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Promising Actions of Certain Medicinal Plants of Bangladesh against Diabetes and Oxidative Stress: A Review

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Abstract

Diabetes is a metabolic illness defined by hyperglycemia that affects 10% of the world's population. Diabetic complications such as blindness, kidney failure, and heart failure can develop if left untreated and are made worse by oxidative stress. Oxidative stress contributes to the rise of diabetic complications, particularly type-2 diabetes. In the blood vessels of diabetic individuals, it causes endothelial dysfunction. Diabetes is one of the leading causes of death worldwide. Nowadays, it is alarming that the number of diabetic patients is increasing dramatically. There are plenty of anti-diabetic drugs available on the market, but they possess several adverse effects and do not completely cure diabetes. It has now become a financial burden on patients, their families, and society as well. Medicinal plants have gained popularity in developed and developing countries over the last two decades because of their vast natural sources and lack of harmful effects compared to modern allopathic medications. According to the World Health Organization, traditional medicines, which are mostly manufactured from plants, are still used by 80% of the population in developing countries for the management and curing of diseases. This review includes 81 Bangladeshi medicinal plants from 51 different families that can be used to treat diabetes and oxidative stress. Among them, *Psidium guajava* (*L.*), *Aloe vera*, *Catharanthus roseus*, *Allium sativum*, *Annona squamosa*, *Cinnamon zeylaniucm*, *Amaranthus esculentus*, *Eugenia jambolana*, *Azadirachta indica*, *Moringa oleifera*, *Spondias pinnata*, *Coccinia grandis* (*L.*), *Momordica charantia L.*, Heretiera fomes, *Trigonella foenum-graecum* were most potent. The fundamental purpose of our study is to find out and highlight certain medicinal plants in Bangladesh that have anti-diabetic and antioxidant capabilities so that the researchers can develop newer anti-diabetic medications with minimal side effects to treat metabolic dysfunction, diabetic complications, and oxidative stress more effectively.

Keywords

Diabetes, Anti-Oxidant, Anti-Diabetic, Oxidative Stress, Medicinal Plants

1. Introduction

Diabetes is becoming the most worrying threat to public health in developed countries as well as in developing countries like Bangladesh [1]. For the very first time, Egyptians introduced the term "Diabetes", and the Greek Physician Aertaeus cut out the word diabetes mellitus. The word diabetes mellitus comes from Greek word diabetes which means siphon "to pass through" and mellitus comes from a Latin word meaning "honey" or "sweet" [2]. Diabetes mellitus (DM) may be described as a metabolic disorder or a group of metabolic diseases manifested by high blood glucose levels, and oxidative stress either because of insufficient insulin production, insulin action, or both. It disrupts the metabolism of proteins, carbohydrates, and fats, leading to chronic hyperglycemia and abnormal lipid profile resulting in several diabetic complications such as retinopathy, neuropathy, ketosis, polyuria, polydipsia, and cardiovascular complexity as well [3] [4] [5]. Approximately 10% of the world's population suffers from diabetes. The risk factors that cause diabetes are diet, obesity, sedentary lifestyle, insulin resistance, high family aggregation, and so on [6] [7]. Depending upon characteristics and cause, there are mainly three kinds of diabetes for instance type-1 diabetes, type-2 diabetes, and gestational diabetes [8]. Type-1 diabetes is insulin-dependent diabetes which is also named adolescent diabetes [5] [7]. Approximately 5% - 10% of the people are affected by this type of diabetes. It is caused by cellular-mediated autoimmune destruction of pancreatic beta cells. The most conventional form of diabetes is type-2 diabetes [8]. Nearly 90% to 95% of the people are affected with type-2 diabetes which is commonly known as adult diabetes [5]. It does not depend on insulin and is therefore recognized as non-insulin-dependent diabetes. It is more common in people over 40 years of age [9] and may be occurred due to a lack of insulin action and insulin secretion [8]. The most common cause of this type of diabetes is obesity which causes insulin resistance [5]. Gestational diabetes is seen during pregnancy and is caused by carbohydrate intolerance which leads to hyperglycemia, although the reason for this form is not fully understood [8]. According to International Diabetes Federation (IDF), the number of patients with diabetes mellitus was 366 million in 2011 and that will be 522 million by 2030 [10], where 4.6 million people die every year owing to diabetes [1]. But according to the current survey report, there are 451 million people aged between 18 - 99 years who are suffering from DM worldwide in 2017 and this number will rise to 693 million by 2045 [3].

Diabetes is therefore considered one of the country's top five most serious diseases [11]. Along with cancer, cardiovascular disease, and cerebrovascular illness, diabetes is indeed the world's third-leading cause of death [11]. As a result, DM is gradually turning over the world's most prolific silent killer [8]. Cause it is said to be irremediable [12].

However, there are lots of synthetic anti-diabetic drugs, for instance, biguanides, glucosidase inhibitors, thiazolidinediones, and metformin commercially available to compress hyperglycemia in diabetes mellitus. Although these drugs reduce hyperglycemia, there are several side effects associated with these drugs like liver problems, diarrhea and lactic acidosis., Afterward, it is inappropriate to use them during pregnancy and the price of medicine is much higher. So, overpassing these problems is a challenge to the medical community [4] [11] [13] [14]. Medicinal plants have been used for human well-being since ancient times [15] [16]. In conformity with WHO, approximately 4 billion people, 75% - 80% of the total population, use herbal remedies as first aid that can improve our healthcare and have fewer side effects, and better compatibility with the human body [1] [15] [16] [17]. As a result, the use of herbal medicine is gaining traction in both developed and developing countries [7]. In the United States, about 25% of the prescribed drugs come from natural sources [15]. So it is difficult to separate plants and humans [16].

Bangladesh is known as an agricultural country and is said to be a rich country of biodiversity. More than 500 medicinal plant species are found here that are effective in curing diabetes [13] [16] and contain numerous antioxidant properties like tannin, flavonoids, phenolic compounds, and alkaloids [3] [4] [18]. In diabetes, extemporaneous formation of free radicals has occurred on account of glucose auto-oxidation, and non-enzymatic protein glycation. When the amount of free radicals increases and the activity of antioxidants decreases, lipid peroxidation, enzymes, and cellular organelles are damaged, which also affects the abnormalities of diabetes. Plants having both antioxidant and anti-diabetic properties can prevent diabetes complications more efficiently than the currently available anti-diabetic drugs [4].

In this review, we have focused on Bangladeshi medicinal plants having anti-diabetic properties along with antioxidant substances. We have mainly attempted to show a comparative analysis of different plant parts and their various doses, and we have also tried to include their local names. This article may also be helpful for healthcare professionals, scientists, and scholars working in pharmacology and therapeutics to launch newer forms of medicine for the treatment of diabetes without or with fewer side effects.

2. Methodology

The data for this review was gathered from many research publications and review articles on ayurvedic plants having anti-diabetic and antioxidant potential in Bangladesh. The following databases have been used to collect reference papers:

Google Scholar, Scopemed, Medline, ResearchGate, PubMed, and Science Direct. For searching information, terms such as botanical plants, medicinal plants, traditional plants, anti-hyperglycemic plants, anti-diabetic plants, a survey of anti-diabetic plants, a survey of anti-diabetic active medicinal plants, a review of anti-diabetic medicinal plants, oxidative stress and an ethnomedicinal plant survey in Bangladesh have been used. We have found 81 Bangladeshi medicinal plants from 51 different families that can be used to treat diabetes and oxidative stress.

3. Results

In the present study, 81 Bangladeshi medicinal plants from 51 different families were noted. It was revealed that the plant parts used having anti-diabetic and antioxidant activity included leaves, bulbs, stems, roots, barks, rhizomes, aerial parts, fruits and seeds as well as whole plants (**Table 1**, **Figure 1**). The most commonly used species that can be used to treat diabetes and oxidative stress *are Psidium guajava* (*L.*), *Aloe vera*, *Catharanthus roseus*, *Allium sativum*, *Annona squamosa*, *Cinnamon zeylaniucm*, *Amaranthus esculentus*, *Eugenia jambolana*, *Azadirachta indica*, *Moringa oleifera*, *Spondias pinnata*, *Coccinia grandis* (*L.*), *Momordica charantia L*, Heretiera fomes, and *Trigonella foenum-graecum.* The study indicated that the common medicinal plant families were Myrtaceae, Liliaceae, Apocynaceae, Alliaceae, Annonaceae, Lauraceae, Amaranthaceae, Asteraceae, Meliaceae, Moringaceae, Anacardiaceae, Cucurbitaceae, Sterculiaceae, and Fabaceae (**Table 1**).

Table 1. List of selected Bangladeshi medicinal plants having anti-diabetic and antioxidant activity.

Family	Botanical name	Local name	Plant part	Extract	Active chemical constituents	Dose (mg/kg)	Test model	Anti-diabetic effects	Antioxidant activity	Ref.
Myrtaceae	*Psidium guajava* (*L.*)	Peyara	Leaf and Fruit	Aqueous	Terpen, Flavonoid, Strictinin, Isostrictinin, Pedunculagin, and Polysaccharides	50 - 800 mg/kg	Streptozotocin (STZ)-induced diabetic rats	Decreased glucose level, Performed various anti-diabetic effect, and hypoglycemic effect	Showed high antioxidant activity. Fruit extracts exhibited weaker antioxidant effects than did the leaf extracts	[19] [20] [21]
Liliaceae	*Allium cepa*	Peyaj	Bulb	_	_	200 mg/kg	Alloxen induced diabetic rat	Controlled the activity of glucose 6 phosphatase and HMG-CO a reductase	_	[22] [23] [24] [25] [26] [27]
	Asparagus racemosus	Satamuli	Root	Ethanolic	Steroidal, Saponins, Polyphenols (1.69%), Phytosterols (0.79%), Ascorbic acid (0.76%), and Flavonoids (0.48%)	1·25 g/kg	Type1 and type 2diabetic rats	Suppressed postprandial hyperglycemia, reversibly increased unabsorbed sucrose content throughout the gut, enhanced glucose transport and insulin action in 3T3-L1 adipocytes	Showed antioxidant activity	
	Aloe vera	Ghritkumari	Leaf	Ethanolic	Pseudoprototinosaponin AIII, and Prototinosaponins AIII	200 and 300 Mg/kg P.o., 28d	Alloxan induced diabetic mice	Glucose uptake and insulin released against glycogenolysis or gluconeogenesis pathway	Showed high antioxidant activity	
Apocynaceae	*Catharanthus roseus*	Nayantara	Full plant	_	Alkaloids, Terpenoids, Steroids, Flavonoids	0.5, 0.75 and 1.0 ml/kg	Alloxan-induced diabetic rabbits.	Dose-dependent reduction in blood glucose was observed	Showed high antioxidant activity (81.70%).	[28] [29] [30] [31] [32]
	Alstonia Scholaris	Saptaparni Devil's tree, Chaitan, Chatim	Leaf	Ethanolic	Alkaloids, Saponins, Terpenoids, Flavonoids, Phenolic compounds, Tannins, Steroids, and Glycosides	100, 200, and 400 mg/kg	Streptozotocin-induced diabetic rats	Reduced blood glucose level	Showed antioxidant activity	

Continued

Alliaceae	*Allium sativum*	Ada	Bulb	Ethanolic	-	0.1, 0.25 and 0.5 g/kg	Streptozotocin-induced diabetic rats.	Garlic alcoholic extract significantly decreased serum glucose	*Allium sativum* (L.) was rich in antioxidants which helped destroy free radicals' particles that could damage cell membranes and DNA.	[33] [34] [35]
Solanaceae	*Capsicum frutescens*	Lal morich	Fruit			40 mg/kg	Type 2 diabetes model of rats	Increased serum insulin concentration in high fat diet	-	[36] [37] [38] [39] [40] [41] [42] [43]
	Capsicum annum	Red pepper	Fruit	Ethanolic	Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) ester Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) ester Capsaicin, Dihtdrocapsaicin, hytolkauran16-ol, Eugenol, 1, 2-benzedicarbixylic acid	Cap-Saicin, dihydrocapsaicin, tridecanoic acid, phytol, Kauran-16-ol, eugenol and 1, 2-benzenedicarboxylic Acid, mono (2-ethylhexyl) este 300 mg/kg	Type 2 diabetes rats.	Amelioration of polyphagia, polydipsia And hyperglycemia, improving glucose tolerance Ability, insulin sensitivity, pancreatic β-cell histology And functions, and improving dyslipidemia Improved hyperglycemia, polydipsia, polyphagia, glucose tolerance ability, insulin sensitivity, and dyslipidemia	_	
	Solanum torvum Swartz	Tit baegun	Fruit	Methanolic	Methyl caffeate	10 mg/kg, 20 mg/kg, 40 mg/kg	Streptozotocin-induced diabetic rats	Decreased glucose level, increased insulin level, Increased expression level of GLUT4	-	
	Datura stramonium L	Shada dhutura	Leaves	Aqueous crude extract	Flavonoids, Glycosides, Alkaloids, Tannins, Saponins, Phenols	-	*In vitro*	Showed α-amylase inhibitory activity	_	
	Withania somnifera (*L.*) *Dunal*	Aswagandha	Root, Leaf	Ethanolic	Flavonoids	100 mg/kg, 200 mg/kg	Alloxen induced diabetic rat	Increased insulin secretion, Decreased oxidative stress.	Showed high antioxidant activity	
Annonaceae	*Annona squamosa*	Ata	Leaf	Aqueous	Flavonoid	55 mg/kg	Streptozotocin-induced diabetic rats	Reduced the concentration of glucose	A. squamosa leaf extracts showed antioxidant activity due to presence of flavonoids in the leaf, which in turn act as strong superoxide radicals and singlet oxygen quenchers.	[44] [45] [46]

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	Ananus Cosmosus	Anaras	Leaves		Flavonoids, Alkaloids, Saponins, Terpenoids, Annonaceous, Acetogenins, Megastigmanes, Cyclopeptides, and Essentialoils	_	*In vitro*	Enhananced insulin sentivity, Regulated the activities of glycogen metabolizing enzymes	Showed antioxidant activity	
Acanthaceae	*Andrographis paniculata*	Kalomegh	Leaf	Ethanolic	Diterpenoid, Flavonoids, and Polyphenols	0.1, 0.2, and 0.4 g/body weight	Normal and Streptozotocin-induced diabetic rats.	Showed antidiabetic effect by increasing glucose metabolism. It also gived hypotriglyceriemic effect	Showed antioxidant activity	[47] [48]
Lauraceae	*Cinnamon zeylaniucm*	Daruchini	Bark	Chloroformic	Cinnamaldehyde (71.50%), Linalool (7.00%), Beta-caryophyllene (6.40%), Eucalyptol (5.40%), and Eugenol (4.60%)	20 mg/kg	Streptozotocin-induced diabetic rats	Insulinotropic effect due to glucose uptake increased through the glucose transporter translocation	-	[49]
Zingiberaceae	*Curcuma longa*	Holud	Bark	Ethanolic	Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin, and Ar-turmerone	1500 mg/kg /d	Type 2 diabetic KK-A(y) mice	EtOH extract stimulated human adipocyte differentiation in a dose-dependent manner, and reduced the blood glucose level	In the DPPH assay, *Curcuma longa* showed excellent scavenging against the radical	[50]
Caesalpiniaceae	*Tamarindus indica*	Tetul	Seed	Aqueous	_	80 mg/100g	Streptozotocin-induced diabetic rats	Showed some important antidiabetic activity with attenuation of hyperglycemia	_	[51]
Piperaceae	*Piper betle*	Betel	Leaf	Aqueous, Ethanolic	_	100, 200, 300 and 1500 mg/kg	Normoglycemic and Streptozotocin-induced diabetic rats	Showed strong antidiabetic activity	Showed high antioxidant activity	[28] [52] [53] [54] [55]
	Piper cubeba L.f	Kabab chini	Fruit	Methanolic	Phenols, Flavonoids	-	*In vitro*	Showed α-amylase inhibitory activit, Increased glucose uptake	Showed high antioxidant activity	
	Piper longum L.	Pipul, Pipla	Roots	Aqueous	Pipperin, Pippalartin, Pipperleguminin, Sterols, and Glycosides, Piperlongumine	200 mg/kg for 30 days	Streptozotocin-induced diabetic rats	Decreased glucose level, Increased insulin level	Showed high antioxidant activity	
Amaranthaceae	*Amaranthus esculentus*	Dherosh	Grain		_	500 g/kg	Streptozotocin-induced diabetic rats	Reduced the glucose level	Showed antioxidant activity	[56] [57] [58] [59] [60] [61]
	Achyranthes aspera L	Udvid nagra	Leaves	Ethanolic	Alkaloids, Phenol, Flavonoids, Saponins, Carbohydrates, Steroids, and Terpenoids	1000 mg/kg	Streptozotocin-induced diabetic rats	Decreased blood glucose	Showed high antioxidant activity	
	Amaranthus spinosus L.	Katanotey	Leaf	Ethanolic	Alkaloids, Saponin, Carbohydrate, Tannin, Protein, Glycoside, Flavonoid, and Phenol	450 mg/kg	Diabetic rat	Inhibited alpha amylase activity	Showed antioxidant activity	
Scrophulariaceae	*Scoparia dulcis*	Chinigura	Whole plant	Aqueous	_	200 mg/kg	Streptozotocin-induced diabetic rats	Reduced blood glucose, increased plasma insulin level	Decreased free radical formation in tissues (liver and kidney)	[62]
Gramineae	*Hordeum vulgare*	Barley	Fruit	Ethanolic	Phenol	200 mg/kg	Streptozotocin-induced diabetic rats	Decreased blood glucose level	_	[63]
Apiaceae	*Cuminum nigrum*	Cumin	Seeds	_	Flavonoids, Alkaloids	0.5 to 1.5 g/kg	Alloxan-diabetic rabbits	Exhibited considerable hypoglycemic activity	_	[4] [56] [64]
	Centella asiatica (*L.*)	Thankuni	Leaf	Ethanolic	Alkaloids, Glycosides, Steroids, Flavonoids, Tannins, and Reducing sugars	500 mg/kg	Alloxen induced diabetic rat	Decreased glucose level	Showed antioxidant activity	
Gentianaceae	*Swertia chirayita*	Tite or Pothi Chirayita or Tikta	Leaf	Aqueous	Mangiferin	200 mg/kg	Streptozotocin-induced diabetic rats	Increased the plasma insulin, Reduced blood sugar	Showed antioxidant activity	[65]
Asteraceae	*Eugenia jambolana*	Jam	Fruitpulp	Ethanolic	Flavonoids, Saponins, Glycosides, and Triterpenoids	50, 100, 200 mg/kg	Alloxan-induced diabetic rat	Increased glucose tolerance activity	_	[66] [67] [68] [69] [70] [71]
	Eclipta alba L	Bhringoraj or Bhringraj	Leaves	Ethanolic	Carbohydrates, Terpanoids, Lactones, Glycosides, Flavonoids, Esters, Steroids, Tannins	200 mg/kg for 30 days	Alloxen induced diabetic mice	Decreased glucose level, increased insulin level	_	
	Enhydra fluctuans Lour.	Helencha, harkuch	Aerial Herbs	Ethanolic	Flavonoids, Tannins, Saponins, Phenolic, Terpenoids, Steroids, and Coumarin compounds	500 mg/kg	Alloxan induced type −2 diabetic rat	Decreased blood glucose, Showed hypoglycemic effect	Showed antioxidant activity	

Continued

	Blumea lacera	Bonomula, shealmoti.	Aerial part, Leaf	Methanolic	Carbohydrates, Saponins, Tannins, Phenols, Polyphenols, Flavonoids, Reducing Sugar, Steroids, Alkaloids, Glycosides	400 mg/kg	Streptozotocin induced diabetic rat	Reduced blood glucose level, showed antihyperglycemic effect, Showed α-amylase inhibitory activity	Showed antioxidant activity	
Meliaceae	*Azadirachta indica*	Neem	Leaf	_	Flavonoids, Tannins, Sterols, Saponins, Anthraquinones, and Alkaloids	25, 48.4, 93.5, 180.9 and 350 mg/kg	Alloxan-induced white male albino mice	The extract lowered blood glucose at all dosages in a dose independent manner	_	[72] [73]
	Swietenia mahagoni L. Jacq.	mahagoni	Bark	Methanolic	_	25 and 50 mg/kg	Streptozotocin-induced diabetic rats	Showed strong hypoglycemic activity	Showed high antioxidant activity	
Anacardiaceae	*Mangifera indica*	Mango	Leaf	Aqueous	_	1 g/kg	Normoglycaemic, glucose-induced hyperglycaemic mice, Streptozotocin-induced diabetic mice	Reduced blood glucose level	_	[74] [75]
	Spondias pinnata	Amra	Fruits	Methanolic	Flavonoids, Tannins, Saponins, and Terpenoids	-	Alloxen induced diabetic rat	Decreased glucose level, Decreased triglycerides and total cholesterol, Decreased LDL, and VLDL, Increased HDL	-	
Malvaceae	*Abelmoschus moschatus*	Muskok dana		Aqueous	Myricetin	100 mg/kg	Streptozotocin-induced diabetic rats	Significantly attenuated the increase of plasma glucose	_	[76]
Legumes	*Glycine max*	Soyabeans	Seed	_	3-O-methyl-D-chiro-inositol (D-pinitol)	1.2 g	Type 2 diabetes mellitus (seven men, eight women; 60.3 +/- 3.1 years old	Controlled postprandial capillary blood glucose the most effectively	_	[77]
Moraceae	*Ficus bengalensis*	Bot	Arial root	Aqueous	_	300 mg/kg	Sub and mild disbetic rats	Decreased blood glucose level	_	[36] [78] [79] [80] [81]
	Ficus benghalensis L.	Bat	Leaves	Ethanolic	Phenolics, Terpenoids/ Terpenes	200 mg/kg, 400 mg/kg body weight	Alloxen induced diabetic rat	Decreased glucose level, Decreased triglycerides, and cholesterol,	Showed antioxidant activity	
	Ficus racemosa L	Joiggi dumur	Stem, Bark	Aqueous, Ethanolic	Tannin, Wax, Saponingluanol acetate, B-sitosterol, Leucocyanidin-3 - O - b - d-glucopyrancoside, Leucopelargonidin-3	Aqueous extract – 500 mg/kg & ethanol extract – 400 mg/kg)	Streptozotocin-induced diabetic rats	Decreased blood glucose	Showed antioxidant activity	
Moringaceae	*Moringa oleifera*	Shojna	Pods	Methanolic	_	150 or 300 mg/kg	Streptozotocin-induced diabetic rats	Reduced serum glucose levels, increased serum insulin levels	Increased antioxidant levels in pancreatic tissue	[82]
Caricaceae	*Carica papaya*	Papaya	Leaf	Ethanolic	Flavonoids, Tannins, Saponins, Triterpenoids, Alkaloids	250, 500, 1000 mg/kg	Alloxan induced diabetic rats	Decreased blood glucose level	_	[83]
Lamiaceae	*Mentha piperita*	Pudina	Leaf	Ethanolic	_	300 mg/kg	Streptozotocin-induced diabetic rats	Decreased the level of blood glucose and creatinine as well as increased level of insulin, glycogen, and body weight	_	[84] [85]
	Ocimum sanctum L	Tulsi	Leaves	Ethanolic	Saponins, Triterpines, and Flavonoids, Tannins, Alkaloids,	200 mg/kg i.p	Alloxen induced diabetic rat	Reduced blood glucose level	Showed antioxidant activity	
Musaceae	*Musa paradisiaca*	Kala	Leaves, Fruit peels	Ethanolic	-	500 mg/kg	Streptozotocin-induced diabetic rats	Reduced blood glucose level	-	[86] [87]
Euphorbiaceae	Emblica officinalis or Phyllanthus emblica L	Amla,	Seeds	Aqueous	Flavonoids, Gallic acids	300 mg/kg	Streptozotocin-induced diabetic rats	Reduced blood glucose level and improved glucose tolerance	Showed antioxidant activity	[88]

Continued

Araceae	*Amorphophallus campanulatus* (*Roxb.*) *Blume*	Ol	Tuber	Methanolic	Betulinic acid, Tricontane, Lupeol, Stigmasterol, Sitosterol	400 mg/kg	Oral glucose tolerance tests (OGTT)	Inhibited amylase activity, Decreased glucose level, Reduced glycated hemoglobin, and nitric oxide, Increased insulin level	Showed antioxidant activity	[28] [45] [89] [90]
	Alocasia macrorrhizos (*L.*) *G. Don* Or Alocasia indica	Mankachu	Rizome	Methanolic	Flavonoids, Cynogenetic glycosides, Ascorbic acid, Gallic acid, Malic acid, Oxalic acid, Alocasin, Amino acids, Succinic acid, and Beta-lectins	500 mg/kg	Alloxen induced diabetic rat	Stimulated insulin secretion from beta cell	Showed antioxidant activity	
Combretaceae	*Terminalia belerica* (*Gaertn.*) *Roxb.*	Bohera	Fruit	Aqueous	Termilignan, Thannilignan, 7-hydroxy-30, 40 -(methylenedioxy) flavone, Anolignan B, Gallic acid, Ellagic acid, b-sitosterol, Arjungenin, Belleric acid, Bellericoside, and Cannogenol 3-O-b-D-galactopyranosyl-(1 ! 4)-O-a-L-rhamnopyranoside	p.o.-up to 11 days; 120 mg/kg	Alloxen induced diabetic rat	Decreased glucose level, Stimulated both the secretion and action of insulin, inhibited protein glycation	Showed antioxidant activity	[1] [7] [10] [36]
	Terminalia chebula	Hortoki	Fruit, Seed	Ethanolic, Chloroform, Aqueous	Shikimic, Gallic, Triacontanoic, Palmitic acid, β -sitosterol, Daucosterol	p.o.-1 month;200mg/kg	Streptozotocin-induced diabetic rats	Decreased glucose level	_	
Cucurbitaceae,	*Coccinia grandis* (*L.*)	Telakucha,	Leaves, Fruits	Aqueous	ß-Sitosterol, Cephalandrol, Cephalandrine A & B,	200 mg/kg for 14 days	Alloxen induced diabetic rat	Reduced glucose level	Showed antioxidant activity	[1] [7] [18] [91] [92] [93] [94] [95] [96] [97] [98]
	Momordica charantia L	Karolla, Uchhe, Usta	Whole plant	Methanolic, Aqueous, Chloroformic	Momordicin, Galactose-binding lectin non -bitter, Diosgenin, Cholestero l, Lanosterol, β -sitosterol, Cucurbitacin glycoside	p.o., 27 -30d; 10 -20 mg/kg	Streptozotocin-induced diabetic mice	Decreased glucose level, glycosylated hemoglobin, and oxidative stress, increased glycogen, Decreased lipid peroxidation	Showed antioxidant activity	
	Momordica dioica	Kakrol	Fruit	Methanolic	Lectins, β-sitosterol, Saponin glycosides, Triterpenes of ursolic acid, Hederagenin, Oleanolic acid, Stearic acid, Gypsogenin, and Momodicaursenol	300 mg/kg	Streptozotocin-induced diabetic rats	Reduced serum glucose, Increased serum insulin and urea levels	Showed antioxidant activity	
	Luffa cylindrica L.	Dhundul.	Fruit	Methanolic	Alkaloids, Glycosides, Flavonoides, Tannins, Terpenoids, Sterols, Saponins, Fats, and Sugars	400 mg/kg	Alloxan induced hyperglycemic rats	Showed hypoglycemic and antihyperglycemic effects	Showed antioxidant activity	
	Luffa acutangula	Zinga, Sponge ground	Fruit	Methanolic	Carbohydrates, Saponins, Phenol, Amino acid, Flavonoids	400 mg/kg	Stroptozotocine induced diabetic rat	Showed alpha-glucosidase inhibitory activity	Showed antioxidant activity	
Flacourtiaceae	*Flacourtia indica* (*Burm.f.*) *Merr*	Katabohori/ Boichi	Leaves	Ethanolic	-	-	Streptozotocin-induced diabetic rats	Alterated fasting blood glucose, serum cholesterol and triglycerides	-	[99] [100]
Rutaceae	*Aegle marmelos*	Bael	Leaf, Seed, Fruit	Ethanolic, Aqueous	Aegeline 2, Coumarin, Flavonoid, Alkaloid	I. p. 14d; p. o. 14d; 1.0 g/kg	Streptozotocin-induced diabetic rats	Decreased glucose level, Decreased glycosylated hemoglobin, Increased C peptide, increased glucose tolerance, increased glycogen,	Showed antioxidant activity	[7] [101]
Sterculiaceae	Heretiera fomes	Sundri	Leaves	Methanolic	Saponins, reducing sugars, Alkaloids, Glycosides, Flavonoids, Tannins, Steroids, and Gums	-	*In vitro*	Showed α amylase inhibitory activity, Increased glucose adsorption	Showed antioxidant activity	[102] [103]
Asparagaceae	*Asparagus racemosus L.*	Sotomuli	Whole plant	Ethanolic	Alkaloids, Flavonoids, Tannins, Saponins, Phenols, Terpenes, Polysaccharides, and Steroids	200 and 400 mg/kg for 21 days	Streptozotocin-induced diabetic rats	Significantly decreased the blood glucose level, significantly decreased thiobarbituric acid reactive substances and significantly increased in reduced glutathione, superoxide dismutase and catalase	Showed antioxidant activity	[36] [104]

Continued

Poaceae	*Cynodon dactylon* (*L.*)	Durva, Dub, Dubla, Durba, Doorva, Neel Doorva	Whole plant	Aqueous	Flavonoids, Sterols	500 mg/kg	Streptozotocin-induced diabetic rats	Decreased glucose level, Decreased TC, Decreased TG, Decreased LDL, Increased HDL	_	[105] [106]
Lythraceae	*Lagerstroemia speciosa* (*L.*) *Pers*	Jarul	Leaves	90% ethanolic	Polyphenol, Corosolic acid	-	Streptozotocin-induced diabetic rats	Increased insulin secretion, decreased glucose level, improved hyperlipidemia, and recovered the beta cell of langerhans islet	-	[107] [108]
Missociaceae	*Mimosa pudica L.*	Lojjaboti	Leaves	Ethanolic	Alkaloids, Tannins and Flavonoids	600 mg/kg	Alloxen induced diabetic rat	Reducted blood glucose level with respect to corresponding control	-	[109] [110]
Fabaceae	*Trigonella foenum-graecum L*	Methi	Leaves	Ethanolic	Vitamin C, E and β carotene, Phenolics	250 and 500 mg/kg for 28 days	Streptozotocin-induced diabetic rats	Decreased glucose level,	Showed high antioxidant activity	[36] [111] [112] [113] [114] [115]
	Sesbania sesban	jainti, jayant	Leaves	Aqueous	Triterpenoids, Carbohydrates, Vitamins, Amino acids, Proteins, Tannins, Saponins Glycosides	500 mg/kg	Streptozotocin-induced diabetic rats	Reduced serum glucose level	Showed antioxidant activity	
	Erythrina variegata	Tiger's Claw, coral tree	Leaf	Methanolic	Alkaloids, Flavonoids, Triterpenoids, and Lectin	900 mg/kg	Streptozotocin induced diabetic rat	Showed plasma glucose lowering activity, Stimulated pancreatic β cells	Showed antioxidant activity	
Menispermaceae	*Tinospora cordifolia*	Gulancha lota	Stem	Methanolic	-	500 mg/kg for 6 weeks	Alloxan induced diabetic rat	Reduced blood glucose, decreased glycosylated, decreased hemoglobin, decreased cholesterol, Decreased free radicals' levels	Showed high antioxidant activity	[38] [116]
Anacar-diaceae	*Lannea coromandelica* (*Houtt.*) *Merr.*	Jiga	Bark	Ethanolic	Flavonoids, Alkaloids, Glycosides, Carbohydrate and Phenolics	500 mg/kg	Alloxan induced type-2 diabetic rat	Reduced blood glucose level significantly, Showed antihyperglycemic effect	Showed antioxidant activity	[117] [118]
Polypodiaceae	*Drynaria quercifolia* (*L.*) *J. Smith*	Pankhiraj, ferns	Stem, Rhizome	Methanolic	Epifriedelinol, Beta-amyrin, Beta-sitosterol, Beta-sitosterol 3-beta-D-glucopyranoside, 3, 4 di hydroxyl benzoic acid, Acetyl lupeol, Aglycone naringenin, and Flavones glycoside	100 μg/ml	Alpha-amylase inhibition assay and glucose uptake assay	Showed antihyperglycemic effect Limited intestinal carbohydrate digestion, Maintained plasma glucose concentration	Showed antioxidant activity	[28] [119]
Verbenaceae	*Clerodendrum viscosum Vent*	Ghetu, Bhat.	Leaves	Ethanolic	Saponin, Flavonoids, Alkaloids, A new glycoside, Clerodendroside, Lupeol, Benzoic acid derivatives, and Beta-itosterol	500 mg/kg	Alloxan induce diabetic rat.	Reduced blood glucose level	Showed antioxidant activity	[120] [121]
	Premna integrifolia	Agnimantha	Bark	Methanolic	Alkaloids, Glycosides, Terpenoids, Carotenoids, and Flavonoids	300 mg/kg	Alloxan induced diabetic rat	Decreased blood glucose level	Showed antioxidant activity	
Rubiaceae	*Xeromphis uliginosa Retz*		Root	Methanolic	Flavonoids, Tannins	500 mg/kg	Alloxan induced diabetic rat	Showed glucose lowering effect, and anti-hyperglycemic effect, Protected beta cell from destroy, and regeneration	Showed antioxidant activity	[122]
Asclepiadaceae	*Gymnema sylvestre*	Medha singi, Gorshar	Whole plant	Methanolic	Alkaloids, Polypeptide, Flavonoids, Tannins, Phenols, Cinnamic acid, Folic acid, Ascorbic acid, Butyric acid, Tartaric acid	30 mg/day	Streptozotocin Induced Diabetic Rats	Lowered blood glucose level (sugar destroyer), Showed antihyperglycemic effect	Showed antioxidant activity (reducing the oxidative stress in cells)	[28] [123] [124]
Scrophulariaceae,	*Scoparia dulcis*	Bon dhonia, Sweet Broom	Aerial Part	Ethanolic	Alkaloids, Carbohydrates, Glycoside, Flavonoid, & Tannins	200 mg/kg	Alloxan induced diabetic rat	Changed serum glucose level, Showed antihyperglycemic effect	Showed antioxidant activity	[14] [125]

Continued

Brassicaceae	*Brassica juncea*	Mustard, Sarsu	Seed	Aqueous	Tannin, Terpenoid, Saponin, Flavonoid, Alkaloid, Phenols, and Cardiac glycoside	100 mg/kg	Streptozotocin induced diabetic rats	Showed antidiabetic activity, and hypoglycemic activity, Depleted serum insulin levels	Showed antioxidant activity	[126] [127]
Berberidaceae	*Berberis aristata*	Daruhaldi	Stem	Methanolic	Alkaloids, Glycosides, Carbohydrates, Saponins	500 mg/kg	Streptpzotocin induced diabetic rat	Reduced blood glucose level	Showed antioxidant activity	[128] [129]
Magnoliaceae	*Michelia champaca*	Sornochampa, champaka	Bark	Ethanolic	Phenolics, Flavonoids, Flavonols, and Proanthocyanidins, Alkaloids, Saponins, Tannins, Sterols	_	*In vitro*	Showed α-amylase inhibitory activity	Showed antioxidant activity	[130]
Actnidaceae	*Saurauia roxburghii*	Bhola kadam	Leaves	Ethanolic	Alkaloids, Carbohydrates, Cardiac glycosides, Flavonoids, Saponins, Terpenes, Steroids	2 g/kg	Alloxan induced diabetic rat	Lowered blood glucose level	Showed antioxidant activity	[121]
Leguminosae	*Acacia catechu*	Khoyer/ Khair	Bark	Ethanolic	Flavonoids, Alkaloids, Glycosides, Flavones, Tannins, Terpenes, Sterols, Saponins, Fats, and Sugars	400 mg/kg	Alloxen induce diabetic rat	Stimulated insulin secretion from beta cell	Showed antioxidant activity	[90] [131] [132]
Palmaceae	*Areca catechu L.*	Supari, betel nut,areca nut	Leaf	Methanolic	Flavonoids, Triterpenoid Compounds, Alkaloids, Steroids, Saponins, Tannins, Glycosides and Carbohydrates	200 mg/kg	Streptozotocin-induced diabetic rats	Reduced and normalized of elevated blood sugar levels	Showed antioxidant activity	[133] [134]

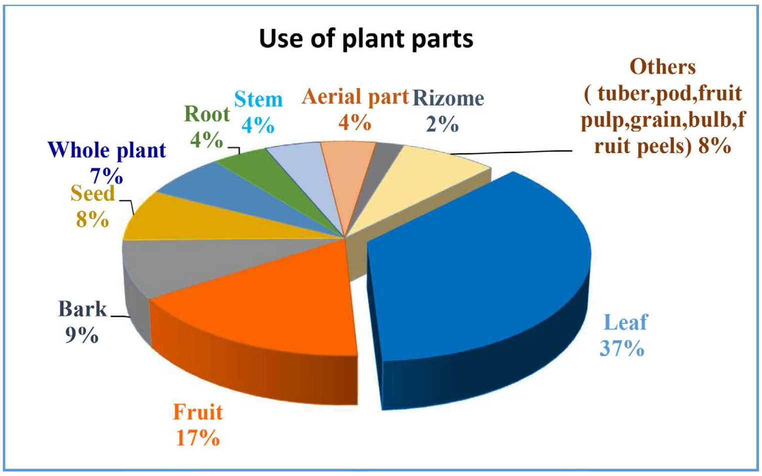

Figure 1. Percentage of plant parts used for the treatment of diabetes and oxidative stress.

4. Discussion

Diabetes mellitus is expanding shockingly. In Bangladesh, diabetes mellitus is becoming a common disorder. Uncontrolled diabetes mellitus leads to many chronic complications such as blindness, heart disease, renal failure, etc. The oral hypoglycemic drugs available on the market have a number of drawbacks such as gastrointestinal discomfort, weight gain, and hepatic dysfunction [7]. Regularly used glucose-lowering drugs may affect the etiology of COVID 19, which may affect the people with diabetes mellitus and initiating the risk of development of severe disease. That's what motivates researchers to look for novel anti-diabetic drugs [92]. So, scientists are trying to treat diabetes mellitus with plant-derived compounds. Moreover, medicinal plants are used to treat diabetes in developing nations, especially to lessen the economic burden of synthetic drugs on people [57]. Plants are known to possess a wide variety of pharmacological effects and therapeutic activities.

The generation of free radicals is one of the most common causes of the development of diabetes. Oxidative stress in diabetes is accompanied by a reduction in the antioxidant status, which can increase the harmful effect of free radicals [135]. Oxidative stress increases complications of diabetes, which include stroke, neuropathy, retinopathy, and nephropathy. It plays a part in the growth of complications of diabetes, especially type-2 diabetes. It leads to endothelial dysfunction in the blood vessels of diabetic patients [136].

Our study revealed that 81 plant species of Bangladesh belonging to 51 families showed significant anti-diabetic and antioxidant activity. Most of the medicinal plants showed anti-diabetic activity by decreasing blood glucose levels. The use of fruits and leaves were the most common plant parts against the diseases (**Figure 1**). Most common active chemical constituents which show antidiabetic and antioxidant effects are flavonoid, saponin, terpenoid, alkaloid, tannins, phenol, steroid, and glycoside. Alloxan induced diabetic rats and Streptozotocin (STZ)-induced diabetic rats were the most frequently utilized diabetic models.

From this review the most significant plants were noted based on their substantial effect against diabetes and oxidative stress namely *Psidium guajava* (L.), Aloe vera, *Catharanthus roseus*, *Allium sativum*, *Annona squamosa*, *Cinnamon zeylaniucm*, *Amaranthus esculentus*, *Eugenia jambolana*, *Azadirachta indica*, *Moringa oleifera*, *Spondias pinnata*, *Coccinia grandis* (L.), *Momordica charantia* L, Heretiera fomes, Trigonella foenum-graecum (**Table 1**) Few of them are narrated below:

Psidium guajava (L.) (Local Name: Peyara) is one of the most common plants in Bangladesh. The hypoglycemic effect of the plants' extract was examined in normal and diabetic rats using a streptozotocin (STZ)-induced diabetes mellitus model. Doses of 50 - 800 mg/kg were given and the effects were dose-dependent. Tannins, polyphenolic compounds, flavonoids, pentacyclic triterpenoids, guiajaverin, quercetin, and other chemical compounds present in the plant are responsible for the hypoglycemic effect. It also showed good antioxidant activity, but fruit extracts exhibited weaker antioxidant effects than leaf extracts because many phytochemical compounds such as flavonoids, phenolic acids and carotenoid were responsible for antioxidant activity. So, fruit part and leaf part showed different antioxidant activity [19] [20] [21].

Aloe vera is another popular plant in Bangladesh. (Local name: Ghritkumari, Family: Liliaceae). Alloxan 200 and 300 mg/kg of plant extract doses were given to alloxan-induced diabetic rats. Pseudoprototinosaponin AIII and prototinosaponin AIII showed anti-diabetic activity. Significant role of these constituents is to uptake glucose and insulin release by glycogenolysis or gluconeogenesis pathway. It showed high antioxidant activity [21].

Catharanthus roseus, which is also known as noyon tara, can be found anywhere in Bangladesh. It produced a maximum reduction in blood glucose of 19.6% (8 h), 31.4% (18 h), and 36.5% (20 h). Observed with C. roseus at doses of

0.5, 0.75, and 1.0 ml/kg body weight respectively. So, the effects were dose depended. It showed good antioxidant activity (81.70%). C. roseus showed rapid normalization of blood glucose levels rather than to control because some β-cells were still surviving to act upon by C. roseus to exert its insulin releasing effect. It can be said that, the mode of action of the active ingredients of C. roseus is probably arbitrated by an enhanced secretion of insulin, like sulphonylureas. C. roseus has indicated a prolonged duration of antidiabetic action after treatment in the period 18 - 24 h. Moreover, the juice has a more prolonged effect (at 1.0 ml/kg) than the glibenclamid, an antidiabetic drug [29] [30].

The anti-diabetic effect of garlic (Bulb Part) ethanolic extract (*Allium sativum* Lantioxidants, garlic.) was investigated in streptozotocin-induced diabetic rats. The result showed that garlic alcoholic extract significantly decreased serum glucose. *Allium sativum* (L.) is also rich in antioxidants, which help destroy free radicals [33] [34] [35].

The leaves of *Annona squamosa* (ata) displayed an anti-diabetic effect. Flavonoids found in the leaf part are responsible for the anti-diabetic effect. Oral administration of A. squamosa aqueous extract to diabetic rats for 30 days significantly reduced the levels of blood glucose, lipids, and lipid peroxidation. The study also revealed that A. squamosa can partially reduce the imbalance between the generation of reactive oxygen species (ROS) and scavenging enzyme activity. So, it can be supplemental as an antioxidant therapy [44].

Terminalia chebula (Combretaceae) has been widely used as a medicinal plant for the treatment of diabetes. The chloroform extract of the seed part showed an anti-diabetic effect by reducing the blood glucose level. The active chemical constituents are Shikimic, gallic, triacontanoic, palmitic acid, β -sitosterol, daucosterol.T. chebula produced a maximum reduction of blood glucose with doses of 200 mg/kg. Effects were dose-dependent reduction of blood glucose. The study also revealed that T. chebula more effectively inhibited the incidence of diabetic nephropathy [1] [7].

Cinnamomum zeylanicum is widely used in alternative systems of medicine for the treatment of diabetes. Cinnamaldehyde is the active ingredient which works against diabetes. Oral administration of CND (20 mg/kg bw) to diabetic rats for 2 months showed significant improvement (p 0.001). The insulinotropic effect of CND increases the glucose uptake through glucose transporter (GLUT4) translocation in peripheral tissues. Additionally, it has been demonstrated to have anti-oxidative, anti-inflammatory, and tumor cell growth inhibitory properties by inhibiting the formation of nitric oxide by LPS-stimulated macrophages and it signifies a wide margin of safety [49].

The oral anti-hyperglycemic effect of the ethanolic extracts of the fruit-pulp of *Eugenia jambolana* (EJ) was investigated in alloxan-induced diabetic rats. Flavonoids, saponins, glycosides, and triterpenoids are the active ingredients responsible for increasing the glucose tolerance level [68].

The hypoglycemic effect of aqueous leaf extracts of A. indica was evaluated in alloxan-induced white male albino mice. Flavonoids, tannins, sterols, saponins, anthraquinones and alkaloids were responsible for antidiabetic effect. Intraperitoneal administration of A. indica decreases the blood glucose level dose dependently at the five doses of 5 mg/kgbwt, 48.4 mg/kgbwt, 93.5 mg/kgbwt, 180.9 mg/kgbwt, and 350 mg/kgbwt [34].

The presence of bioflavonoids in *Moringa oleifera* is responsible for the stimulation of glucose uptake in peripheral tissues and the regulation of the activity and or expression of the rate-limiting enzymes involved in carbohydrate metabolism and flavonoids work as an insulin secretagogue or insulin mimetic. It also increased antioxidant levels in pancreatic tissue and decreased oxidative stress. So, it has significant antidiabetic and antioxidant properties [83].

The hypoglycemic effect of aqueous leaf extracts of A. indica was evaluated in alloxan-induced white male albino mice. Flavonoids, tannins, terpenoids, sterols, saponins, anthraquinones and alkaloids were responsible for the antidiabetic effect. Among them, terpenoids are heart-friendly since they assist in lowering blood sugar levels and diastolic blood pressure. Anthraquinones are also used to treat peripheral neuropathy. Intraperitoneal administration of A. indica decreases the blood glucose level dose dependently at the five doses of 5 mg/kgbwt, 48.4 mg/kgbwt, 93.5 mg/kgbwt, 180.9 mg/kgbwt, and 350 mg/kgbwt [34].

Administration of Carica papaya methanolic leaf extract of 250, 500, and 1000 mg/kg B.W was examined on alloxan-induced diabetic rats. Continuous induction of Carica papaya leaf extracts decreased blood glucose levels, especially at a dose of 1000 mg/kg body weight [84].

Momordica charantia L (Karolla) has an effective dose of 10 - 20 mg/kg for 27 - 30 days and contains bitter substances such as charantin, vicine, glycosides, and karavilosides along with polypeptide-p, plant insulin. These compounds are hypoglycemic in action and lower blood sugar levels by increasing glucose uptake and glycogen synthesis in the liver, muscles, and fat cells. They also enhance insulin release from pancreatic beta cells and restore or encourage the proliferation of insulin-secreting cells. Another bioactive substance found in bitter melon, called lectin, has insulin-like activity and aids in appetite suppression [7] [137].

From above discussion, we can see that most of the plants contain alkaloids, flavonoids, tannins, saponins, and phenolic compounds. Some possibilities concern how they affect the creation and release of pancreatic ß cells, the improvement of insulin sensitivity, or the insulin-like activity of plant extracts. According to, flavonoids increase lipogenesis and glucose transport in adipocytes, resulting in a reduction in blood sugar. The alkaloids encourage pancreatic islet regeneration, which in turn restores insulin secretion. It has also been demonstrated that tannins and saponins have hypoglycemic properties [72]. The elimination or reduction of diabetic complications may be the result of all of these activities.

Among 81 medicinal plants, *Psidium guajava* (L.), Aloe vera, *Catharanthus roseus*, *Allium sativum*, *Annona squamosa*, *Cinnamon zeylaniucm*, *Amaranthus* *esculentus*, *Azadirachta indica*, *Moringa oleifera*, *Spondias pinnata*, *Coccinia grandis* (L.), *Momordica charantia* L, Trigonella foenum-graecum responded more swiftly and relatively at a lower dose than others in mice or rats, making them more successful in treating lower blood glucose levels. Although the reduction of blood glucose has been observed only in test animals like rabbit, mice or rat, the effects can be same as human body due to their anatomical, physiological and genetic similarity. When blood glucose levels drop, there is a significant likelihood that the number of complications related to diabetes will also decrease in humans. So, these most significant plants also help reduce diabetic complications.

5. Conclusions

Diabetes is a metabolic illness that has become a global health concern. Many studies manifest oxidative stress playing a vital role during diabetes, including impairment of insulin action and advancement of the complication incidence. As a result, there is a significant need for proper and adequate therapy for this disorder, which requires the development of treatments with minimal side effects and lower costs than the currently available synthetic medications. Because of several limitations related to the use of established synthetic anti-diabetic drugs, the hunt for innovative anti-diabetic therapies from natural sources should be a matter of concern to us.

From this review, it can be concluded that various research institutions or organizations should give more attention to medicinal plants available in Bangladesh and take necessary steps to extract active phytochemicals from them and it will certainly assist the treatment and management process of diabetes and oxidative stress. And we hope that it will be the groundbreaking step in the health sector.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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