A Mechanistic Insight on Phytoconstituents Delivering Hypoglycemic Activity: A Comprehensive Overview

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Abstract: Diabetes is a long-term (chronic), challenging lifestyle (metabolic) disorder in which the body cannot regulate the amount of sugar in the blood and majorly affecting endocrine system and metabolic functions. Its complications majorly affect the neurons (as developing neuropathy), kidney (as nephropathy), and eye (as retinopathy). Diabetes also results in other associated problems, such as diabetic foot ulcers, sexual dysfunction, heart diseases etc. In the traditional medicines, the search for effective hypoglycemic agents is a continuous and challenging approach. Plant-derived bioactives, including alkaloids, phenols, glycosides, anthocyanins, flavonoids, saponins, tannins, polysaccharides, and terpenes, have been established to target cellular and molecular mechanisms involved in carbohydrate metabolism. Numerous diabetic patients select the herbal or traditional medicine system as an alternative therapeutic approach along with the mainstream anti-diabetic drugs. However, due to restrictive hurdles related to solubility and bioavailability, the bioactive compound cannot deliver the requisite effect. In this review, information is presented concerning well researched phytoconstituents established as potential hypoglycemic agents for the prevention and treatment of diabetes and its associated disorders having restricted solubility and bioavailability related issues. This information can be further utilized in future to develop several value added formulation and nutraceutical products to achieve the desired safety and efficacy for the prevention and treatment of diabetes and its related diseases.

Keywords: diabetes; flavonoids; metabolic disorders; molecular mechanism; phytoconstituents

1. Introduction

The World Health Organization (WHO) declares Diabetes mellitus as one of the commonest types of metabolic disorders with multiple etiologies involving chronic hyperglycemia, abnormalities in the metabolic rate of carbohydrates, proteins and fats, as well as fluctuations in the secretion of insulin and insulin activity [1]. Diabetes is a chronic condition that contributes to abnormalities in blood sugar levels due to the dysregulation of insulin, leading to insufficient insulin production or insufficient use of insulin due to inefficient pancreatic function [2]. As per the available literature it is categorized as one of the largest epidemics disease/disorders worldwide. According to the International Diabetes Federation (IDF), Southeast Asia, approximately, 537 million people were affected with diabetes worldwide, 90 million people in Southeast Asia, and 774 million cases were reported in India in 2022, mostly among the adult age group (8.3%) [3].

According to the latest predictions, diabetes will threaten 9.3% (463 million populations under the ages of 20 to 79 years) by 2019 and increase to 10.2% (578 million) through 2030 and 700 million through 2045 [3,4]. Throughout the world, people living with diabetes experience a severe, long-term condition that has a significant impact on their lives, families, and societies. According to estimates, it caused four million deaths globally in 2017. Diabetes accounted for USD 727 billion loss in global health expenditures in 2017 [5].

Among diabetes, type-2 *Diabetes mellitus* (T2DM) accounts for 90% of the total number of cases, which is continues to rise daily due to overburden of associated factors such as aging, rapid urbanization and obesity [6]. In recent years, T2DM was reported to be growing in young adults and matter of concern. Currently, there is no clear explanation for the rising number of diabetic patients. The increased prevalence of diabetes is also due to improved survival rates (in some populations) due to early detection, better diabetes management, and a reduction in premature death rate. Diabetes reports numerous side effects due to the abnormal functioning of insulin or absence of insulin such as coronary artery disease, retinopathy, foot ulcers, nephropathy and neuropathy [7]. Interestingly, the utilization of ethanobotanicals and traditional remedies for separation of several phytoconstituents has been currently well established for the treatment and management of diabetes and its related complications. Therefore, several such phytoconstituents exhibiting potent anti-hyperglycemic action, reviewed in the present communication, might play a significant role in the prevention and treatment of diabetes and its associated complications along with their molecular mechanism.

2. Classification of *Diabetes mellitus*

Earlier Diabetes were classified as: Insulin Dependent *Diabetes mellitus* (IDDM) and Non-Insulin Dependent *Diabetes mellitus* (NIDDM), respectively. Currently, diabetes has been replaced by a new classification system, shown in Figure 1.
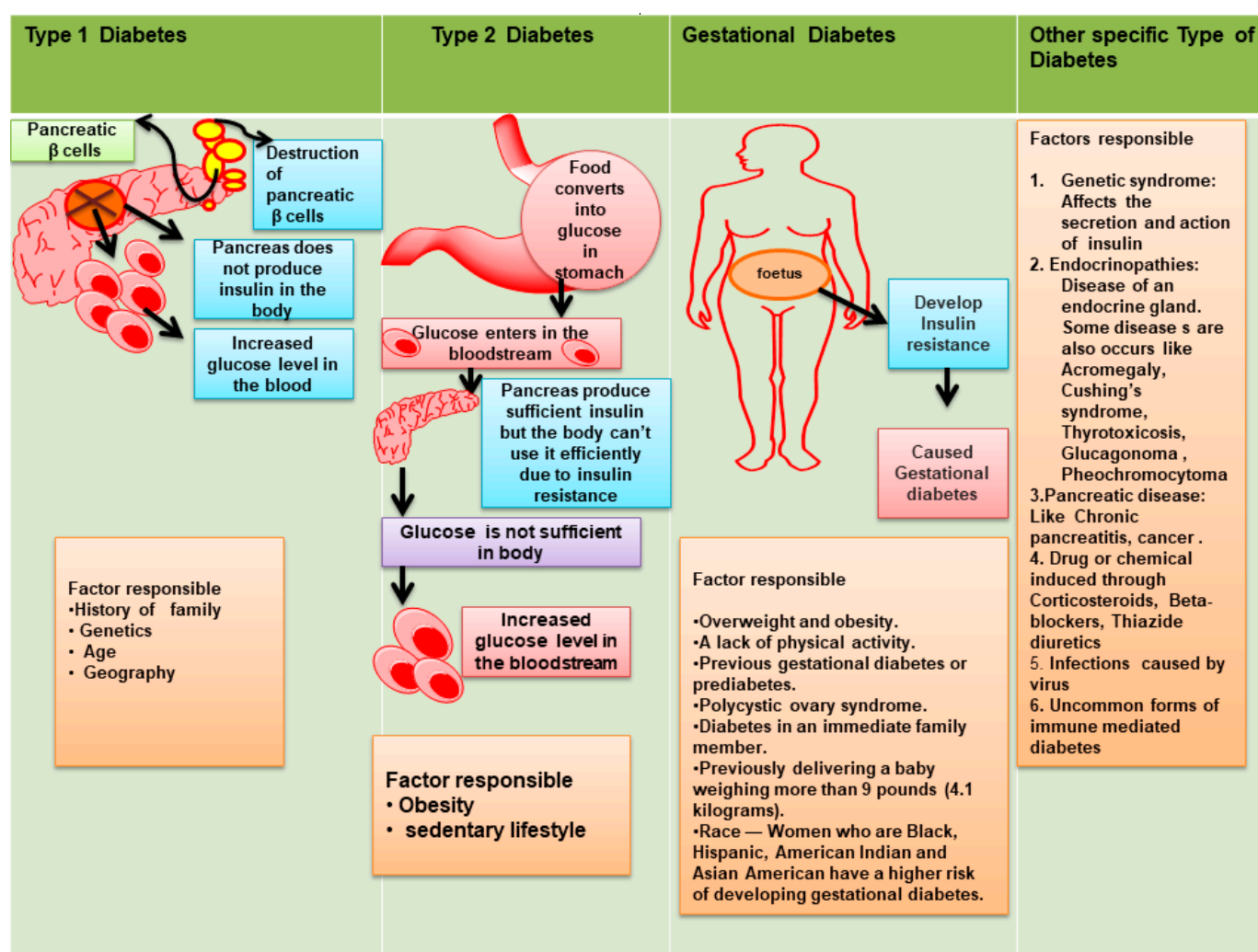

Figure 1. Types of *Diabetes mellitus* (new classification system).

Type 1 *Diabetes mellitus* (T1DM), T2DM, others (as related with secondary conditions, genetic disorders of β-cell functions, pancreatic disease, endocrine disease), and gestational diabetes [8]. In brief:

- T1DM is recognized by autoimmune destruction of β-cell responsible for production of insulin. T2DM leads to the development of insulin resistance [9].
- Gestational diabetes mellitus (GDM) represents an increase in glucose level and is commonly seen during second or third trimesters of pregnancy.
- Monogenic diabetes caused through various genetic reasons and grouped together under the term "Other Specific Types" [10].

2.1. T1DM

T1DM is characterized as an autoimmune disorder caused by destruction of pancreatic β-cells responsible for insulin-production. The detailed pathophysiology of T1DM was shown in Figure 2. A decrease in insulin increases the body's production of ketone bodies in cases of high blood sugar levels, resulting in severe side effects, including liver damage, hypertension, renal failure, coma, and death in severe cases [2,11].
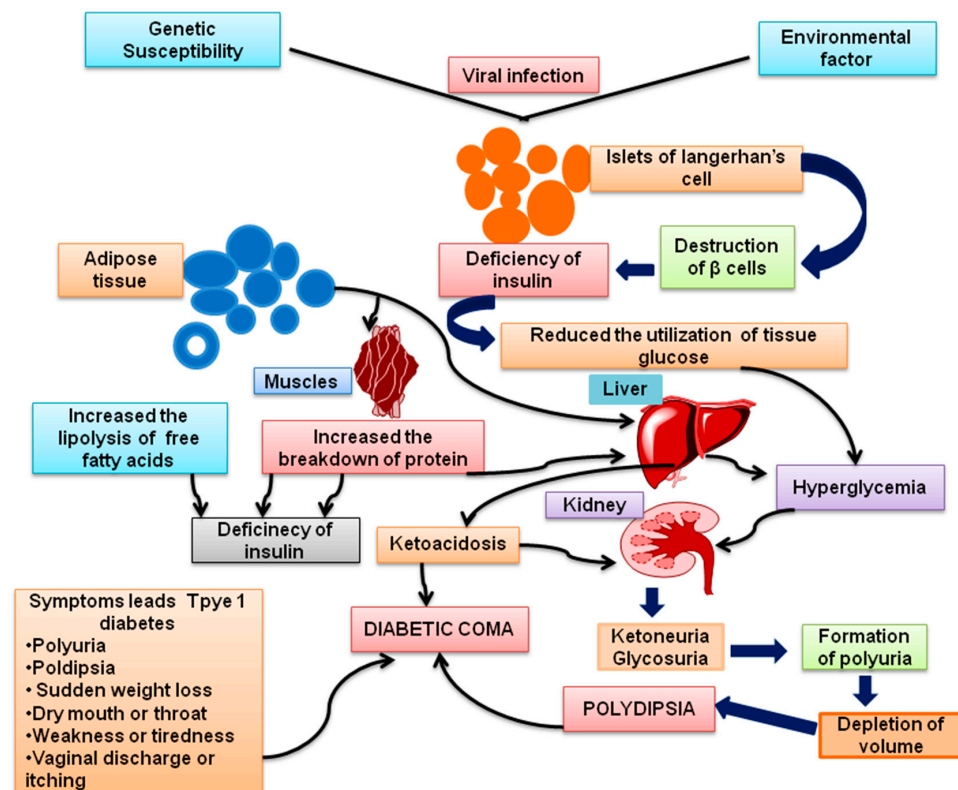
Figure 2. Pathophysiology of Type 1 *Diabetes mellitus* (T1DM).

The progression of T1DM are as follows:

Phase 1 is asymptomatic, refers with normal glucose tolerance and fasting glucose conditions followed by the presence of 2 or >2 pancreatic auto antibodies.

Phase 2 signs and symptoms include the existence of 2 or >2 pancreatic auto antibodies and dysglycemia, which is condition of impairment of fasting glucose condition (glucose of 100–125 mg/dL) or impairment in glucose tolerance (140–199 mg/dL after 2-h) or a ranges of hemoglobin A1c approximately 5.7–6.4%. This is also the condition where individuals become asymptomatic.

Phase 3 is the phase of clinical signs and symptoms which seem to occur and presence of two or more than two pancreatic auto antibodies [12,13].

T1DM in pediatrics characteristically shows hyperglycemic symptoms. In youth the symptoms may occur if not assessed and treated immediately, this might result in a health emergency. Hyperglycemic patients severely affected with polydipsia, polyuria, and polyphagia. If these symptoms are ignored, the patient may develop DKA (Diabetic ketoacidosis), which necessitates hospitalizations and treatments with intravenous fluids, potassium, and insulin with attentive monitoring. The development of sign and symptoms in people with T1DM might be more varied. The diagnosis is confirmed either glucose level in plasma or hemoglobin A1c (HbA1c) monitoring. If individual has sudden onset of symptoms, the plasma glucose level should be used for diagnosis rather than HbA1c. T1DM can be diagnosed when a patient's random plasma glucose level is more than or equal to 200 mg/dl followed with characteristic symptoms. A fasting glucose level in plasma more than or equivalent to 126 mg/dL can also be utilized for diagnosis. However, the oral glucose tolerance test (OGTT) is only used in exceptional cases [14].

2.2. T2DM

T2DM, commonly known as non-insulin dependent diabetes, or adult-onset diabetes, is majorly caused due to insulin resistance. However, in recent decades, a reduction in the functions of β-cell has been recognized as a key problem associated with T2DM. Moreover, T2DM progresses when β-cells no longer have the capability of producing sufficient insulin, leading to weight gain and obesity. T2DM is further associated with increase glucagon levels, decrease adiponectin levels, enhanced leptin levels, and decreased concentrations of interleukin-6, cytokine signal suppressors, and retinal binding proteins. There are several factors associated with T2DM, including a combination of life style choices and genetics. Some of the common factors responsible for causing diabetes include living a sedentary lifestyle, drinking alcohol, smoking, and inactivity, which may result in a reduction of insulin sensitivity and glucose tolerance, leading to obesity [8,15]. The pathophysiology of T2DM includes proper functioning of adipose tissues (endocrine organ), which may be responsible for the secretion of several types of hormones and cytokines (e.g., IL-6, TNF-α, and resistin) followed by chronic inflammation and insulin resistance. Additionally, over-weight patients associated with metabolic syndrome commonly present low levels of adiponectins and develop resistance to leptin. Leptin is a hormone responsible for orexigenic action, which regulates the energy balanced via suppression of starvation [10], whereas adiponectin (peptide) is synthesized by adipocytes having insulin sensitizing properties with anti-atherogenic, and anti-inflammatory effects [16]. This type of metabolic dysfunctions leads to insulin-resistance which predominantly affects adipose, muscles, and hepatic tissues [10]. During this period, insulin does not exhibit anti-lipolytic activity due to an increase in the production and secretion of free fatty acids in the blood [17]. Further, elevations in plasma free fatty acid (FFA) concentration are associated with increases in the synthesis and secretion of glucose in the liver [10]. Subsequently, the concentrations of cholesterol and triglycerides are also increased, particularly in LDL (low-density lipoprotein) [18], followed by obstructive impacts on the cardiovascular system [19]. Additionally, numerous genes that raise the risk of T2DM have been found as a result of GWAS (genome-wide association study), and only a few genes were found necessary for the function of β-cells and its development, as well as regulation of β-cell mass. These outcomes confirm the actual contribution of insulin resistance and also in dysfunctioning of β-cell that are involved in the pathophysiology of T2DM. Particularly, in the primary phase, T2DM pathologies might be asymptomatic with quite minor sign and symptoms, which might be neglected. The sign and symptoms, including extreme dehydration and starvation, frequent urination, blurred visualization, fatigue, slow restoration of injuries, stinging and discomfort or numbness in the hand/feet. Diagnosis is performed by determination of FPG ($\geq$126 mg/dL), OGTT ($\geq$200 mg/dL) or by HbA1 ($\geq$48 mmol/mol or 6.5%). Subsequently, chronic hyperglycemic condition is exposed to tissue, i.e., mainly blood vessel, increases the risk of the developments of co-morbidities including micro-vascular

and macro-vascular complications. All these types of complications are responsible for reduction in life expectancy by up to ten years with diabetic patients [10].

2.3. GDM

GDM is not considered as pathophysiological condition and develops mainly during pregnancy. T1DM develops during pregnancy, but not detected and mainly undiagnosed. However, T2DM, which was discovered during pregnancy and typically occurs in the third trimester of pregnancy, are classified as GDM [10].

2.4. Other Specific Type of Diabetes (Monogenic Diabetes)

This group includes deficiencies of β-cell (formerly recognized as MODY or maturity onset diabetes in youth) or other related defects in action of insulin. Additionally, diseases associated with exocrine pancreas, e.g., inflammation in pancreas (pancreatitis) and cystic fibrosis in pancreas are also included. People with pancreatic dysfunction caused by various types of medicines, chemicals, and infections constitute less than 10% of all *Diabetes mellitus* cases. However, people associated with dysfunction owing to endocrinopathies (e.g., acromegaly) other than diabetes are also included [10].

3. Complications of Diabetes

Various organs affected by diabetes, eventually lead to serious complications as shown and discussed in Figures 3 and 4. Diabetes complications are mainly divided into two types i.e., microvascular and macrovascular. A microvascular complication includes damage to the nervous system (neuropathy), renal system (nephropathy) and eye (retinopathy). While macrovascular complications, including cardiac disease, stroke, and peripheral vascular disease. Particularly, peripheral vascular disease leads to non-healable bruising or trauma followed by gangrene and amputation. Diabetes complications during pregnancy includes tooth disorder, low level immunity against influenza, pneumonia and macrosomia infections followed by other birth related complications. T1DM and T2DM patients can experience same types of complications, but the timing and frequency of their occurrences can vary [20]. The details of these complications are as follows:
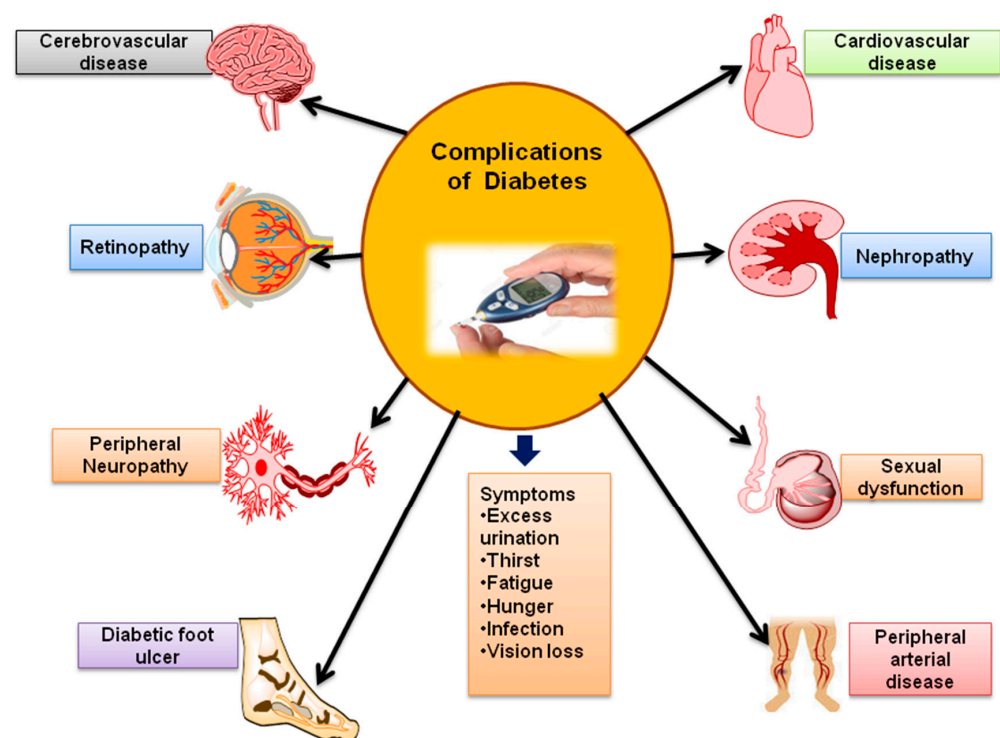

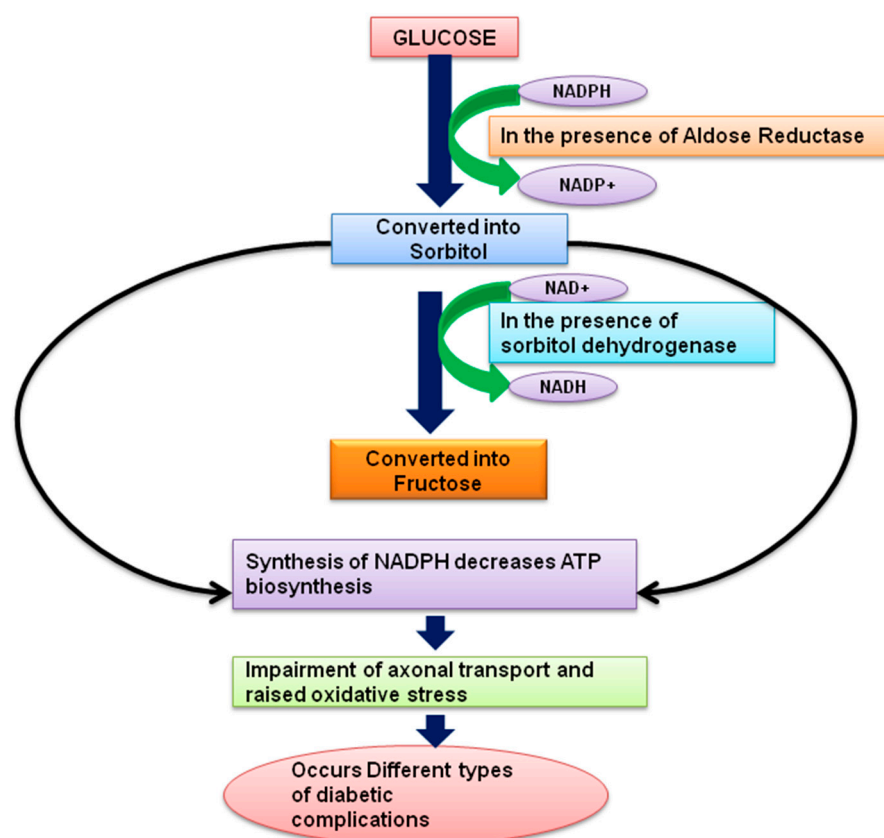**Figure 3.** Complications associated with *Diabetes mellitus*.

Figure 4. Pathophysiology of Diabetes complications.

3.1. Diabetic Nephropathy (DN)

Clinically, DN is slow in progression (approximately 10–20 years) and majorly leads to the development of proteinuria followed by declination in glomerular filtration rate (GFR). If untreated, the resulting uremia can be fatal. The kidneys help regulate the levels of fluids and salts in the body, which is vital for controlling blood pressure and protecting cardiovascular health. Therefore, DN can also referred as chronic kidney disease (CKD) characterized by the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions, and GFR loss in diabetics [21]. These physiological changes majorly contribute further progression and development of nephropathy and its development. In diabetes, the alteration of toxin filtration into the blood is most commonly affected. Furthermore, kidney regulates fluid balance and blood pressure by releasing hormone such as erythropoietin. Additionally, vitamin D cell activation in the kidneys is directly affected by high glucose concentrations in several ways including smooth muscle cells, mesangial cells, endothelial cells, podocytes, muscle fibroblasts, cells of tubular and collecting duct systems [22].

Several studies reported that kidneys exhibit glomerular hyperfiltration as a result of changes in hemodynamic brought though changing blood pressure within and outside the kidney. Initial studies suggested that hyperfiltration of the glomerulus caused the most serious kidney damage including harms to glomerulus, main kidney's filtration system and pre-glomerular vessels. Recent data suggest that diabetic individuals whose glomerular filtration rate is normal or even higher are effectively protected against end-stage kidney problems [23]. It has been further suggested that these hemodynamic changes result from changes in the metabolic conditions, signal transduction, release of vasoactive factors, and intrinsic abnormalities in glomerular arterioles. Proteuria, the accumulation of albumin in the urine, is sometimes linked to changes in renal hemodynamic and is associated with alteration within the glomerular filtration difficulties, specifically, podocytes which are glomerular epithelial cells. Hyperplasia and hypertrophy (during early diabetic conditions)

of the kidney are typically seen along with enlargement of the kidney, when diabetes is diagnosed. As a result of glomerular hypertrophy, expanded mesangial cells and thickens the basement membrane of the glomerular are observed within the glomeruli. In diabetes, the proximal tubule is responsible for the greatest change in growth, constituting more than 90% of the cortical mass. Several studies have proposed that the development of extracellular matrix in the tubular component of the kidney (tubule interstitial fibrosis) is a significant contributor to the progression of renal disease in diabetic patients [24].

3.2. Diabetic Retinopathy (DR)

Diabetic retinopathy majorly leads to blindness or loss of vision and is generally attributed to diabetic macular edema (DME) due to impaired central vision and proliferative diabetic retinopathy (PDR), in turn due to the development of new blood vessels and fibrous tissues, resulting in the fractional detachment of retinal and preretinal or vitreous hemorrhage. The progression of DR involves numerous pathophysiological pathways, including oxidative stress, stimulation of the growth factors in the eye's vasculature, as well as inflammation and activation of both protein kinase C and hexosamine pathway [25]. Further, DR is also considered the chief vascular disease and proposed to be caused by diabetic retinal neurodegeneration (DRN) as per recent study [26]. A meta-analysis included 35 studies have been conducted world-wide from 1980 to 2008, suggested the occurrence of DR and PDR among patients with diabetes to be 35.4 and 7.5% respectively [27]. However, according to recent systematic review, the annual prevalence of DR all over the world ranges from 2.2% to 12.7% and the annual prevalence of disease progression ranges from 3.4% to 12.3%, respectively [28]. Further, alteration of blood sugar level, blood pressure, and dyslipidemia are well known risk factors associated with development and progression of DR. Further, DR is classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is additionally categorized as mild, moderate and severe non-proliferative diabetic retinopathy. Mild non-proliferative diabetic retinopathy is caused by the existence of microaneurysms (bulging in the walls of blood capillaries), and hemorrhages (dots and blots) occurs in the retina. Patients belonging to this category must be observed during every 9–12 months of period. However, severe non-proliferative diabetic retinopathy develops the retinal hypoxia, and subsequently, changes in circulation lead to the development of more severe lesions. Particularly, hemorrhages are widespread during later stages of non-proliferative diabetic retinopathy, as indicated by bleeding in venous, cotton-wool spots (localized infractions of the nerve fiber layer in the retina) and intra retinal microvascular abnormalities (IRMA). In another way, the progression of DR during proliferative stage forms new blood vessels on the disc or in another place on the retina. This could be ruptured suddenly or even after vigorous exercises resulted to preretinal or vitreous hemorrhage. Such a type of patient must be referred for immediate treatment because they have a higher risk of losing their vision. Additionally, remission only occurs after the activation of neovascularization for the development of fibrous tissues but sometime leads to fear of retinal detachment [24].

3.3. Diabetic Peripheral Neuropathy (DPN)

DPN encompasses a wide variety of medical pathology that can cause dysfunction of the peripheral nervous system [26]. Patients suffering from DPN present with symptoms, such as tingling, numbness, and burning sensations, respectively. DPN is caused by a variety of factors and is considered as one of the most important prevalence subtypes leading to severe complications. Consistently, a high level of glucose in blood serum seems to cause damage to minor blood vessels that provide oxygen and nutrients to the nerves. The distal sensory and autonomic nerve fibers are damaged first, resulting in the gradual loss of protective senses in both the skin and foot joints [27–29].

DPN is often associated with the impairment of motor, sensory, and autonomic nerve systems. An important cause of damage to peripheral nerves include oxidative stress, sorbitol accumulation, advanced glycosylation end products, disruption of hexosamine,

PKC, and polymerase pathways. Neurovascular destruction with poor repair process and improper function of endothelial cells have also been implicated [30].

3.4. Sexual Dysfunction

Sexual dysfunction occurs frequently in T2DM patients, despite the fact that it has a highly significant impact on quality of life. The factors that contribute to erectile dysfunction (ED) in diabetic patients includes neuropathic, vasculopathic, and hormonal changes, respectively. Additionally, ED could be used as a diagnostic tools and can be utilized as an early biomarker of diabetic complications. In brief, ED (range 35–90%) is associated with inability or incapacity to obtain and maintain an erection during sexual activity observe for a minimum of three-month time frame [24,31]. Additionally, diabetic patients suffer from ED more frequently than non-diabetics. However, it is estimated that half of them will be affected within 10 years of diabetes diagnosis [24,32]. A study conducted to understand the prevalence of ED on recently diagnosed T2DM patients suggested 33.3% without ED, 19.4% had mild ED, 15.4% had mild-to-moderate ED, 10.4% had moderate, and 21.6% had severe ED, indicating that ED can appear early in T2DM [33].

Diabetic women are more likely to experience depression as compared to non-diabetics, and BMI was the only factor that correlated with female sexual dysfunction (FSD) [34]. Whereas, FSD is characterized by a persistent reduction of sexual desire, persistent decline in arousal, dyspareunia, and difficulty obtaining orgasmic effects [24]. Studies suggest women with T2DM are more likely to develop FSD (2.49 odds ratios) [34], while earlier studies indicated that women with T2DM are more likely to develop FSD between 12–88%. Neither the pathogenesis of FSD nor the risk factors for its development are fully understood in diabetic women. The presence of T2DM in women with FSD is higher with greater risk for blood sugar imbalances [35].

3.5. Heart Stroke and Heart Diseases

Approximately 65% of death in people with diabetes is due to cardiovascular disorder. The main causes of mortality associated with diabetes are ischemic heart disease and stroke. People with diabetes also have a 2–4-fold higher death rate due to heart disease and strokes, when compared to those without diabetes. A diabetic person often suffers from hypertension or hyperlipidemia, which are risk factors associated to cardiovascular diseases, similar to those for non-diabetics [36]. Diabetes increases the risk of coronary arterial diseases because diabetics are generally at greater risk of atherosclerosis, myocardial infarctions, strokes, and weakening of cardiac functions. Therefore, diabetes patients are generally prescribed for both management and treatment strategies, including glycemic control, renin-angiotensin-receptor enforcement (using statins or fibrates), and antiplatelet therapy such as aspirin [37]. Diabetes can also damage the myocardium without hypertension or coronary artery disease, and this condition has been termed as diabetic cardiomyopathy, which was further characterized as diastolic dysfunction [38]. Diastolic dysfunction refers to the inability of the heart to get relax properly and fill properly throughout the diastolic phase of the cardiac cycle. Despite this, long-term blood glucose control, as determined by biochemical HbA1C measures, is still the best predictor of cardiovascular diseases risks in both T1DM and T2DM conditions [14,16,39].

3.6. Diabetic Foot Ulcer

A diabetic foot ulcer (DFU) is a major health concern among people with diabetes due to its negative effects on physical and psychological well-being. Further, DFU involves increased risks of recurrence, amputation, and mortality [40]. In brief, DFU, is defined as a wound that penetrates the dermis (the deep vascular and collagenous inner layer of the skin) and spreads downward below the ankle in a diabetic patient. According to the WHO, limb amputation has a relative 68% mortality rate during five years and second in place after lung cancer. In diabetic patients with foot ulcers, impaired arterial blood flow accounts for about 80%, neuropathy for 50%, while approximately 20% have both the conditions. DFU

is primarily associated with vascular insufficiency, peripheral neuropathies and reduces the ability to resist infections. Certainly, the problem gets more complicated with the induction of oxidative stress. Diabetic foot problems tend to occur due to physical or mechanical trauma resulting in cutaneous ulcers [41]. In patients with diabetes, neutrophils, fibroblasts, and leukocytes exhibit impaired activity, while inflammatory cells migrate and act less effectively at the ulcer site [42,43].

Additionally, other risk factors that contribute to macrovascular diseases, including hyperlipidemia, smoking, and high blood pressure, increase the risk of foot problems by disrupting the foot physiology, blood supply, and immune response to traumas and infection. The predisposing factors for DFU in diabetic's shows characteristic features in male rather than females, who have more than 10-year history of previous ulcers or diabetes. Additionally, vascular disorders, neural disorders, and other related factors, including a sedentary lifestyle, smoking, poor glycemic control, etc., are other associated factors for the progression of DFU [43].

4. Molecular Mechanism of Phytoconstituents Exhibiting Antihyperglycemic Action Might Be Useful for Prevention and Treatment of Diabetes and Its Associated Complications

Diabetes and its complications have been treated with different categories of drugs, such as biguanides, sulfonylureas, α-glucosidase inhibitors and glinides either individually or in combination as evidence from past literature. The major challenges include severe side effects associated with the use of these drugs [44]. There are number of medications that prevents absorption of glucose from gut, such as chlorpropamide, tolazamide, and glibenclamide etc. [45]. From both past and current research, several ethnobotanicals and traditional remedies have been thoroughly investigated for their separation of several bioactive phytoconstituents for the treatment and management of diabetes and its related complications. Therefore, several such phytoconstituents are reviewed in the present communication exhibiting a significant role in the treatment and prevention of diabetes and its associated complications. In Table 1, phytoconstituents effective for treatment of diabetes and related complications are discussed along with their molecular mechanism as per past literature.

Table 1. Phytoconstituents exhibiting antihyperglycemic action.

Sub-Class	Phytochemicals	BCS * Class	Solubility (Aqueous)	Bioavailability (Oral)	Molecular Weight and Melting Point (°C)	Molecular Mechanism
Alkaloids						
Isoquinoline	Berberine [46]	III [47]	Poor [47]	Low (0.68%) [48]	336.4 and 145 °C	Improves metabolism of glucose by glycolysis stimulation via reduction in the mitochondrial oxidation of glucose. Additionally caused AMPK activation as a result of mitochondrial inhibition, which improves the AMP/ATP ratio [49–58].
Pyridine	Trigonelline [59]	NF	Good [60]	57.37% [61]	137.14 and 218 °C	Cell regeneration, insulin secretion, glucose metabolism, reactive oxygen species, axonal extension, and neuron excitability are some of key targets mechanism. Reported to play significant role in alleviating kidney damage in n-STZ-diabetic rats [62–67].
Piperidine	Fagomine [68]	NF	NF	77.50% [69]	147.17 and 188 °C	Reduced levels of lipids and blood sugar by improving insulin sensitivity and antioxidant enzyme activity followed by decreased in lipid peroxidation. Further, improves oxidative damage by high glucose in HUVECs via the AMPK/SIRT1/PGC-1 pathway [70–74].
	Carpaine [75]	NF	48.12 µg/mL [75]	0.55 score [76]	478.7 and 119–120 °C	Glucose transport, carbohydrate digestion and absorption [77,78].
Terpenoid	Gentianine [68]	NF	Soluble [79]	NF	175 and 84–86 °C	Significantly improve adipogenesis, which was correlated with a considerable rise in PPAR-, GLUT-4, and adiponectin mRNA expression [80,81].
Glycosides						
Anthranoids	Aloin [77]	NF	Soluble [82]	5.51 to 6.60% [83]	418.4 and 148 °C	Decreased serum glucose and significantly increased serum insulin levels. It was shown that serum levels of MDA and SOD were significantly decreased, while blood GSH was significantly increased as compared to diabetic rats. Produce an inhibitory effect on the vascular acute inflammatory response caused by the STZ-induced pancreatic islet lesions responsible to increases the vascular permeability [84–89].
	Emodin [90]	II or IV [91,92]	Poor [93,94]	Low [95]	270.24 and 266–268 °C	Have significant glucose lowering effect and mixed type inhibition and non-toxic in the case of prolonged use in treating diabetes. Increase insulin sensitivity and glucose tolerance by activating PPAR and modifying genes involved in metabolism. Further, prevent cataract in diabetic patients by hydrogen bonding with Ser302 in the specificity pocket of aldose reductase [96–121].
	Rhein [122]	NF	Poor [123,124]	>50% (Low) [124]	284.22 and >300 °C	Ameliorate levels of TGF-β_1, renal fibrosis, metabolism, and oxidative stress status [125,126].

Table 1. *Cont.*

Sub-Class	Phytochemicals	BCS * Class	Solubility (Aqueous)	Bioavailability (Oral)	Molecular Weight and Melting Point (°C)	Molecular Mechanism
Amino acids, amines and carboxylic acid derivatives						
Organosulfur	Allicin [68]	I [127]	2.5% or more oil soluble [128,129]	>65% [130]	162.3 and 25 °C	Blood sugar reduction, insulin levels improvement, and regain in GLUT4 and IRSs expression induced by diabetes and also improve of diabetic nephropathy [131].
	Alliin [68]	III [127]	Soluble [129]	16.5% [132]	177.22 and 163 °C	Lowered the amount of a serum enzyme (alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase). Protection against glucose or MG induced glycation of SOD to prevent glycation-mediated diabetic complications [133].
Amino acids	Betaine [68]	NF	157 g/100 mL [134]	100% [135]	117.15 and 310 °C	Improves glucose tolerance, insulin action, multiple genes function expression (dysregulated during diabetes). AMP-activated protein kinase involvement, alleviates endoplasmic reticulum stress, anti-inflammatory and anti-oxidant effects for improved insulin sensitivity and better blood glucose clearance [136,137].
	Isoleucine [68]	NF	Poor [138]	Low [138]	131.17 and 285.5 °C	Lower postprandial blood glucose level [139].
	Alanin [68]	NF	NF	NF	89 and 300 °C	Prolonged glucocorticoid and glucagon signalling, liver alanine catabolism, promotes hyperglycemia and skeletal muscle atrophy [140].
Coumarins derivatives						
Furocoumarin	Marmesin [77]	NF	NF	NF	246.26 and 189–191 °C	Improve regeneration of pancreatic β cells and insulin secretion [77].
Flavanoids						
Flavonols	Kaempferol [68]	II [141]	Low [141]	Low to moderate [142]	286.24 and 277 °C	In obese mice, increased lipid metabolism through PPAR- and SREBP-1c downregulation reduced adipose tissue development, hyperlipidemia, and diabetes. Additionally, restore to almost normal plasma glucose, insulin, lipid peroxidation products, and enzymatic and non-enzymatic antioxidants [143].
	Quercetin [143]	I, II or IV [144]	0.3 µg/mL [145]	16% [146]	302.23 and 316.5 °C	Decreases lipid peroxidation, increases in antioxidant enzymes (like SOD, GPX, and CAT) activities, inhibition of insulin-dependent activation of PI3K, and reduction in intestinal glucose absorption by inhibiting GLUT2 [143]
	Fisetin [147]	II [148]	<1 mg/mL [148]	Poor [148]	286.24 and 330 °C	Act as a dose-dependent manner for high glucose's activation of PKR and decrease of p67 [147,148].
Isoflavones	Genistein [149]	II [141]	0.81 µg/mL [145]	Poor [145]	270.24 and 301.5 °C	Improve insulin sensitivity and the expression levels of the NGF, BDNF, decreased Aβ deposition and hyperphosphorylated Tau protein concentration [149,150].
	Diadzein [151]	IV [152]	8.215 µg/mL [145]	66.9%, 45.2%, 65.7%, and 57.9% [153]	254.24 and 323 °C	Significantly reduced the level of aldose reductase and sorbitol dehydrogenase. Prevent the change in 'a' and 'b' wave amplitude and latency by electroretinography [151].
	Chrysin [154]	II [155]	Low [155]	0.003–0.02% [155]	254.24 and 285.5 °C	Inhibit dose dependently both α-amylase and α-glycosidase enzyme, also reduce glycation, possess greater antioxidant, antidiabetic and antiglycating activities [156].

Table 1. *Cont.*

Sub-Class	Phytochemicals	BCS * Class	Solubility (Aqueous)	Bioavailability (Oral)	Molecular Weight and Melting Point (°C)	Molecular Mechanism
Flavanones	Hesperidin [68]	II [141]	1.4 µg/mL [145]	Poor [157]	610.6 and 250–255 °C	Improvement in plasma insulin levels and total blood lipid profiles [158].
	Eriodictyol [159]	NF	−2.34 [160]	NF	288.25 and 269–270 °C	Activation of the Nrf2/HO-1 pathway, protects RGC-5 cells from high glucose-induced oxidative damage, inflammation, and cell death [159].
	Naringenin [68]	II [161]	45 µg/mL [145]	5.8% [162]	272.25 and 251 °C	Prevent ATF4 and CHOP nuclear translocation in diabetic kidneys and hyperglycemic renal cells. Also prevent apoptosis by down regulating expression of apoptotic marker proteins. Further, lowered serum glucose level, enhanced glucose tolerance, and restored insulin levels in diabetic rats [163].
Flavones	Diosmin [164]	IV [165]	Poor [165]	Poor [166]	608.5 and 277–278 °C	Significantly improved the lipid profiles, increased blood sugar, reduced body weight, walking ability, thermal hyperalgesia, and cold allodynia It restores MDA, NO, superoxide dismutase activity and glutathione levels fell in diabetic rats [164].
	Morin [167]	IV [168]	0.25 mg/mL [169]	0.45% [170]	302.23 and 303.5 °C	Attenuates serum glucose, aminotransferases, urea and creatinine. Also enhances insulin/IGF-1 signalling activation and skeletal deficits brought on by hyperglycemia [171].
	Apigenin [68]	II [141,172]	2.16 µg/mL [145,172]	2.0% [145]	270.24 and 347.5 °C	Improve glycogen synthesis, insulin secretion, cholesterol synthesis and glycogen synthesis [143].
	Baicalein [173]	IV [174]	0.057 mg/mL [174]	2.2% [174]	270.24 and 256–271 °C	Significantly reduced blood glucose and LPS levels, as well as inflammation, lipid profile, and insulin resistance. Exhibit prebiotic-like effects to alter gut flora and ameliorate metabolic abnormalities connected to T2DM [173].
	Tangeretin [175]	NF	Poor [176]	27.11% [177]	372.4 and 154 °C	Modulates through increased insulin production, hepatic enzymes are activated, and the antioxidant capability of the compound lowers blood glucose levels in STZ-induced diabetic rats [175].
	Isorhamnetin [178]	II [179]	Poor [179]	Poor [180]	316.26 and 311–314 °C	Decreased glycaemia, improved oxidative status, decreased inflammation, modulated lipid metabolism, and improved adipocyte differentiation via controlling relevant signalling pathways [178].
	Wogonin [181]	NF	Poor [182]	Poor [183]	284.26 and 203–206 °C	Improved and restored SOD1/2 and CAT activity, ROS and MDA generation and expression of inflammatory markers (IL-1, IL-6, TNF, PAI-1 and NF-B). Additionally, reducing oxidative stress and inflammation may help to lessen the damage of the cardiomyocyte caused by hyperglycemia [181].
	Rutin [184]	II [185]	Poor [185]	Poor [185]	610.5 and 125 °C	Improve cognition and exhibit antinociceptive effects in diabetic rats [184].

Table 1. *Cont.*

Sub-Class	Phytochemicals	BCS * Class	Solubility (Aqueous)	Bioavailability (Oral)	Molecular Weight and Melting Point (°C)	Molecular Mechanism
Flavonolignan	Silybin [186]	II [187]	Low [187]	Poor [187]	484.4 and 164–174 °C	Improve glycated haemoglobin level, restoration of liver glycogen content and serum insulin regeneration [186].
	Silymarin [188]	II [189]	<100 µg/mL [189]	Poor [189]	482.4 and 167 °C	Hypoglycemic potential was due to its antioxidant activity by reducing insulin resistance, in diabetics with liver problems to recover liver function and also demonstrated effectiveness in reducing blood glucose level [190].
Anthocyanins	Delphinidin [191]	NF	NF	0.49% [192]	338.69 and −17.77 °C	Have anti-glycation activity, decrease the rate of albumin and HbA1c glycation and used for treatment of diabetes complications [191].
Polyphenol and its derivative						
Diferuloylmethane	Curcumin [193]	II [194]	11 ng/mL [194]	1% [194]	368.4 and 179–182 °C	Improve glycaemia and the consequences associated with diabetes, such as liver problems, adipocyte dysfunction, neuropathy, nephropathy, vascular illnesses, pancreatic problems, and others [193,195].
Terpenoids						
Pentacyclic	Ursolic acid [196]	IV [197]	<1 µg/mL [197]	Poor [197,198]	456.7 and 284 °C	Reduce DNA damage, GR enzyme activities, and MDA levels in diabetic rats followed by improvement in GSH, CAT, SOD, and GSH-Px levels and enzyme activities [196].
Diterpenoid	Andrographolide [199]	II [200]	Poor [201]	Poor [201]	350.4 and 231–232 °C	Lowered triglyceride, LDL, and blood sugar levels in comparison to controls. Stimulate the insulin release, and inhibits the absorption of glucose through inhibition of the enzyme alpha-glucosidase and alpha-amylase [202].

NF: Not found and BCS: Biopharmaceutical Classification System (I: high solubility, high permeability and generally very well-absorbed compounds; II: low solubility, high permeability and exhibits dissolution rate-limited absorption; III: high solubility, low permeability and exhibits permeability-limited absorption; IV: low solubility, low permeability: very poor oral bioavailability). * https://pubchem.ncbi.nlm.nih.gov/ (accessed on 18 May 2022).

These phytoconstituents (some time non-nutritive and anti-pathogenic) are produced by plants in order to protect themselves, but they may also protect humans against several diseases [203,204]. Interestingly, phytoconstituents, based on their biological activity, are one of the most effective sources for prevention and treatment of *Diabetes mellitus*. Currently, several herbal products are well established in the market, e.g., pancreatic tonic, diabecon, diasulin, bitter gourd powder, chakrapani, dia-care, epinsulin, and syndrex etc. [205].

According to the WHO, approximately 65–80% of the total population in developing countries rely on medicinal herbs. The developments of new products from natural sources are also currently encouraged as only 15% out of 300,000 plant species have been evaluated scientifically for the establishment of any pharmacological potential.

Since ancient times, various extraction procedures have been used to produce extracts from medicinal plants including maceration, infusion, percolation and decoction [206]. Researchers have been found about 800 plants having potential to prevent and inhibit diabetes progression [44]. WHO data regarding prevention and treatment of diabetes with traditional medicinal plants are very clear and majorly based on safety and efficacy parameters [205]. There are large number of phytoconstituents which have been reported and discussed as potential agents to inhibit diabetes progression, such as polyphenols, alkaloids, glycosides, amino acids, terpenoids, peptidoglycans, glycolipids, saponins, and other compounds (Figure 5). These phytoconstituents can relieve metabolic dysfunctioning by reversing them as well as delaying the progression of diabetes [207]. Some of the selective phytoconstituents that have been already established for the treatment and prevention of diabetes and its complication are discussed herewith:
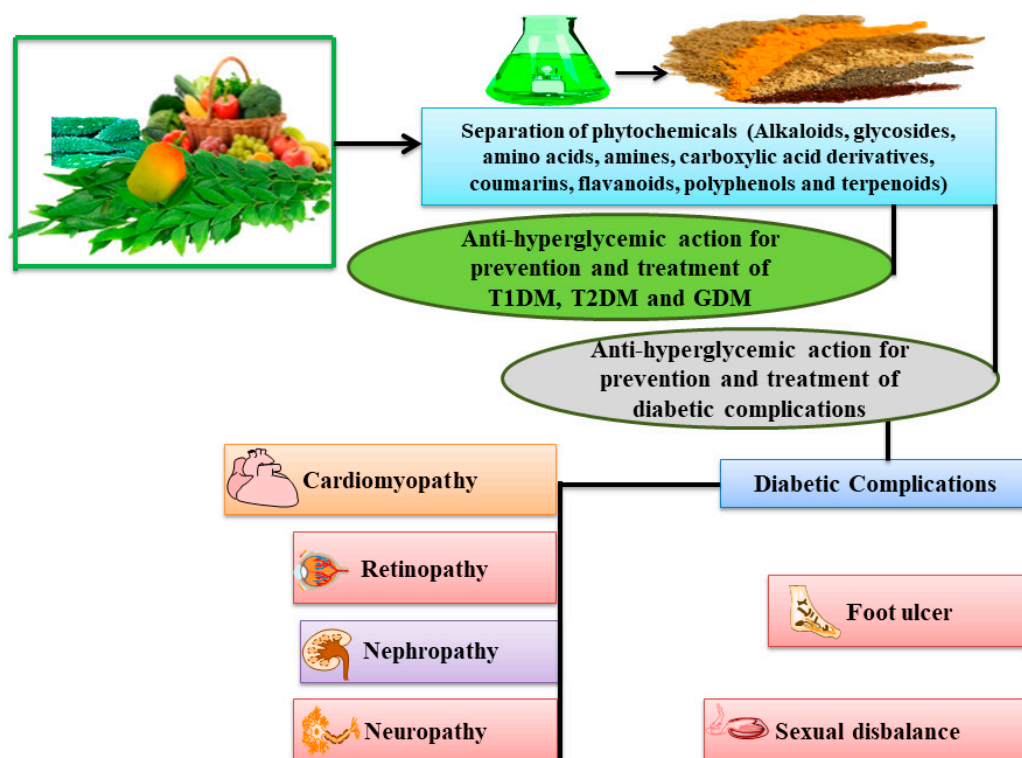

Figure 5. An overview for prevention and treatment of diabetes and its associated complications by phytoconstituents.

4.1. Flavonoids

Flavonoids are plant metabolites that belongs to the family of water-soluble polyphenolic compounds and is composed of two benzene rings connected by a short three carbon chain [208,209]. There are several phenolic compounds classified by their chemical structure, including: flavones (kaempferol, quercetin, isorhamnetin and myricetin etc.), flavan-3-ols (e.g., epicatechin, catechin and gallocatechin etc.), anthocyanidins (e.g., mal-

vidin, peonidin, cyanidin, delphinidin, and petunidin etc.), flavones (e.g., apigenin, luteolin, baicalein, chrysin), isoflavones (daidzein, genistein, glycitein and biochanin A) and flavanones (eriodictyol, hesperedin and naringenin) [208,210,211]. A number of flavonoids possess anti-hyperglycemic properties via antioxidant capacity and ability to modulate certain cell signaling pathways. A flavonoid can be found in vegetables, herbs, fruits, beverages, chocolates, and plants [143,212]. Researchers have isolated the flavonoids from plants described below that have anti-hyperglycemic properties.

4.1.1. Diosmin

Diosmin is naturally occurring flavonoid found mainly in citrus plants. Diosmin is an anti-hyperglycemic principle isolated from several plants including *Scrophularia nodosa*. Researchers suggested that it has an inhibitory effect on diabetes, which are mediated by decreases the levels of glycosylated hemoglobin and an increased in glutathione peroxidase activity. A reduction in the concentrations of plasma glucose, an increase in liver glycogenolysis, and an improvement in insulin levels were observed in patients getting treatment with diosmin. Aside from that, it enhanced the levels of both vitamins C and E [213]. In another study, a potential mechanism of action that is responsible in the improvement of CVD after treatment with diosmin was suggested due to a considerable reduction in pro-inflammatory mediators, such as IL-6 and TNF-α, as well as pro-angiogenetic factors [214].

4.1.2. Morin

Morin is a flavonol isolated from several plants, including *Prunus dulcis*, *Chlorophora tinctoria*, and *Psidium guajava* (Guava leaves) [213]. This flavonol showed increased antioxidant effects for improving the anti-hyperglycemic properties and reducing the insulin resistance via improvement in oxidative stress; normalizing the lipid and lipoprotein levels, and decreased TNF-α [215]. Studies on morin have shown it to reduce the inflammatory action of cytokines IL-1 and IL-6 in diabetic rats [216]. The mechanisms by which morin showed its anti-hyperglycemic effects have been attributed due to the restoration of both insulin and leptin sensitivity followed by reduction in hyperlipidemia and accumulation of liver lipids [217]. In another study, morin was found to reduced glucose-6-phosphatase activities, increased hexokinase activity, and decreased insulin levels [167]. In a very recent study, the potential significance of morin supplements in protecting against hyperglycemia–induced skeletal impairments due to the activation of insulin/IGF-1 signaling was suggested [171].

4.1.3. Fisetin

Fisetin is a flavonoid found in apples, grapes, strawberries, onions, cucumbers, and grape sap. Fisetin has been found to have a potential activity in prevention of diabetes by inhibiting mitochondrial pyruvate transport and decreasing the redox mechanism of cytosolic NADH/NAD. It works by decreasing glycogen breakdown, lowering blood glucose levels, increasing insulin levels, and securing the expression of gluconeogenic genes, like phosphoenol pyruvate carboxykinase. Further, Fisetin was found to inhibit hyperglycemia via lowering nuclear factors like IL-β, NF-kB p65 unit levels, and serum nitric oxide during study on rat model [213,218]. A recent study reported that fisetin alleviates high blood glucose levels on podocyte damage and with streptozotocin-induced diabetic nephropathy mice. The effect was due to restoring cyclin-dependent kinase inhibitor 1B (CDKN1B)/ribosomal protein S6 kinase β-1 (P70S6K)-mediated autophagy and inhibiting NLRP3 inflammasome. The study further provided a new vision for the renoprotective properties of fisetin in diabetic persons [219].

4.1.4. Hesperidin

Hesperidin is a naturally occurring flavonoid found in citrus plants, particularly in *Citrus aurantium* [213]. Hesperidin decreases the risk of diabetes by inhibiting the synthesis of free radicals and pro-inflammatory cytokines [220]. Hesperidin treatment has been found to normalize lipid levels, increase adiponectin, reduces the level of thio-barbituric

acid reactive substances (TBARS), and also decreases lactate dehydrogenase (LDH) activities [221]. Recently, it was reported that hesperidin treatment reduced oxidative stress and mitochondrial dysfunction in HG-persuaded insulin resistance, partially by suppressing miR-149 silencing mediated by DNA (cytosine-5)-methyl transferase 1 (DNMT1) [222].

4.1.5. Eriodictyol

Eriodictyol, is a natural flavonoid compound mostly found in lemon with profound use in the prevention and treatment of diabetes and obesity [223]. Furthermore, it has been reported that eriodictyol have shown potent anti-hyperglycemic action via inhibition of oxidative stress, promotes mRNA expression of peroxisome proliferation-activated receptor gamma (PPARγ) and adipocyte-specific fatty acid-binding protein (AFABP) along with the protein expression of PPARγ in differentiated 3T3-L1 adipocytes. It also reduces endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factors (VEGF), intercellular adhesion molecules (ICAM-1), and lipid peroxides [159,224–226]. It was further demonstrated that eriodictyol acts as an innovative insulin secretagogue with a glucose-dependent insulintropic activity via a cAMP/PKA pathway as an evidence from in vitro and in vivo model [227]. It was further reported that eriodictyol inhibits the invasion, proliferation, migration, and stimulation of apoptosis in retinoblastoma by regulating the PI3K/Akt pathway [228].

4.1.6. Naringenin

Most of the citrus fruits and tomatoes contain abundant amounts of naringenin, known for significant antioxidant action [213]. Naringenin inhibits the activity of α-glucosidase and interferes with genes convoluted in the metabolism of lipids and inhibits the uptake of glucose. Further, naringenin was found to act through the activating AMP-activated protein kinase (AMPK), the improvement of antioxidant properties, decreasing insulin resistance, and improving hepatic function markers [229]. In a very recent study, treatment with naringenin suppressed the nuclear translocation of activating transcription factor-4 (ATF-4) and cyclophosphamide, hydroxyl daunorubicin, oncovin and prednisone (CHOP) in both hyperglycemic renal cells and diabetic kidneys. Additionally, apoptosis was inhibited by naringenin in hyperglycemic renal cells and diabetic kidney tissues by downregulating expression of apoptotic marker proteins. It was further concluded that naringin protected from hyperglycemic renal damage via oxidative stress reduction and improvement in antioxidant defense response [163].

4.1.7. Apigenin

Apigenin is a flavonoid which is extensively found in citrus, vegetables, tea, and nuts. It acts by improving antioxidant parameters, improving glucose transporter 4 (GLUT4) translocation, and preserving beta cells [143]. A study explored effects of Apigenin (20 mg/kg) in diabetic rats, finding that it improved the renal impairment, reduced the oxidative stress and fibrosis (reduction in type IV collagen, fibronectin, and transforming growth factor-1) [230]. It also controlled inflammation (reduced production of IL-6, NF-κB and TNF-α) and apoptosis by dramatically preventing MAPK activation (by increasing Bcl-2 expression and decreasing Bax and caspase-3 production). Apigenin alleviated kidney damage caused by diabetic nephropathy through reduce oxidative stress and fibrosis and blocked the mitogen- activated protein kinase (MAPK) pathway.

4.1.8. Kaempferol

A flavonol which is found mainly in *Ginkgo biloba*, grapefruits, tea, edible berries, and vegetables. Kaempferol was reported to have apoptosis inhibition, reducing the activity of caspase-3 in β-cells, improving cAMP signaling and increasing the production and secretion of insulin. Additionally, it results in reducing IL-1β, TNF-α, lipid peroxidation, nitrite and glycosylated hemoglobin levels [143,231]. Another study investigated the activity of kaempferol on rat renal proximal tubular epithelial cell (NRK-52E) and primary human

renal proximal tubule epithelial cells (RPTEC). Finding of study suggested that kaempferol was able to inhibit hyperglycemia-induced RhoA (Ras Homolog Family Member A) activation, reduce oxidative stress, pro-inflammatory cytokines (TNF-α and IL-1β), and fibrosis (expression of TGF-β1, and extracellular matrix protein). As a result, kaempferol was concluded to possess a therapeutic effect for the treatment of diabetic nephropathy [232]. In another study, kaempferol present in the unripe soybean leaf have been demonstrated the ability to reduce glycosylated hemoglobin levels via the downregulation of liver fatty acid synthase activity [143].

4.1.9. Chrysin

Chrysin is the flavonoid and an important phytoconstituents of *Oroxylum indicum*. Studies reveals number of biological sources of chrysin, which includes *Pelargonium peltatum*, *Passiflora caerulea* and *Tilia tomentosa*. Chrysin, when administered orally resulted to prevents nephropathy via decreased the levels of TGF-β, collagen-IV protein expression and fibronectin in the kidneys followed by significant reduction of IL-1β and IL-6 levels [233]. Chrysin therapy was further established to improve both lipid peroxidation and insulin levels [234]. In another study, chrysin was discovered to have similar effects as metformin, both of them able to decrease the levels of glucose and triglycerides, inhibit the production of pro-inflammatory cytokines (involves in the progression of diabetes), and thus improve atherosclerosis and other related cardiovascular conditions [235].

4.1.10. Baicalein

The fruit of *Oroxylum indicum* and the *roots* of *Scutellaria baicalensis* are one the rich sources of baicalein content. Baicalein was found to lower food intake significantly, improve body weight and levels of fasting blood glucose, followed by normalization of renal function and renal oxidative stress. Molecularly, these events are co-related with inhibition of NF-κB activation, reduction of expression of inducible nitric oxide synthase (iNOS) and transforming growth factor beta (TGF-β), followed by up-regulation of AMPK [236]. Recently, baicalein in the treatment of diabetic nephropathy was studied by reducing inflammation and oxidative stress via activation of the Nrf2-mediated antioxidant signaling pathway and suppression of the MAPK-mediated inflammatory signaling pathway [237].

4.1.11. Luteolin

Luteolin is a rich source of flavonoid in vegetables and fruits, including carrots, peppers, cabbage, and apples. The phytoconstituents luteolin promotes insulin action and PPARγ transcriptional activation. Luteolin was found to reduces inflammatory cytokines including monocyte chemotactic protein-1 (MCP-1), increased the levels of adiponectin and improving the secretion of insulin [234,238]. A study demonstrated the protective effect of luteolin on cardiac tissues of STZ-induced diabetic mice via altering Nrf2-mediated oxidative stress and NF-κB mediated inflammatory responses, suggesting the usefulness of luteolin as a potent therapeutic agent for the treatment of diabetic cardiomyopathy [239].

4.1.12. Tangeretin

Targeretin is a flavonoid most abundantly found in peels of citrus fruits. An oral administration of tangeretin (200 mg/kg bw) reduced total cholesterol, blood glucose, resistin, leptin, IL-6, and MCP-1 [143,240]. Subsequently, tangerine (100 mg/kg bw) when administered orally to diabetic rats for 30 days, the levels of HbA1c and plasma glucose got decreased while the levels of insulin and hemoglobin got increased, respectively. Additionally, it was shown that tangeretin increases the glycolytic enzymes and regulates glucose metabolism in the hepatic tissues of diabetic rats by promoting insulin production from the β-cells of the pancreas by antioxidant mechanism [143,175]. In 3T3-L1 adipocytes, tangeretin boosted the production of the insulin-sensitizing protein adiponectin while concurrently reducing the secretion of the insulin-resistance protein monocyte chemotactic protein-1 (MCP-1), as evidenced by another study [234]. Recently, tangeretin was

demonstrated to significantly reduce high glucose levels, inducing the expression of VEGF, IL-1β, interleukin 6 (IL-6), and transforming growth factor beta 1 (TGF-β1) to improve diabetes [241].

4.1.13. Isorhamnetin

The isorhamnetin compound has been identified and isolated from *Hippophae rhamnoides*, *Oenanthe javanicus,* and *Ginkgo biloba*, and will be used to ameliorate diabetes. Mechanistically, isorhamnetin was able to reduce the oxidative stress, production of sorbitol, and interfere the metabolism of lipids in a diet induced mouse model [242]. Recently, isorhamnetin was demonstrated to improve the condition of insulin resistance in a T2DM induced rat model [243].

4.1.14. Wogonin

Scutellaria baicalensis is a rich source of wogonin, which has the potential to improve the lipid metabolism and insulin sensitivity by inhibiting AMPK and PPARα [234,244]. In a very recent study, wogonin was found to prevent glomerulopathy and podocytes injury by modulating the Bcl-2-mediated interaction between autophagy and apoptosis. Additionally, wogonin demonstrated as a potential therapeutic agent against diabetic kidney disease [245].

4.1.15. Rutin

Rutin is commonly present in various edible fruits such as grapes, lemons, berries, oranges, buckwheat, limes and peaches. Rutin was found to enhance insulin secretion, restore glycogen content, decreased oxidative stress, inhibit the productivity of AGEs, downregulate IL-6 production, reduce TNF-α levels, and improve liver antioxidant activity [234,246]. In another study, rutin was able to reduce the oxidative stress, apoptosis, and inflammation and exhibit cardiac and myocardial functions in streptozotocin induced diabetic rats [247].

4.1.16. Quercetin

Various fruits and vegetables, including onions, berries, apples, pepper, and coriander, are a rich source of quercetin. A study on quercetin found that it inhibits GLUT-2, increases the levels of antioxidant enzymes, and reduces the absorption of intestinal glucose, suggesting its anti-diabetic effects. Further, quercetin was found to induce cell proliferation by blocking tyrosine kinase enzyme [143,234]. The effectiveness of quercetin on 50 male SD rats including five groups viz. normal control, 50 mg/kg STZ-induced diabetes, and three (30 mg/kg for Quercetin (QE), 10 mg/kg for Resveratrol (RS), and combination) was assessed. The results showed that QE, RS, and combined treatments effectively decreased high serum blood glucose levels, insulin levels, and dyslipidemia in diabetic rats. Further, QE significantly reduced oxidative stress, tissue injuries biomarkers and improve hematological parameters, associated with ketoacidosis and hyperlactatemia majorly responsible for diabetes related complications [248]. Quercetin 3-o-glycoside and quercetin, a component of *Vaccinium vitis,* shows hypoglycemic effects by stimulating AMPK [233].

4.1.17. Genistein

This flavonoid is derived from a soya-isoflavones that occurs naturally in legumes and abundantly found in *Genista tinctoria* and *Sophora subprostrala*. Genistein significantly reduces renal thiobarbituric acid reactive substances (TBARS), increases blood insulin levels, and improves glucose tolerance without adversely affecting body weight [249]. Another study shown the beneficial effects of genistein by improving brain insulin signaling, increases neurotrophic support, and alleviates AD-related pathology in the obese diabetic mouse brain [149].

4.1.18. Daidzein

Daidzein is a Soy isoflavones flavonoid that naturally occurs in soybeans, fruits, and nuts. A study found that daidzein improves the metabolism of lipids and glucose level, insulin sensitivity, and phosphorylated AMPK in muscles [250]. Daidzein was found to act on VEGFA, INS, INSR, IL-6, TNF, and AKT1. In brief, Daidzein participates in the AGE-RAGE signaling pathway, insulin resistance, HIF-1 signaling pathway, FoxO signaling pathway, and MAPK signaling pathway. It may also control type 2 diabetes, inflammation, atherosclerosis, and diabetes complications, such as diabetic retinopathy, diabetic nephropathy, and diabetic cardiomyopathy [251].

4.1.19. Delphinidin

Delphinidin showed anti-diabetic properties mediated by antioxidant activity and decreases in albumin and hemoglobin glycation. It is most commonly available in eggplants, carrots, berries, grapes tomatoes, sweet potatoes, red cabbages, and red onions [252]. It exhibits, antioxidant, anti-mutagenic, anti-angiogenic, and anti-inflammatory effects [253]. Another study showed that the administration of 100 mg/kg of delphinidin to diabetic mice for eight weeks was able to decrease the albumin rate and HbA1c glycation [191]. The anti-diabetic effect of delphinidin due to the inhibition of the uptake of glucose in mice jejunal tissue and human intestinal cell lines via free fatty acid receptor 1 (also known as GPR40) was further established [254].

4.1.20. Cyanidin

Cyanidin is an anthocyanin flavonoid used in treating diabetes through regulating the enzymes, alpha-glucosidase, pancreatic alpha-amylase, inhibiting apoptosis and improvement in antioxidant status. Furthermore, it also inhibits apoptosis while simultaneously enhancing antioxidant activity [252]. In another study, cyanidin chloride liposomal formulations were formulated and found to be effective against diabetes mellitus complications [191]. Similarly, a study reported the potential effect of cyanidin on STZ-induced diabetic rats via pancreatic apoptosis inhibition, insulin receptor phosphorylation activation, and improvement in healthier β-cells [255].

4.1.21. Pelargonidin

Pelargonidin is an antioxidant molecule and was found to be present in blackberries, cranberries, raspberries, and blueberries [252]. Subsequently, pelargonidin was found to improve hyperglycemia, oxidative stress level, glucose in-tolerance, and insulin resistance as evidenced in a study conducted using db/db mice. Furthermore, pelargonidin enhanced serum lipid levels, impaired hepatic dysfunction, and mitigated type-2-diabetes via modulating glucose and lipid metabolism [256].

4.2. Saponins

Saponins are glycosides mostly found in plants as surface-active compounds consisting of sugars connected to a hydrophobic aglycone moiety called sapogenins also known by triterpenoid or steroid. Saponins are the active chemical moiety present in several herbs exhibiting anti-hyperglycemic action. In a study saponins was found to be responsible for the hypo-glycemic abilities of *Anabasis articulata* via improvement in insulin production. Additionally, *Astragalus membranaceus,* saponins was found to greatly ameliorates oxidative stress and AGES formation [233]. The saponins obtained from *Entada phaseoloides* elevate serum insulin level, alleviate hyperglycemia, and decrease lipids [257]. In another study, saponins (from *Garcinia kola*) were able to significantly reduce the levels of glucose in plasma and insulin in blood using alloxan induced diabetes rats [258]. Similarly, saponins obtained from *Helicteres isora* reduce serum lipid and plasma glucose levels with increased GLUT-4 at the same time. *Momordica charantia* has natural saponins and effective in improving diabetes [259]. Comparatively, saponins significantly induce AMP-activated protein kinase (AMPK) activation as similar as troglitazone [260]. *Moreover, Solanum anguivi* Lam.

fruits were found to exhibit potent anti-hyperglycemic, hypolipidemic, and antioxidant effects due to the existence of saponins in an alloxan-induced diabetic rats model [261]. A study further reported potent anti-hyperglycemic action of saponin extract from *Solanum anguivi* [262]. A study demonstrated that *Platycodi radix* extracts containing saponin shows recovery of AMPK/ACC phosphorylation in the muscle of obese mice to improve obesity and insulin resistance by activating AMPK/ACC pathways and decreasing adipocyte differentiation [263]. Subsequently, saponins rich fractions of *Polygonatum odoratum* were found to improve glucose uptake and relieve diabetes symptoms via the upregulation of superoxide dismutase activity and downregulation of melondialdehyde levels in another study [264]. Several saponins isolated and found to be effective as anti-hyperglycemic agents are discussed below:

4.2.1. Diosgenin

Diosgenin, a saponin isolated from *Dioscorea rotundata*, was found to improve glucose 6-phosphatase enzyme function [233]. Both diosgenin and fenofibrate were found to reduced lipid accumulation in the liver and decrease hepatic triglyceride (TG) content. Contrarily, while diosgenin considerably reduced the level of ALT, fenofibrate significantly increased the levels of ALT and aspartate aminotransferase. Additionally, diosgenin also improved AMPK and ACC phosphorylation followed by suppressing the liver X receptor (LXR) α in the liver [265].

4.2.2. Arjunolic Acid

Arjunolic acid is a triterpene saponin found in *Terminalia arjuna* that protects against from several metabolic diseases, including diabetes and its complications. A recent study shown that arjunolic acid could be a promising candidate for the protection of retinal cells in STZ-induced inflammation and oxidative stress via AMPK/mTOR/HO-1 mediated autophagy pathways [266]. Further, the effect of orally administered arjunolic acid in preclinical model of Type 2 diabetes mellitus was found to shown significant reduction towards normalization of both fasted and random blood glucose samples, restore body weight and improved the conditions of polyphagia, polydipsia and glucose tolerance, respectively [267]. Additionally, arjunolic acid was found to reduce serum HbA1c, triglyceride and low-density lipoproteins without altering high density lipoproteins.

4.2.3. Platyconic Acid

Platyconic acid was isolated from *Platycodi radix* have found to regulates insulin-induced uptake of glucose in 3T3-L1 adipocytes. This substance is well known for increasing glycogen storage and decreasing disaccharide storage in the liver. It also improved insulin signaling, increased GLUT4 and adiponectin expression in adipose tissues [268].

4.3. Alkaloids

Alkaloids are secondary plant metabolites isolated from bacteria, fungi and animals. An alkaloid is a natural compound containing basic nitrogen atoms. Few researchers have worked with alkaloids having specific types of amines. The categories of alkaloids are mentioned below [269]:

- True alkaloids (Atropine, morphine and, nicotine etc.)
- Protoalkaloids (Adrenaline, ephedrine and, mescaline etc.)
- Polyamine alkaloids: Example; Spermidine, epinephrine, putrescine and spermine.
- Pseudoalkaloids: Example; Caffeine, theophylline and, theobromine, etc.

Alkaloids have potent hyper-glycemic effects that can be demonstrated by their significant impact on various experimental models as evidenced in several studies conducted in the past. A study demonstrated that an alkaloid containing extract obtained from Fenugreek was found to have anti-hyperglycemic properties via elevated serum insulin levels, decreased serum lipids and lipid peroxidation, using streptozotocin-induced dia-

betic rats [233,270]. Some of the potent alkaloids exhibiting antihyperglycemic effects are discussed here:

4.3.1. Koenidine

A study demonstrated uptake of glucose and translocation of GLUT-4 are enhanced in L6-GLUT-4 myotubules after treatment with koenidine. Additionally, koenidine could be beneficial to diabetes and insulin resistance conditions as evidenced by an experiment performed on streptozotocin-induced diabetic rats [271].

4.3.2. Canthin-6-One Derivatives

A study demonstrated that the administration of a partially purified alkaloids fraction (Canthin-6-one derivatives) from roots of *Aerva lanata* was found to significantly reduce the levels of serum glucose in blood and thus prevent diabetes on streptozotocin-nicotinamide induced rats model [272].

4.3.3. Vindoline I, Vindolidine II, Vindocine III and Vindocine IV

In another study, alkaloids isolated from *Catharanthus roseus* were found to have a potent anti-hyperglycemic effect. The four alkaloids obtained from *C. roseus*, i.e., Vindoline I, Vindolidine II, Vindocine III and Vindocine IV, showed increased glucose transport to pancreatic βTC6 or myoblast C2C12 cells and hence exhibited the strongest activity. Further, vindocine III and IV inhibited the protein tyrosinase phosphatase-1B (PTP-1B), as well as treated oxidative damage caused by hydrogen peroxide [273].

4.4. Tannins

Tannins are the polyphenolic biomolecules which are naturally occurring in tea, coffee, grapes, wine, dry fruits, apricot, mint, barley, dry fruits, peaches, rosemary, basil, pomegranates, amla, cloves, rye, rice, oat and strawberries etc. [274].
Tannins are mainly classified as:

1. Hydrolysable tannins (gallic acid),
2. Non-hydrolysable or Condensed tannins (flavones), and
3. Phlorotannins (phloroglucinol).

Some studies have reported that medicinal plants containing tannins exhibit anti-hyperglycemic effects [275]. Tannins play a significant role in the treatment of diabetic neuropathic pain (DNP) due to their higher antioxidant activity. Further, neuroprotective beneficial effects of tannins in diabetic problems due to its potential antioxidant and anti-inflammatory effects were also demonstrated [276]. Some of the potent studies on tannins are discussed herewith:

4.4.1. Catechin

A study showed that (25 mg/kg and 50 mg/kg of catechin administered orally for 28 days) reduced the levels of melondialdehyde (MDA) and improved GSH, SOD, and catalase levels in diabetic rats induced by STZ [277].

4.4.2. Epigallocatechin

In STZ-induced diabetic rats, treatments with epigallocatechin (EGCG) reduced hyperalgesia responses (as measured by hot plate, tail immersion, formalin, and carrageenan-induced paw edema tests). Further, treatment with epigallocatechin for 10 weeks caused STZ-induced diabetic rats reflected paw withdrawal threshold (PWT), suggesting an improvement of mechanical hyperalgesia and tactile allodynia [278,279].

4.5. Terpenes

Terpenoids are secondary metabolites composed of repeating isoprene units with a number of structural variants [280]. They are classified into monoterpenes, diterpene, triterpenes, tetraterpenes, hemiterpenes, sesquiterpenes, sesterpenes, and polyisoprenes.

Terpenes and their derivatives protect against several diseases and have a number of beneficial characteristics [281]. Generally, terpenes were found to have an antihyperglycemic effects, as evidence by both in vitro and in vivo studies. They have an excellent antioxidant property and a potential inhibitory effect against α-glucosidase enzyme. Moreover, terpenes were also found to improve the levels of insulin, glucose uptake in tissues and inhibited several carbohydrate metabolism signaling pathways [280,281]. A number of monoterpenes have been shown to improve glucose uptake by up regulating the translocation of glucose transporter (GLUT4), improves the insulin signaling pathway, improved insulin secretion, ameliorating cytokines proinflammatory effects and, protecting pancreatic cells [280]. Additionally, terpenes are responsible for maintaining sugar level via increase in the levels of glycogen, fructose-1,6-bisphosphatase and glucose-6-phosphatase. Further, activities of glucokinase and glucose-6-phosphate dehydrogenase were reduced [280]. Sesquiterpenes are more efficient as compared to other terpenes due its tightly arrangements of the structure. On the other hand, triterpenes with more hydrophilic groups were preferred for multi-targeting effects as anti-hyperglycemic [281,282]. Chi et al. (2013) worked on limonene protection, which might be mediated by inhibiting nuclear factor-κB (NF-κB) [283]. Terpenes, e.g., limonene, 3-carene, β-caryophyllene, and α-pinene, have been reported to bind directly with gamma-aminobutyric acid receptors, resulting in decreased activity of acetylcholinesterase and lipoxygenase activities. Molecularly, terpenes reduce lipid peroxidation induced by ROS formation, NO release, transforming growth factor (TFG)-1, and type I procollagen secretions, phosphorylation of various MAPK-related signaling molecules, production of O_2, and H_2O_2-inducedastrocytic cell death. Additionally, terpenes also increased superoxide dismutase, catalase and peroxidase activities, reduced glutathione content, and restored the mitochondrial membrane [284]. Several studies quoted earlier that both terpenes and terpenoids are involved in the in the suppression of microglia mediated inflammations in acute and chronic neurological diseases [285,286].

4.5.1. Linalool

Researchers have reported the antioxidant and anti-inflammatory activity of the monoterpene linalool by in vitro and in vivo studies showing that the molecules have a strong neuroprotective characteristic property, acting in NF-κB activation and preventing its nuclear translocation [287].

4.5.2. α-Pinene

Studies show the photoprotective effects of α-pinene (present in essential oils of coniferous trees) on human skin epidermal keratinocytes from inflammatory signaling [288]. The researchers determine that α-pinene inhibits the UVA-induced expression of inflammatory proteins, such as IL-6 and TNF-α. Furthermore, it has been recommended that the anti-inflammatory property of alpha-pinene is due to its inhibitory effects of MAPK pathways via the suppression of JNK and ERK phosphorylation [289].

4.6. Glycosides

The presence of glycosides in *Gymnema sylvestre* was found to exhibit anti-hyperglycemic effects on experimental model [233]. Similarly, residues isolated from *Jatropha curcus*, were found to have significant anti-hyperglycemic effects on streptozotocin induced animal model [290]. Activity was further correlated with events, such as lowering of serum α-amylase, lactate dehydrogenase activity, reduction of oxidative stress, and modulation of melondialdehyde levels. The cardiac glycosides extracted from the seeds of *Securigera securidaca* (Fabaceae) lower the blood glucose levels via the stimulation of insulin secretion [291].

5. Nutrivigilance (Compounds' Adverse Effects)—As a Possible Limitation of Their Use

Among phytochemicals, several nutrivigilance studies have been conducted and some noticeable adverse effects have been observed [292]. In this context aloin has been re-

ported to cause bloody diarrhea, cardiac dysrhythmias, peripheral edema, red coloration of the urine, weakness, weight loss, stomach cramps, itching, redness, rash, and pruritus [293]. Alanin was associated with paraesthesia [294]. An overdose of diadzein was stomach upset, constipation, flatulence and diarrhea [295]. Similarly, hesperidin is associated with stomach pain, diarrhea, and headache [296]. Naringenin is associated with cough, dizziness, headaches, flushing sensation, palpitation, angioedema, liver dysfunction, and myositis [297]. Apigenin is associated with upset stomach, muscle relaxation and sedation [298]. Baicalein was involved for some time in fatigue and shortness of breath [299]. Silybin was found to be associated with gastrointestinal problems, headache, dizziness and pruritus [300].

6. Conclusions

Diabetes and its related complications represent one of the challenging situations in today's world, affecting many people of all age groups. Many studies are currently taking place to provide sustainable, safer, and effective solutions, including antidiabetic drugs and insulin therapy. Despite many years of research into the use of bioactive compounds as hypoglycemic agents, none of them have been used alone in the treatment of DM due to restricted solubility and bioavailability related hurdles. Therefore, it is necessary to say that there is a potential source of antidiabetic drugs, even as an idea can be converted through application of advanced drug delivery system. This source can be further utilized to understand the safety and efficacy in details via clinical research. This will support the development of several value-added nutraceutical and pharmaceutical products with potent antihyperglycemic action in the near future.

Abbreviations

ACC	Acetyl-CoA Carboxylase
AFABP	Adipocyte-specific Fatty Acid Binding Protein
AGEs	Advanced Glycation Endproducts
ALT	Alanine Aminotransferase
AMPK	AMP-activated Protein Kinase
ATF-4	Activating Transcription Factor-4
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
Bw	Body weight
cAMP	Cyclic Adenosine Monophosphate
CDKN1B	Cyclin-Dependent Kinase Inhibitor 1B
CHOP	Cyclophosphamide, Hydroxyl daunorubicin, Oncovin and Prednisone
CKD	Chronic Kidney Disease
CVD	Cardio Vascular Diseases
DFU	Diabetic Foot Ulcer
DKA	Diabetic Keto Acidosis

DME	Diabetic Macular Edema
DN	Diabetic Nephropathy
DNMT1	DNA (cytosine-5)-methyl transferase 1
DPN	Diabetic Peripheral Neuropathy
DR	Diabetic Retinopathy
DRN	Diabetic Retinal Neurodegeneration
ED	Erectile Dysfunction
EGCG	Epigallocatechin
eNOS	Endothelial Nitric Oxide Synthase
ERK	Extracellular signal-regulated kinase
FFA	Free Fatty Acids
Fox	Forkhead Box
FPG	Fasting Plasma Glucose
FSD	Female Sexual Dysfunction
GDM	Gestational Diabetes Mellitus
GFR	Glomerular Filtration Rate
GLUT4	Glucose Transporter 4 IL-1beta
GSH	Glutathione
GWAS	Genome-Wide Association Studies
HbA1	Hemoglobin A1
HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
HG	High Glucose
HIF-1	Hypoxia-Inducible Factors-1
HO-1	Heme Oxygenase
HUVECs	Human Umbilical Vein Endothelial Cells
ICAM-1	Intercellular Adhesion Molecules
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
IL-1beta	Interleukin 1-beta
IL-6	Interleukin-6
iNOS	Inducible Nitric Oxide Synthase
INS	Insulin
INSR	Insulin Receptor
IRMA	Intra Retinal Microvascular Abnormalities.
IRSs	Insulin Receptor Substrate
JNK	c-Jun N-terminal kinase
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LPS	Lipopolysaccharides
LXR	Liver X Receptor
MAPK	Mitogen Activated Protein Kinase
MCP-1	Monocyte Chemotactic Protein-1
MDA	Melondialdehyde
MG	Methyl Glyoxal
MODY	Maturity Onset Diabetes of the Young
NAD	Nicotinamide Adenine Dinucleotide
NADH	Nicotinamide Adenine Dinucleotide Hydrogen
NF-kB	Nuclear Factor Kappa B
NGF	Nerve Growth Factor
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NLRP3	NLR family pyrin domain containing 3
NPDR	Nonproliferative Diabetic Retinopathy
Nrf2	Nuclear factor erythroid 2 related factor
OGTT	Oral Glucose Tolerance Test
PAI-1	Plasminogen activator inhibitor-1
PDR	Proliferative Diabetic Retinopathy
PI3K-PKB/Akt	Phosphoinositide-3-kinase–protein kinase B/Akt

PKA	Protein kinase
PKC	Protein kinase C
PKR	Protein kinase R
PPARγ	Peroxisome proliferation-activated receptor gamma
PTP-1B	Protein tyrosinase phosphatase-1B
PWT	Paw withdrawal threshold
QE	Quercetin
RAGE	Receptor for advanced glycation endproducts
RGC-5	Retinal ganglion cell-5
RhoA	Ras Homolog Family Member A
ROS	Reactive Oxygen Species
RPTEC	Renal proximal tubule epithelial cells
SOD	Superoxide dismutase
SREBP-1c	Sterol Regulatory Element Binding Protein 1c
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBARS	Thio-barbituric acid reactive substances
TFG-1	Transforming growth factor
TGF-β	Transforming growth factor beta
TNF-α	Tumor Necrosis Factor alpha
mTOR	Mammalian target of rapamycin
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

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