Ankita
School of Pharmacy & Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Himachal Pradesh, India

Naveen Singh
School of Pharmacy & Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Himachal Pradesh, India

Roshmi Ray
School of Pharmacy & Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Himachal Pradesh, India

Effectiveness of *Aloe vera* in patients with diabetes mellitus

Ankita, Naveen Singh and Roshmi Ray

Abstract
The main aim is to identify the effectiveness of *Aloe vera* in patients with diabetes mellitus. Diabetes mellitus is a group of metabolic disorder which is characterized by high blood sugar level for a prolonged time. Diabetes mellitus is a chronic disorder which is caused due to insulin deficiency or insulin resistance or both factors. Nearly all patient with type 1 diabetes and >60% of patients with type 2 diabetes. Insulin therapy and other oral hyperglycemic drugs are currently available therapies which is used for the treatment of diabetes have their own side effect & adverse effect. So, the herbal drugs are a great preference which is having less side effect & adverse effects as compared to allopathic drugs. *Aloe vera* is a succulent plant belonging to the Liliaceae family. A number of pre-clinical and clinical trials demonstrate a blood glucose lowering effect for *Aloe vera* gel preparations in different forms. It has been stated that to reduce fasting blood glucose and triglyceride levels in type 2 diabetic patients the oral administration of the *Aloe vera* juice should be effective. *Gymnema sylvestre* is another medicinal plant which has potent anti-obesity and anti-diabetic activities. The extract of Gymnema leaf is administered by a diabetic patient; there is an increase in insulin release due to the stimulation of pancreas. The combination of herbal drugs and anti- diabetic drugs was investigated in diabetic patients showed significant effects.

Keywords: Diabetes mellitus, *Aloe vera*, *Gymnema sylvestre*, Anti-diabetic effect, Treatment, Blood glucose level

Introduction

Diabetes mellitus: The description of diabetes (Madhumeha) can be traced back in 1000 BC (Caraka Samhita). Madhumeha is the disease in which the patient passes recurrent urine which is characterized as astringent and sweet is defined by Caraka Samhita (1000 BC) and Susruta Samhita (1000-600 BC). The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) which can be produced by high blood sugar [1]. The word diabetes comes from Greek word which means "a passer through" and the word mellitus comes from the classical Latin word mellitus, meaning "sweet" [2]. Diabetes mellitus is a group of metabolic disorders which is characterized by high blood glucose levels for a prolonged time. Diabetes mellitus is a chronic disorder which is caused due to insulin deficiency or insulin resistance or both factors [3]. In the development of diabetes there are several pathogenic processes implicated. These pathogenic processes range from autoimmune destruction of the pancreatic beta cells with following insulin deficiency and other abnormalities that result in resistance to insulin action. In diabetes the deficient action of insulin on target tissues is the origin of the abnormalities in carbohydrate, fat, and protein metabolism [4].

Etiologic Classification of Diabetes Mellitus

Diabetes mellitus are classified into one of two broad categories on the basis of the considerable majority of diabetic patients that is type 1 diabetes mellitus or type 2 diabetes mellitus. In addition, gestational diabetes is classified as having women who arises diabetes for the period of their pregnancy. There are a variety of unusual and diverse types of diabetes that are included in the "Other Specific Types". These unrelated forms of diabetes are caused due to infections, drugs, endocrinopathies, pancreatic destruction, and genetic defects [5].

- **Type 1 diabetes mellitus:** It is also called type-I, Insulin- Dependent Diabetes Mellitus (IDDM) or juvenile diabetes. It is characterized by autoimmune destruction of pancreatic beta cells which generally leads to insulin deficiency. Before the age of 25 about 95 percent of persons with type-1 diabetes mellitus develop the disease, with an increased

Corresponding Author
Ankita
School of Pharmacy & Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Himachal Pradesh, India

incidence in the white population and equal prevalence in both sexes.

- **Type 2 diabetes mellitus:** It is also called type-II or Non Insulin-Dependent Diabetes Mellitus (NIDDM), or adult-onset. It is characterized by peripheral resistance to insulin, beta cell dysfunction and an insulin secretory defect of the pancreatic beta cell. In diabetes mellitus type 2 is the most common form and it is mostly related with a family history, older age, unhealthy diet, obesity and lack of exercise [6].
- **Gestational diabetes mellitus:** It is defined as glucose intolerance which is first acknowledged during pregnancy. The majority of women who develop gestational diabetes mellitus, the disorder have its onset in the third trimester of pregnancy. The woman should be given an oral glucose tolerance test at least 6 weeks after the pregnancy ends and be rechecked as having diabetes, normal glucose tolerance, impaired glucose tolerance, or impaired fasting glucose. Gestational diabetes complicates about 8-9% of all pregnancies, though the rates may double in populations at high-risk for type 2 diabetes [5].
- **Other Specific Types of Diabetes:** There are a variety of unusual and diverse types of diabetes that are included in other specific types. They are caused by genetic defects in insulin action, genetic defects of the beta cell, diseases of the exocrine pancreas, drug or chemical-induced diabetes, endocrinopathies, infections [7].

Signs and Symptoms of Diabetes
The signs and symptoms of diabetes include Polyuria - increased urination, Polyphagia - excessive appetite, Polydipsia - excessive thirst, Unusual weight loss or weight gain, Fatigue, Nausea perhaps vomiting, Blurred vision, whitish urine with sweetish odor, In women, frequent vaginal infections, In men and women, yeast infections, Slow-healing of sores or cuts in the skin/mucosa, Itching of the skin, particularly in the region of groin or genitals, Dryness in mouth, palate and throat, Excessive sweating and foul smelling of the body, Lethargy, Numbness and burning sensation in hands and feet etc. [1, 8]

Epidemiology of Diabetes Mellitus
In developing countries the prevalence of diabetes and pre-diabetes are progressively more. People with Pre-diabetes often have the chances of going on to develop diabetes by up to 60% simply through losing even just a moderate amount of weight, increasing physical activity levels, and adopting a healthy balanced diet. The approximately 1.6 billion adult were overweight and at least 400 million were obese worldwide in 2005, estimates according to world health organization (WHO). It is estimated that the number to reach 2.3 billion and 700 million, respectively, by 2015. Paralleling these trends, about 300 million people were estimated to have diabetes globally in 2010 and this number expected to increase to near about 450 million by 2030 [7]. In the last decade the studies carry out have highlighted that not only is the prevalence of diabetes high but also that it is increasing rapidly in the urban population [9].
In India it is projected that there are approximately 33 million adults with diabetes and this figure is likely to increase to 60 million by the year 2025 [10]. In all cases of diabetes about 5% to 10% of cases are of type 1 diabetes. Autoimmune, genetic, and environmental factors are the risk factors include in type

1 diabetes. In all diagnosed diabetes cases accounts for 90% to 95% of type 2 diabetes. Women have a 20% to 50% increased risk for developing type 2 diabetes later in life who have had gestational diabetes [11]. It is predicted that in the next two decades the prevalence of type 2 diabetes mellitus is becoming prominent. In developing countries where the majority of patients are aged between 45 and 64 years much of increase occurs [12].

Pathophysiology of Diabetes mellitus
Diabetes mellitus is a complex metabolic disorder and its main characteristic is hyperglycemia. It is related with an increased risk of microvascular and macrovascular disease [13]. Type-1 diabetes mellitus is a chronic autoimmune disease which is associated with destruction of pancreatic beta cells producing insulin. It is generally leading to deficiency of insulin secretion which results in metabolic derangements. Besides from the loss of insulin secretion, there is excessive secretion of glucagon's in type 1 diabetes mellitus patients due to irregular function of pancreatic alpha-cells. However, in patients with type 1 diabetes mellitus, glucagon's secretion is not suppressed by hyperglycemia but normally hyperglycemia leads to reduced glucagon's secretion. The consequence improperly elevated glucagon's levels make worsen the metabolic defects due to insulin deficiency. Deficiency of insulin leads to elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues [14]. Impaired glucose, lipid and protein metabolism are the major metabolic derangements, which result from insulin deficiency in type-I diabetes mellitus [15].
Type 2 diabetes mellitus is characterized by insulin resistance of peripheral tissues, insulin secretory defect of the pancreatic beta cell, impaired regulation of hepatic glucose production, and eventually leading to beta cell dysfunction [16]. The main problems of type 2 diabetes
Mellitus are insulin resistance and impaired insulin secretion. Therefore, insulin becomes less effective at stimulating glucose uptake and at regulating the glucose release because insulin could not bind with the special receptors [17]. Gestational diabetes mellitus is not distinguished and includes family history of diabetes mellitus, obesity, complications in previous pregnancy and advanced parental age. Pre-existing diabetes mellitus is necessary to detect which has a much worse prediction for the fetus [18].
Genetic and environmental risk factors and gene–environment interactions in some cases can directly impact β-cell function. The chronic high blood glucose levels are related with pathophysiology of diabetes and apart from these, they are also related to microvascular and macrovascular complications. These microvascular and macrovascular complications can enhance morbidity and mortality for people with diabetes [19].

Complications of Diabetes
The complications of diabetes are categorized into major types that are acute and chronic complications. The acute complications of diabetes mellitus are diabetic ketoacidosis (DKA), hyperglycemia, hyperosmolar state, hypoglycemia, diabetic coma, respiratory infections [20]. The chronic complications of diabetes mellitus are broadly divided into micro-vascular and macrovascular complications. Microvascular complications include retinopathy, neuropathy, nephropathy, while macrovascular complications consist of cardiovascular diseases, peripheral artery diseases (PAD), coronary artery diseases, stroke [21].

Diagnosis of Diabetes Mellitus
By checking the glucose level the diabetes can easily be determined. Blood glucose levels are 80mg / dL on fasting and up to 160 mg / dL in the postprandial state for healthy men. The diabetes can be diagnosed in laboratory by:-
▪ Finger Stick Blood Glucose.

▪ Fasting Plasma Glucose.
▪ Oral Glucose Tolerance Test.
▪ Glycosylated Hemoglobin or Hemoglobin A1c [22].

American diabetes Association, 2011 Diagnostic Criteria for Diabetes Mellitus

Table 1: Diagnostic Criteria for Diabetes Mellitus

	Normal Glucose Tolerance	Impaired glucose Tolerance 'Prediabetes'	Diabetes Mellitus
Fasting plasma glucose	<100 mg/dl	100-125 mg/dl	>/=126 mg/dl
2 hr plasma glucose an Oral Glucose Tolerance Test (OGTT)	<140 mg/dl	140-199 mg/dl	>/=200 mg/dl
Random Blood glucose+ Symptoms of diabetes			>/=200 mg/dl
A1C	<5.6%	5.7-6.4%	>/=6.5%

Treatment of Diabetes mellitus
The main objective for treatment of diabetes mellitus is reducing blood glucose concentrations to normal levels [23]. Various types of medicines, acquiring different exercise or yoga therapy or diet plan can be prevented diabetes mellitus by regulating the blood sugar level.

The insulin treatment for type 1 diabetes mellitus and other oral hypoglycemic drugs such as sulfonylureas, thiazolidinediones, and peptide analogs for treatment of type 2 diabetes mellitus are currently available therapies of diabetes mellitus [24]. For effective management of diabetes involves medical treatment including pharmacotherapy or anti-diabetic drugs for type 2 diabetes mellitus. There are different types of pharmacotherapy or anti-diabetic drugs available for the treatment of diabetes. These anti-diabetic drugs comprises biguanides, sulfonylureas, non-sulfonylureas, alpha-glucosidase inhibitors, thiazolidinedione or insulin sensitizer, glucagon-like-peptide-1-receptor agonist, dipeptidyl-peptidase-4 inhibitor, sodium- glucose- co-transported type 2 inhibitors and insulin therapy [25].

Lifestyle changes, including diet and exercise are the general treatment for diabetes for all patients. To prevent complications of diabetes the regular monitoring of blood glucose levels is important. For certain patients with diabetes, renin-angiotensin-aldosterone system blockers like ACE inhibitors or angiotensin II receptor blockers, statins, and aspirin often are given to prevent complications [26].

Allopathic drugs are used for the treatment and management of diabetes have their own adverse effect and side effects like hypoglycemia, hyponatremia, nausea, vomiting, flatulence, diarrhea or constipation, alcohol flush, headache, dizziness, weight gain, lactic acidosis, pernicious anemia, dyspepsia, joint pain. Therefore, herbal drugs are a great preference which is having less adverse effects & side effects as compared to allopathic drugs [22]. The various indigenous plants and polyherbal formulations have been experimented for treatment of diabetes mellitus. Medicinal plants which have been studied for treatment of diabetes mellitus are *Trigonella foenum graecum*, *Allium sativum*, *Gymnema sylvestre*, *Syzigium cumini* and *Aloe barbadensis,* etc. [27]

Aloe vera (*Aloe barbadensis*)
Aloe vera is a very essential and effective herbal plant with various health applications or medicinal effects. *Aloe vera* is a drought-resisting, perennial, succulent plant belonging to the Liliaceae family [28]. The term *Aloe vera* derives from the Arabic word "Alloeh" meaning "shining bitter substance," while "Vera" in Latin means "true" [29]. *Aloe vera* can be divided into two basic products that are the latex and the gel.

The latex is a bitter yellow liquid under the epidermis of the leaf and the gel, a colorless and tasteless material in the internal part of the leaf. The main characteristic of the *Aloe vera* plant is its high-water content, ranging from 9999.5%. The remaining 0.5-1.0% solid material is reported to contain over 75 different potentially active compounds including water-soluble and fat-soluble vitamins, enzymes, minerals, simple/complex polysaccharides, organic acids and phenolic compounds [30].

A number of valuable effects of *Aloe vera* have been found like wound healing, anti-ulcer effects, anti-inflammatory, anti-oxidant effects, anti-cancer activity, anti-diabetic effects, anti- hyperlipidemic activity, teeth and gum protection, laxative effects, genital herpes, asthma, HIV infection, functional and nutraceutical foods, anti-microbial agent, cosmetic applications [31].

Anti-diabetic effect of *Aloe-Vera*
Aloe vera has been used in different countries worldwide for its soothing, curative and rejuvenating properties. *Aloe vera* gel consist numerous beneficial effects such as antioxidant, anti diabetic, increases the decrease level of glutathione by four times in diabetic rats [24]. There is some preliminary evidence to recommend that oral administration of aqueous extract of *Aloe vera* might be useful in reducing blood glucose in diabetic patients and in lowering blood lipid levels in hyperlipidemia [30]. It has been stated that to reduce fasting blood glucose and triglyceride levels in type 2 diabetic patients the oral administration of the *Aloe vera* juice should be effective with or without combination of a conventional anti-diabetic agent [32].

Researchers have established that aloe plants consisting polysaccharides can be control blood sugar, stimulate the body's own antioxidant production and even lower cholesterol. Aloe polysaccharides are very effective to remove waste and other toxins and also improve the property of immune cells. *Aloe vera* juice is used to improve digestive functioning which helps to maintain sugar level in blood and enhances absorption of nutrients [33].

A number of pre-clinical and clinical trials demonstrate a blood glucose lowering effect for *Aloe vera* gel preparations in different forms. In a study on streptozotocin-induced diabetic rats, oral administration of *Aloe vera* gel extensively reduced the fasting blood glucose, hepatic transaminases, plasma and tissue cholesterol, triglycerides, in a study on streptozotocin- induced diabetic rats [34]. Lophenol, 24-methyl- lophenol, 24-ethyl-lophenol, cycloartanol and 24-methy- lenecycloartanol are the five phytosterols of *Aloe vera* which showed anti-diabetic effects in type-2 diabetic mice.

Aloe vera contains different active compounds like polysaccharides which are used to increase the insulin level and exhibit hypoglycemic properties [27].

Aloe vera contains active components which also help in lowering high blood pressure. This makes *Aloe vera* tremendously suitable for wide scale treatment to all diabetic situations. *Aloe vera* helps in reducing serum cholesterol and increasing levels of high density lipoprotein cholesterol [35].

Comparative evaluation of anti-diabetic effect of *Aloe vera* and *Gymnema sylvestre*

In treatment of diabetes herbal medicines are gaining interest because of their minimal side effects [36]. The different medicinal herbs exhibit anti-diabetic effects such as *Aloe vera* (AV) and Gymnema Sylvester (GS) showed anti-hyperglycemic and hypolipidemic effects in animal studies and clinical studies. Aloe barbadensis Miller belongs to the Liliaceae family and there are over 360 species. A number of pre-clinical and clinical trials demonstrate a blood glucose lowering effect for *Aloe vera* gel preparations in different forms [34]. The *Gymnema sylvestre* belongs to the Asclepiadaceaea family. *Gymnema sylvestre* has potent anti-obesity and anti- diabetic activities and in the ayurvedic system it is known as "Meshasringa". *Gymnema sylvestre* contains an active component that is gymnemic acids which is a mixture of saponins. Gymnemic acid are a potent inhibitor of glucose absorption in the intestine and decrease body weight [37]. *Gymnema sylvestre* contain primary chemical constituents which include gymnemic acid, calcium oxalate, tartaric acid, gurmarin, glucose, betaine, choline, lignin, cellulose, albumin, butyric acid and anthraquinone derivatives [38].

The fatty acid accumulation in the circulation and the accumulation of triglycerides in muscle and liver are decreased by the several components extracted from gymnema [36]. Gymnemic acids can reduce the blood sugar levels by inhibiting the absorption of sugar molecules by the intestine. *Gymnema sylvestre* was also found to have a viable role in regenerating insulin as well as β-cell and increasing the insulin secretion [39]. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules and it inhibits the glucose receptor sites in the intestine. Due to inhibition of glucose receptor site it prevents the absorption of sugar molecules by the intestine which reduces blood sugar level. In the same way, Gurmarin also interferes with the ability of taste buds on the tongue to distinguish between sweet and bitter [40].

It has been stated that to reduce fasting blood glucose and triglyceride levels in type 2 diabetic patients the oral administration of the *Aloe vera* juice should be effective (32). In *Gymnema sylvestre* leaves have been found a use in lowering serum cholesterol, triglycerides and also to treat adult onset diabetes mellitus (NIDDM). When extract of Gymnema leaf is administered by a diabetic patient, there is an increase in insulin release due to the stimulation of the pancreas. *Gymnema sylvestre* leaves and especially Gymnemic acids are different mechanisms of action to exert their hypoglycemic effects.

- it increases insulin secretion,
- promotes regeneration of islet cells,
- it causes inhibition of glucose absorption from intestine,
- Increases utilization of glucose,

For increased utilization of glucose by insulin-dependent pathways it is shown to increase enzyme activities, an increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase. The main function of the gymnemic acids is to stop the glucose molecule from binding to the receptor on the intestine [41].

The effect of *Aloe vera* in combination with anti-diabetic drugs was investigated in diabetic patients and usually has been shown to have an additive effect. The combination interaction of *Aloe vera* with glibenclamide, a sulphonylurea, shows effect by inhibiting ATP sensitive potassium channels in pancreatic β cells, resulting in depolarization of cell membrane and subsequent insulin release. It showed no effect on cholesterol levels and had no toxic effects on kidney or liver function and no effect on cholesterol levels. For example, *Aloe vera* has been shown to produce a greater anti-hyperglycemic effect when compared to the individual therapy with glibenclamide, pioglitazone [42, 43].

Gymnema sylvestre separately received by patients showed substantial efficacy as compared to glibenclamide found in several other studies. The combination of *Gymnema sylvestre* with glibenclamide showed significant hypoglycemia effects. So it should be included in the treatment plan under the observation of the practitioner and the combination of herbs and anti-diabetic drugs need to be evaluated with more trials [44].

Discussion

A number of pre-clinical and clinical trials demonstrate a blood glucose lowering effect for Aloe -Vera gel preparations in different forms. It has been stated that to reduce fasting blood glucose and triglyceride levels in type 2 diabetic patients the oral administration of the *Aloe vera* juice should be effective. *Gymnema sylvestre* is another medicinal plant which has anti- diabetic effect, the extract of Gymnema leaf is administered by a diabetic patient; there is increase in insulin release due to the stimulation of pancreas. The main function of the gymnemic acids is to stop the glucose molecule from binding to the receptor on intestine and reduce the blood sugar level. Other several studies where a combination of herbal drugs and antidiabetic drugs has been investigated in diabetic patients need to be evaluated with more trials.

Conclusion

Aloe vera is a medicinal plant that has been used for its various beneficial properties. It is concluded that *Aloe vera* plant and its preparations in different forms has anti-diabetic effect. A number of pre-clinical and clinical trials showed blood glucose lowering effects. The oral administration of *Aloe vera* should be effective in reducing blood glucose level in diabetic patients and also used in hyperlipidemia to lower the blood lipid levels. *Aloe vera* helps in reducing serum cholesterol and triglycerides levels. *Aloe vera* contains active compounds like polysaccharides which are used to increase the insulin level and exhibit hypoglycemic properties. *Gymnema sylvestre* is another medicinal plant which has anti-diabetic and anti- obesity effects. The main function of Gymnemic acids can reduce the blood sugar levels by inhibiting the absorption of sugar molecules by the intestine. Other several studies where a combination of herbal drugs and anti-diabetic drugs has been investigated in diabetic patients showed significant effects which need to evaluated with more trials. Therefore, herbal drugs are a great preference because of its less side effects and adverse effects as compared to allopathic drugs.

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