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Review article

Traditional Methods of Diabetes Mellitus Treatment

Khalid Abdulkareem Mohammed[1]*

ABSTRACT

Diabetes mellitus is one of the most common metabolic diseases in the world, and the incidence of this disease is not limited to specific age groups, and it appears among men and women and there is no effect on gender, age, and geographic area on the outbreak of this disease. Synthetic and natural materials have been used to control blood sugar levels in diabetics. The current study sheds light on the importance of this disease and the extent of its spread in the world, in addition to its most important types, which are Insulin-dependent diabetes mellitus (IDDM) Insulin-independent diabetes mellitus (IIDM), and Gestational diabetes. The current study showed the most important herbal extracts that were used and are still used today in many countries to control hyperglycemia in diabetics, especially *Brassica olerace*. The effect of these herbal extracts is due to the presence of some active substances that reduce high blood sugar levels, and the most important of these substances are phenols and alkaloids. The effect of these substances on insulin-producing cells was discussed, as well as their direct and indirect effect on controlling high blood sugar in laboratory animals and people suffering from various types of diabetes. The study concluded that the use of herbal medicine is effective in reducing hyperglycemia in the patients with diabetes, in addition to being safe and having no side effects on patients who use them.

Keywords: Diabetes mellitus, Herbal medicine, Insulin-dependent diabetes, Insulin-independent diabetes.

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1. INTRODUCTION

Most conventional approaches and remedies utilized for the management of diabetes rely on the utilization of herbal medicine. Herbal medicine entails the utilization of plants for medicinal intentions. Throughout a significant portion of human history, plants have constituted the foundation for medical treatments, and this form of traditional medicine continues to be widely practiced in the current era [1]. One of the most practical plants employed in herbal medicine is *Brassica oleracea*. *B. oleracea* pertains to the Brassicaceae (Cruciferae) botanical family. The wild variant of this plant originated along the Atlantic coast of Western Europe and the Mediterranean basin. *B. oleracea* has been cultivated as a vegetable for over 2,500 years, and through selective breeding, distinct characteristics of the plant have been developed [2]. Diabetes encompasses a chronic metabolic disorder typified by elevated blood glucose levels. This condition arises either due to inadequate endogenous insulin production by the pancreatic beta cells, known as type 1 diabetes, or impaired insulin secretion and/or action, referred to as type 2 diabetes. Type 1 diabetes represents an autoimmune ailment characterized by T-cell-mediated destruction of the pancreatic beta cells. In the case of type 2 diabetes, there is a gradual progression of insulin resistance and beta cell dysfunction, which are strongly linked to obesity and a sedentary lifestyle [3]. Given the higher incidence of the risk factors, the prevalence of diabetes is escalating worldwide, with developing nations experiencing a more pronounced impact. Current estimates project a 69% increase in the number of adults affected by this disease between 2010 and 2030, in contrast to a 20% increase observed in developed countries [4].

Significant advancements have been made in the field of synthetic drug development. However, ongoing investigations are being carried out to explore natural and cost-effective food

* Correspondence: **Assistant Professor, Dr. Khalid Abdulkareem Mohammed.** E. mail: khalid.kreem@yahoo.com
Department Chemistry, College of Science, University of Baghdad, Baghdad, Iraq.
Full list of author information is available at the end of the article.

sources for managing hyperglycemia and hypertension associated with diabetes. This is achieved through the consumption of diets rich in legumes, fruits, vegetables, herbs, and spices. These plant-based foods contain essential nutrients such as vitamins, minerals, and dietary fibers, as well as bioactive compounds including polyphenols, carotenoids, and alkaloids [5,6]. These bioactive compounds have specific structure-function benefits [7] and have the potential to prevent and reduce the occurrence of early stages of chronic diseases such as type II diabetes and cardiovascular diseases, along with their complications. Many plant foods and specific varieties of certain species contain hypoglycemic compounds that act as anti-metabolites, effectively blocking specific disease pathways, including the oxidation pathway of fatty acids (5,8]. Medicinal herbs and seeds derived from plant sources are known to have low toxicity levels and possess various therapeutic properties. Consequently, they are considered to be safer alternatives to synthetic drugs. Natural plant and food sources also offer α-amylase and α-glucosidase inhibitors, which contribute to controlling postprandial hyperglycemia [9] with minimal side effects [10].

The levels of phenolic phytochemicals in leaves, stems, fruits, and seeds of numerous plant sources are being evaluated, as they are known to exhibit high antioxidant activity [11]. Phenolic phytochemicals serve as a defense mechanism for plants against abiotic and biotic stresses, but they also offer significant benefits in preventing and combating chronic diseases associated with oxidative stress in humans [12]. The presence of specific phenolic compounds in plant foods is strongly correlated with high antioxidant activities and substantial amounts of α-amylase and α-glucosidase inhibitors. These compounds play a vital role in managing hyperglycemia and related complications of hypertension [10].

The utilization of artificial drugs in the treatment of diabetes and glucose control in diabetic patients is often accompanied by various side effects [13]. Furthermore, these drugs tend to be costly, prompting many research centers worldwide to focus on the use of natural plant-based products for glucose level control in diabetic patients. The present study offers substantial evidence regarding the effectiveness of different compounds extracted from *B. oleracea* var. capitata and other plants in reducing blood glucose levels in diabetic patients [14].

2. DIABETES MELLITUS

Diabetes mellitus, commonly known as diabetes, refers to a collection of metabolic diseases characterized by prolonged periods of elevated blood sugar levels. This abnormal increase in blood sugar manifests in symptoms such as frequent urination, increased thirst, and heightened hunger. If left untreated, diabetes can lead to various complications. These complications include acute conditions like diabetic ketoacidosis and nonketotic hyperosmolar coma, as well as serious long-term complications such as heart disease, stroke, kidney failure, foot ulcers, and damage to the eyes [15]. Diabetes mellitus is now emerging as a prevalent metabolic disorder, arising from the inability of the body to properly respond to high blood glucose levels. Type II diabetes mellitus accounts for approximately 90-95% of all diagnosed diabetic cases [16]. The epidemic nature of type II diabetes is closely linked to obesity, with the World Health Organization (WHO) reporting that over 220 million individuals were affected by the condition in 2009 [17]. Projections suggest that the number of people afflicted with diabetes will exceed 350 million by 2030 [18]. The incidence of diabetes patients experiencing complications is steadily increasing, leading to hospital admissions due to diabetes itself or its associated complications, such as stroke, hypertension, amputation, nephropathy, neuropathy, retino-pathy, cardiovas-cular issues, impotence, and skin lesions. An analysis of mortality trends in the United States between 1970 and 2002 revealed the largest reductions in age-adjusted death rates were for stroke (63%) and heart disease (52%) [19,20]. The growing number of individuals affected by diabetes indicates a global epidemic. The prevalence of this disease was estimated to be 2.8% in 2000 and is projected to rise to 4.4% by 2030. While the prevalence of diabetes is anticipated to increase across all age groups, it is expected that there will be a particularly pronounced increase in the proportion of patients aged 45–64 years [21]. A previous study demonstrated that individuals with diabetes who have inadequate health literacy and hypertension possess less knowledge about their condition compared to those with sufficient health literacy [22].

2.1. Insulin-dependent diabetes mellitus (IDDM)

Diabetes mellitus results from the body's failure to produce enough insulin. This form was previously referred to as IDDM (type 1 diabetes) or "juvenile diabetes". The cause is unknown. Type 1 diabetes occurs as a result of auto-immune beta-cell destruction in the pancreas, characterized by a total absence of insulin production. Type 1 diabetes is responsible for 5% to 10% of all cases of diabetes. Associated risk factors include autoimmune, genetic, and environmental factors. Till the present time, known solutions to prevent diabetes have not been discovered [23]. Type 1 diabetes onset is relatively early in life, in childhood or adolescence, and usually before the age of thirty. This type of diabetes is a relatively homogeneous disease in which the insulin secretion of beta cells in the pancreas declines and eventually ceases totally [24, 25].

2.2. Insulin-independent diabetes mellitus (IIDM)

Type 2 diabetes can be linked to be accounting for around 90 percent of all cases, it is a chronic metabolic disorder, in which the body is unable to utilize glucose from food because of the inability of the pancreas to produce insulin or produces insufficient insulin, or the insulin itself is inactive [26]. Type 2 develops when there is an unexpected increased resistance against the action of insulin and the body cannot produce proportionate insulin to counter the resistance. The incidence of Type 2 diabetes in children and adolescents is noted to be on a dramatic increase. It accounts for 90% to 95% of all diagnosed cases of diabetes [23, 27].

2.3. Gestational diabetes

Gestational diabetes is the third main case and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level.

3. DIANETES MANAGEMENT BY TRADITIONAL HERBAL MEDICINES

A multitude of scholarly articles have been published regarding the use of medicinal plants in the treatment of diabetes in various regions across the globe [28]. These articles have also explored the specific use of medicinal plants in certain areas, such as West Africa [29], Central America [30], and Asia [31].

These reviews have shed light on the fact that a significant portion of the global population relies on traditional medicine for the management of diabetes. This reliance on traditional medicine has been acknowledged by the World Health Organization (WHO), which estimates that approximately 80% of the populations in African and Asian countries depend on traditional medicine for their primary healthcare needs [32]. The WHO recognizes traditional medicine as an accessible, affordable, and culturally accepted form of healthcare that is trusted by a large number of people. It is seen as a way to address the increasing prevalence of chronic non-communicable diseases, despite rising healthcare costs and global austerity measures [32].

Although significant progress has been made in the development of synthetic drugs, researchers are currently investigating natural and cost-effective food sources for managing hyperglycemia and hypertension in the early stages of diabetes. This research focuses on diets that are rich in legumes, fruits, vegetables, herbs, and spices. These plant-based foods provide essential nutrients, such as vitamins, minerals, and dietary fibers, as well as bioactive compounds like polyphenols and carotenoids [5]. These bioactive compounds have specific structure-function benefits that are beneficial for managing diabetes [33]. Many plant-based foods and specific varieties of certain species contain compounds that have hypoglycemic properties. These compounds act as anti-metabolites, blocking specific disease pathways, including the oxidation pathway of fatty acids [8]. Medicinal herbs and seeds derived from plants are known to have low toxicity levels and possess various therapeutic properties, making them a safer alternative to synthetic drugs. Natural plant and food sources also provide α-amylase and α-glucosidase inhibitors, which can help control postprandial hyperglycemia with minimal side effects [7, 34].

Researchers are currently evaluating the levels of phenolic phytochemicals in herbs and seeds derived from various plant sources. These phytochemicals have high antioxidant activity and are used by plants to protect themselves from environmental and biological stresses. They also have potential benefits in preventing and treating chronic diseases in humans that are linked to oxidative stress [35]. The presence of certain phenolic compounds in plant-based foods is associated with high antioxidant activity, as well as high levels of α-amylase and α-glucosidase inhibitors. These compounds play a role in managing hyperglycemia and related complications, such as hypertension [36].

3.1. Medicinal Plants with Antidiabetic

Many examples of plants and their extract that used in diabetes treatment in several places all over the world there are several examples of plants uses for controlling the blood sugar and managing the debits such as, *Abelmoschus moschatus* Medik (Malvaceae) (Liu *et al.,* 2007), *Acacia arabica* (Lam) Wild. (Mimosaceae), *Achyranthes aspera L (*Amaranthaceae), *Acosmium panamense* Schott. (Leguminosae), *Allium cepa* L. (onion): (Liliaceae), *Allium sativum* L. (garlic): (Liliaceae), *Annona squamosa* L (Annonaceae), *Artemisia herba-alba* Asso (Med). (Asteraceae), *Astragalus membranaceus* Bunge (Fisch.) (Leguminosae, *Bauhinia candicans* Benth (Leguminosae), *Bauhinia forficate* Link. (Caesalpinaceae), *Bidens pilosa* L (Asteraceae), *Biophytum sensitivum* (L) DC. (Oxalidaceae), *Bixa orellana* L. (Bixaceae), *Brassica nigra* (L) Koch (Brassicaceae), *Bryonia alba* L. (Cucurbitaceae), *Caesalpinia bonducella* (L) Roxb . (Caesalpinaceae), *Cajanus cajan* (L) Millsp. (Papilionaceae), *Carum carvi* L.(CC) (Apiaceae) / *Capparis spinosa* L. (CS) (Capparidaceae), *Casearia esculenta* Roxb. (Flacourtiaceae), *Cassia auriculata* L.(Caesalpinaceae), *Catharanthus roseus* (L)G.Don.(Apocynaceae), *Chamaemelum nobile* (L) All. (Asteraceae), *Cichorium intybus* L.(Asteraceae), *Clausena anisata* (Willd) Benth. (Rutaceae), *Coriandrum sativum* L (Apiaceae), *Cuminum cyminum* L (Apiaceae),*Cuminum nigrum* L (Apiaceae), *Cyamopsis tetragonoloba* (L) Taubert . (Papilionaceae), *Dioscorea dumetorum* (Kunth) Pax. (Dioscoreaceae), *Enicostema littorale* blume (Gentianaceae) , *Fraxinus excelsior* L (Oleaceae), *Garcinia kola* Heckel (W & C Afr)((Clusiaceae), *Gongronema latifolium* Endl. (Asclepiadaceae), *Helicteres isora* L., As. (Sterculiaceae), *Hypoxis hemerocallidea* conn Corm (African potato) (Hypoxidaceae), Inula *racemosa* Hook.f. (Asteraceae) *Lepidium sativum* L. (Brassicaceae), Mangifera *indica* L. (Anacardiaceae), *Momordica charantia* L. (Cucurbitaceae), *Morinda lucida* Benth. (Rubiaceae), *Myrcia uniflora* Barb., Rods. (Myricaceae), *Ocimum sanctum* L. (Lamiaceae), *Pterocarpus marsupium* Roxb. (Papilionaceae), *Retama raetam* (RR) (Forssk) Webb . (Papilionaceae), *Salacia reticulate* W. (Celastraceae), *Telfaria occidentalis* Hook. (Cucurbitaceae) [37], and *Brassica oleracea* var. capitata. There are several components that participate in controlling the sugar in the patients of diabetes such as phenolic and alkaloid compounds [14].

3.2. Phenolic compounds

A diverse array of phenolic compounds have been identified as the active components in some of the plants discussed in this review. For instance, anthraquinone glycosides derived from Morinda citrifolia exhibited a reduction in blood glucose levels in STZ-induced diabetic mice at a dosage of 100 mg/kg [38], which also can be clear in the case of *B. oleracea* var. capitata [14]. Despite this, the use of a registered herbal product called Tahitian noni juices (TNJ) is quite prevalent in Nigeria for various ailments, including diabetes. The administration of 1ml / 150 mg body weight of TNJ to rats twice daily for four weeks, both before and after the induction of diabetes with alloxan, resulted in a significant decrease in blood sugar levels, suggesting a preventive effect of the extract against alloxan-induced diabetes [39]. However, the presence of these phenolic compounds in the marketed product has not been confirmed. Kolaviron, a mixture of flavanones isolated from Garcinia kola Heckel (bitter kola), which is highly regarded in many parts of West Africa, has been found to lower blood sugar levels in normal and alloxan-induced diabetic mice at a dosage of 100 mg/kg, as well as inhibit rat lens aldose reductase (RLAR) activity [40]. Furthermore, several isolated flavonoids have been identified as bioactive constituents. Isoscutellarein (8-hydroxyapigenin), a flavonoid isolated from the hot water extract of Bixa orellana L. leaves, has been identified as an aldose reductase inhibitor. Rutin and quercetin, isolated from Bauhinia monandra Kurz leaves, have been identified as anti-hyperglycemic constituents in alloxan-induced diabetic rats [41]. A bioassay-guided fractionation of the stem bark of Cassia fistula L. led to the identification of catechin as the bioactive agent. Catechin was found to decrease plasma glucose levels in STZ-induced diabetic rats, with direct effects on glucose metabolizing enzymes and the expression of the glucose transporter GLUT4 [42].

The antioxidant properties of flavonoids, particularly their ability to scavenge free radicals, have been associated with the presence of aromatic hydroxyl groups in the benzo-γ-pyran

structure. These properties have been shown to protect pancreatic islet cells from oxidative stress and aid in the regeneration of β-cells, as demonstrated by epicatechin found in green tea [43] and quercetin [44]. More importantly, these flavonoids can prevent the formation of advanced glycated end products (AGEs) and other diabetic complications that arise from high levels of oxidative stress, such as atherosclerosis, nephropathy, neuropathy, retinopathy, and erectile dysfunction [45]. Therefore, the presence of quercetin, epicatechin, and other potent antioxidant flavonoids in a wide range of plants, including Irvingia gabonensis and *B. oleracea* var. capitata, contributes to their use in the holistic management of diabetes and the prevention of diabetic complications [14].

Other types of flavonoids have also demonstrated a direct impact on specific therapeutic targets in the context of diabetes. To illustrate, the introduction of naringin or hesperidin into the diet of mice has been observed to modulate the activity of enzymes responsible for glucose metabolism. Specifically, there was an increase in hepatic glucokinase activity and a decrease in hepatic glucose-6-phosphatase activity in diabetic mice [46] and GK type-2 diabetic rats [47]. These two particular flavonoids are present in all citrus fruits and have also been identified in Senna alata [48] and Rauvolfiavomitoria [49], suggesting they may contribute to the observed effects. Myricetin is another flavonoid that has demonstrated direct positive effects in the realm of diabetes, specifically through enhanced glycogen metabolism and improved insulin sensitivity [50].

3.3. Alkaloids

A number of investigations have assessed the antidiabetic properties of alkaloids derived from various plant components [51]. Odoh and Ezugwu (2012) carried out an examination to establish the effect of alkaloids from Acanthus montanus leaf (AAML) on diabetes. The experiment involved the intraperitoneal administration of AAML to alloxan-induced diabetic rats at doses of 100, 200, and 400mg/kg for durations of 4 and 8 weeks. The researchers discovered that the intraperitoneal administration of AAML alkaloids was safe and could potentially provide beneficial effects as an immunostimulant, hepatoprotective, and hypocholesterolemic agent when administered over an extended period of time [52]. Tiong et al. (2013) documented the antioxidant and antidiabetic activities of the primary alkaloids isolated from the extract of C. roseus (L.) G. Don leaves [53]. Agrawal et al. (2013) revealed that the methanol extract of Aerva lanata Linn. roots (AL) was fractionated using different solvents. The partially purified alkaloid basified toluene fraction (PPABTF) at a dose of 20mg/kg exhibited significant effects on streptozotocin-nicotinamide-induced type-II NIDDM in rats. This activity may be attributed to the presence of alkaloids such as canthin-6-one derivatives. Therefore, numerous investigations have demonstrated the antidiabetic effects of alkaloids derived from diverse plants [54]. Most studies conducted by various researchers have focused on the direct impact of phenolic compounds and alkaloids derived from different plant parts on reducing glucose levels in experimental animals, including rats, rabbits, and mice [55].

4. CONCLUSION

The current study showed that the use of various herbs to control of sugar in blood of patients suffering with diabetes is safe and free of many of the side effects that can appear from the use of chemically manufactured drugs. The study showed that there are large numbers of herbs that can be used to control diabetes. Phenol and alkaloids play an important role in maintaining blood sugar levels in diabetic' patients.

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Conflict of interest

The authors declare that they have no conflict of interests.

Ethical Approval

This review was approved by the Ethical Committee of the University of Baghdad, Baghdad, Iraq (No 214, 2022).

Author contributions

Khalid A. Mohammed: Conceptualization; Data curation; Formal analysis; Investigation; Resources; Supervision; Validation; Visualization; Roles/Writing - original draft; and Writing - review & editing.

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Author affiliation

1. *Department Chemistry, College of Science, University of Baghdad, Baghdad, Iraq.*

ORCID IDS:

1. Khalid A. Mohammed: https://orcid.org/0009-0006-2092-0228