styles in current medicine.[31]

Pharmaceutical manuscripts of Persian medicine offer plenty of natural remedies for the management of *Ziabites*. Natural medicines were applied solely (mono-ingredient) or in combination to other medicaments (multi-ingredients). Early practitioners applied three main categories of medicaments. First approach was based on nutritional therapy (*Tadbir ba Ghaza*) and life style modification. In this condition, natural agent with opposite temperament compared to the type of *Ziabites* was administered. In the other word, foods or beverages such as beer, milk, barely soap, Plum and courgette khoresht, yogurt and verjuice which possess cold temperament were applied for hot type of *Ziabites*.[32] On the other hand, medicinal herbs in form of simple or compound dosage forms were administered to manage the disorder. Most cited natural medicaments concerned to either hot or cold *Ziabites* are shown in Table 4. Other than the natural pharmacotherapy, special physical manipulations (*A'mal-e-yadavi*) have also being applied by early Persian physicians. These approaches were usually involved venesection (*Fasd*), cupping (*Hijamat*) and massaging (*Dalk*). Regarding the type of *Ziabites* and also patient's dystemperament, these interventions were applied before or after herbal therapy.[11] In addition to physical manipulation, other approaches were also considered. As an example, sitting in water was recommended by Rhazes. He believed that this procedure tightens the muscles of bladder and suppresses thirst.[33]

Discussion and Conclusion

Before mid of the nineteenth century, it was believed that diabetes is a disease related to kidney function.[34]

Table 4: Most prevalent medicinal plant for the management of Ziabites

Scientific name	Traditional name	Part	Current findings	Fraction/Constituent(s)
Hot type of Ziabites (Ziabites-e-har)				
Berberis vulgaris L.	Ambarbaris	Fruit	Hypoglycemic effect in normal and streptozotocin-induced diabetic rats[43].	Aqueous and saponins extracts.
Cichorium intybus L.	Hendeba	Aerial	Reduction in glucose-6-phosphatase activity, Lowering the concentration of blood glucose[44].	Ethanol extract
Citrus aurantium L.	Limoo	Fruit	Tissue lipid lowering effect in genetic diabetic mice[45].	Aqueous extract made by decoction
Citrus medica L.	Otroj	Fruit	Hypoglycemic activity[46].	Hexane extract (monoterpenes and sesquiterpenes).
Coriandrum sativum L.	Kazboreh	Seed	Hypoglycemic, insulin-releasing and insulin-like activity[47]. Reduction in serum glucose and increasing the insulin release[48].	Aqueous extract Ethanol extract
Cucumis sativus L.	Ghasa'a	Fruit	Antidiabetic effects in streptozotocin induced rats[49].	Ethanol extract
Cucurbita pepo L.	Ghar'a	Fruit	Increasing serum insulin level, Reducing the blood glucose level, Improving the glucose tolerance[50,51].	Protein-bound polysaccharide, Total polyphenols, flavonoids and ascorbic acid.
Cydonia oblonga Mill.	Safarjal	Fruit	Reduction in blood glucose level in streptozotocin-induced diabetic rats[52].	Ethanol extract
Hordeum vulgare L.	Shaeer	Seed	Reduction in serum glucose in diabetic rats[53].	Aqueous extract
Lactuca sativa L.	Khas	Leaf	-	-
Lens culinaris Medik.	Adas	Seed	-	-
Malus pumila Mill.	Toffah	Fruit	-	-
Nymphaea alba L.	Niloofar	Flower	-	-
Oxalis acetosella L.	Hommaz	Fruit	-	-
Papaver somniferum L.	Khashkhah	Seed	-	-
Plantago ovata Phil.	Bazreghatoona	Seed	Reduction in serum glucose in diabetes via inhibition of intestinal glucose absorption[54].	Aqueous extract
Portulaca oleracea L.	Baghlatol-hamgha	Aerial	Reduction in fasting blood sugar, Modulation of blood lipid and glucose metabolism[55].	Polyunsaturated fatty acids, flavonoids, polysaccharides
Prunus amygdalus Batsch	Lawz	Seed	Hypoglycemic effects[56]	Proportionate fractions
Prunus domestica L.	Ejjas	Fruit	-	-
Punica granatum L.	Romman	Flower	Reduction in fasting blood glucose[57]. Inhibitory effect on alpha-glucosidase activity[58].	Aqueous extract
Pyrus communis L.	Komsari	Fruit	-	-
Rheum ribes L.	Ribas	Root	Stimulating the insulin release[59]. Effects on lipid and glucose profile in type II diabetic hypercholesterolemia patients[60].	Anthraquinone glycosides of aloe emodin, emodin, and chrysophanol derivatives.
Rhus coriaria L.	Somagh	Fruit	Inhibition of a glycoside hydrolase and α-amylase[61].	Ethyl acetate extract
Rosa damascena Mill.	Vard-e-ahmar	Flower	Inhibitory effect on α-glucosidase and suppressing the carbohydrate absorption from intestine[62].	Methanol extract
Santalum album L.	Sandal	Bark	Potential antihyperlipidemic activity in streptozotocin induced diabetic rats[63].	Ether fraction
Spinacia oleracea L.	Esfanakh	Leaf	Reduction in blood glucose level[64].	Aqueous extract
Tamarindus indica L.	Tamr	Seed	Inhibition of glucose-6-phosphatase, Reduction of glutamate oxaloacetate transaminase and glutamate pyruvate transaminase activity[65].	Aqueous extract
Viola odorata L.	Banafsaj	Flower	-	-
Vitis vinifera L.	Hesrem	Fruit	Remarkable antidiabetic effect[66].	Ethanol extract containing condensed tannins and flavonoids.
Zizyphus sativa L.	Onnab	Fruit	Hypoglycemic activity in normal and alloxan-diabetic rats[67].	Ethanol extract
Cold type of Ziabites (Ziabites-e-barid)				

Contd...

Table 4: Contd

Scientific name	Traditional name	Part	Current findings	Fraction/Constituent(s)
Alpinia officinarum Hance	Khoolanjan	Root	-	-
Apium graveolens L.	Karafs	Seed	Changes in blood lipid profiles[68].	Aqueous extract
Boswellia sacra Flueck.	Kondor	Gum	-	-
Cinnamomum verum J.Presl	Darsini	Bark	Anti-diabetic effect via upregulation of mitochondrial uncoupling protein-1[69].	Aqueous cinnamon extract
Cocos nucifera L.	Narjil	Fruit	Reduction in fasting blood glucose[70].	Hydro-methanol extract
Cuminum cyminum L.	Kommoon	Seed	Hypoglycemic activity, Increasing the insulin level[71].	Ethanol extract
Cyperus longus L.	Soad	Root	-	-
Echium amoenum Fisch.	Lesanol-sowr	Leaf	-	-
Ficus carica L.	Tin	Fruit	Lowering the post-prandial glycemia[72].	Aqueous decoction
Foeniculum vulgare Mill.	Razianaj	Seed	Hypoglycemic effect[73]	Seed fixed oil extract
Juglans regia L.	Jowz	Leaf	Inhibitory effects on α-glucosidase activity and reduction in fasting sugar[74].	Methanol Extract
Melissa officinalis L.	Badranjbooyeh	Leaf	Reduction in serum glucose and improvement of glucose tolerance due to enhanced glucose uptake and metabolism as well as inhibition of gluconeogenesis in liver[75].	Essential oil
Prunus amygdalus Batsch	Lawzol-morr	Seed	Hypoglycemic effects[56].	Proportionate fractions
Rheum palmatum L.	Ravand	Bark	Activation of peroxisome proliferator-activated receptor-γ[76].	Emodin
Thymus vulgaris L.	Hasha	Aerial	-	-
Trigonella foenum-graecum L.	Holbeh	Seed	Reduction in fasting blood glucose and improving the hemorheological properties[77].	Whole seed powder, Extract

However, in 1922, the isolation of insulin from animal pancreas confirmed the diabetes as an endocrine disorder.[35] Findings from main manuscripts of Persian medicine revealed that there are some similarities between the disorder of *Ziabites* and what is currently accepted as diabetes mellitus. Unusual thirst, polyuria and weight loss are some of the main similarities. On the other hand, *Ziabites* may also be closed to diabetes insipidus. But it should be noted that polyuria would not be stopped in this type of diabetes even if no fluid is ingested.[32] In the type II of diabetes, a large group of affected patients may have no notification about their disorder and serum glucose evaluation should be carried out to confirm the disorder. It seems that in medieval time, also a large number of patient with this type of diabetes were left uncured in due to lack of paraclinical examinations. With reference to the management of *Ziabites*, many instructions regarding health maintenance were recommended by Persian scholars. Considering the six essential parameters (*Setteh-e-Zarurieah*) were highly emphasized by early Persian practitioners. Similar to these rules, current medicine has also rendered considerable recommendation. Avoidance of environmental pollution,[36] scheduled and adequate exercise and sport,[37] appropriate sleep and awareness (sleep less than six hours is mentioned as a main predisposing factor for diabetes),[38] eluding stress and psychological tensions[39] as well as proper nutritional regimen and rich fiber foods have high impact on diabetes.[40] Concerning the treatment of different types of *Ziabites*, medicinal plants having specific temperament which was related to either hot or cold *Ziabites* were used for the treatment. Totally 46 different medicinal herbs were found as cure for hot or cold types of *Ziabites*. A search through considered databases revealed that almost 70% of reported medicaments were active for anti diabetic effects. Most considered mechanisms for medieval herbs were as reduction in serum glucose level or fasting blood sugar, increasing serum insulin level or stimulating the insulin release and inhibition of intestinal glucose absorption [Table 2].

It was believed that there are differences between various types of temperaments in different patients. In this regard, Persian practitioners differentiated *Ziabites* regarding the patient's temperament and used the relevant medication. This fact can be corresponding with what is accepted as pharmacogenetic in current medicine.[41] However, differences in temperament are also evaluated regarding the endocrine and immune system.[42] Therefore, according to the temperament, administration of similar medication for patients suffering from a disease should be avoided.

As *Ziabites* is composed of hot and cold types in TPM, different treatments have been recommended for each individual types of the disease and patients. However, this approach is not yet considered by contemporary medicine.

Current research was a survey to clarify the knowledge of medieval Persian scientists on disorder of diabetes and related pharmacological intervention strategies. Reported remedies are based on centuries of experience and thus might be of beneficial for further studies to the management of diabetes and related unwanted effects.

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