

ADVANCES IN UNDERSTANDING CELLULAR MECHANISMS OF CARDIOVASCULAR COMPLICATIONS AND RETINOPATHY IN DIABETES: THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS

Abstract

Comprehensive knowledge of the pathophysiology, aetiology, and clinical course of diabetes mellitus is paramount to prognosticating cardiovascular and ocular complications. This chapter investigates the mechanisms and processes governing the progressive development of cardiovascular complications and retinopathy in patients with diabetes. We also aimed to determine the diabetes prevention and management potential of multimodal treatments (including phytochemical methods). Thirty-four research articles were analysed to determine the pathophysiology, cellular mechanisms, and biomarkers associated with cardiovascular and ocular complications of diabetes. Data sources included PubMed Central, Web of Science, and JSTOR. Data extraction was guided by the advanced filters of the respective databases. Primary and secondary research articles with the latest evidence on the pathobiology and treatment of diabetic complications were extracted for this updated review. The predominant causes of diabetic retinopathy and diabetic macular edema include haemorrhage and retinal capillary aneurysms. Diabetes type, age at diagnosis, and race are independent predictors of the risk and incidence of non-proliferative and proliferative diabetic retinopathy (NPDR/PDR). In addition, 75% of diabetes-related deaths

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are attributed to cardiovascular complications including peripheral vascular disease, thromboembolism, stroke, nephropathy, coronary artery disease, and atherosclerosis. Training researchers and physicians on the therapeutic efficacy of phytochemical methods against NPDR/PDR and diabetes-related cardiovascular diseases is needed to increase their use in adjuvant treatments. In addition, comprehensive knowledge of the pathophysiology/cellular mechanisms of diabetes is paramount for improving treatment outcomes. Future studies should investigate the medicinal value of various plant extracts, including their phytochemicals, to transform the therapeutic landscape for diabetes management.

Keywords: Diabetes; NPDR; PDR; retinopathies; cardiovascular; phytochemicals; Rutin; Quercetin; Hesperidin

I. INTRODUCTION

Patients with diabetes remain predisposed to life-threatening complications including cardiac arrest, coronary artery disease, myocardial infarction, and stroke (1) (**Figure 1**). Currently, 4.2 million or 28.5% of individuals with diabetes (age ≥ 40 years) experience retinopathy; possibly, this complication will affect 93 million or 34.6% of people worldwide by 2050. Notably, 80% of patients with a history of diabetes > 20 years develop retinopathy (2). Evidence reveals the possibility of preventing a $>90\%$ incidence of diabetic retinopathy with proper monitoring and treatment of ocular disease (3). Several studies indicate that a long-term history of diabetes increases the risk and incidence of diabetic retinopathy (4). At least 12% of patients with diabetic retinopathy develop blindness annually in the United States, and retinopathy in diabetes is the primary contributor to blindness in patients age 20-64 years (5). Retinal degeneration-related microvascular breakdown is the primary outcome of diabetic ischemic maculopathy. Affected patients are at high risk of developing central vision loss (6,7). Diabetic retinopathy is classified by neovascularization in interconnected vascular lesions and is categorized into proliferative and non-proliferative subtypes (8). Ocular inflammation and edema are the outcomes of liquefied collections in the retinal fovea or macula lutea (9). The findings of the Diabetes Control and Complications Trial (DCCT) indicate improved treatment outcomes in patients with diabetes who received critical care and achieved glycemic control via metabolic memory phenomenon or legacy effect (10-12). Clinical studies have revealed the incidence of pericyte disintegration and mortality based on the disintegration of endothelial cells due to advanced glycation end products (AGEs), oxidative stress, and hyperglycemia (13). Patients with diabetic retinopathy usually do not develop reportable symptoms during the initial stages; however, progressive disease (in its advanced stages) triggers ocular complications. Diabetic retinopathy affects vascular supply in both eyes and induces retinal vasculitis. This further leads to retinal microaneurysms, macular edema, and inflammation. Complications include bilateral complete vision loss, appearance of eye floaters or black spots (hindering vision), poor night vision, drusen or white spots on the retina, color vision deficiency/color blindness, and eyesight issues (14).

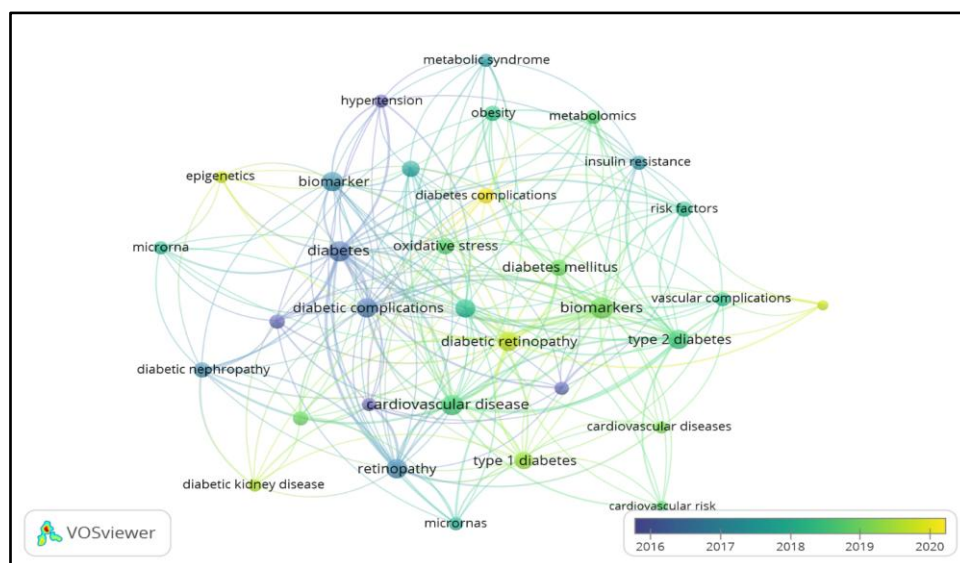


Figure 1: Bibliometric Analysis of Keywords in Publications on Diabetes and its Complications

Co-occurrence of keywords. The size of the nodes indicates their frequency of occurrence. The curves between the nodes represent their co-occurrence in the same publication. The shorter the distance between two nodes, the larger is the number of co-occurrences of the two keywords. Keywords such as “Diabetic Retinopathy,” “cardiovascular disease,” “T1DM,” “T2DM,” “Insulin resistance” and “Biomarkers” occurred most common. *Source: VOS viewer.*

II. PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

High oxidative stress in the retina is the outcome of glucose oxidation, maximum oxygen uptake, and accumulation of polyunsaturated fatty acids, which eventually induce reactive oxygen species (ROS), thereby altering the expression of vascular endothelial growth factor (VEGF) (15,16). Retinopathy is the outcome of prostaglandin E2 and cyclooxygenase-2 (COX-2) activation, and the induction of inflammatory mediators by oxidative stress. Other pathophysiological processes involved in the development of diabetic retinopathy include renin-angiotensin system (RAS) stimulation, activation of protein kinase C, and accumulation of AGEs (17,18). Diabetic retinopathy further develops due to hyperglycemia-induced metabolic stress, leading to vascular damage and neuralgia. Leaking and fragile blood vessels replace damaged vessels following the noticeable degeneration of retinal endothelial cells (19,20). The nonreceptor protein tyrosine kinase (Src) is regulated upstream by pericyte-induced angiopoietin 1, which interacts with the TIE2 endothelial cell receptor. The induction of angiopoietin 1 and TIE 2 activates platelet-derived growth factor and transforming growth factor signaling in endothelial cells (21). In addition, the proinflammatory cytokines interleukin (IL)-17A, IL-6, tumour necrosis factor (TNF), and monocyte chemoattractant protein (MCP)-1 are potential markers of diabetic retinopathy based on their attribution to endothelial cell death and vascular leakage (22,23).

III. BIOCHEMICAL AND CELLULAR PATHWAYS RESPONSIBLE FOR DIABETIC RETINOPATHY

To date, the current literature does not elaborate on viable mechanisms and pathways with their attributions to retinal deterioration in diabetes, which is predominantly the outcome of poor glycemic control. Diabetic retinopathy involves a range of complex mechanisms induced by the hexosamine pathway, oxidative stress, polyol pathway, inflammatory mediators, AGEs, and protein kinase C. Diabetic retinopathy progresses with mitochondrial dysfunction and ROS activation induced by nicotinamide adenine dinucleotide phosphate (NADPH) stimulation. The vicious cycle of ROS induction is prolonged by the continuous damage to mitochondrial cells under the influence of superoxide radicals from the mitochondrial electron transport chain (ETC). Patients with diabetes develop high levels of metabolic disruptions, hormonal imbalances, and hyperglycemia. Inflammatory processes in diabetes are governed by adhesion molecules, elevated capillary density, increased blood flow, neurotrophic factors, inflammatory compounds, vasoactive agents, and chemokines. The early stages of diabetic retinopathy are also associated with angiogenesis, apoptosis, and vascular permeability (24-30).

IV. BIOMARKERS OF DIABETIC RETINOPATHY

The diagnostic assessment of diabetes relies on findings from the oral glucose tolerance test, fasting blood glucose level test, and glycated hemoglobin (HbA1C) evaluation. Glycemic control must be measured by determining the HbA1C level, which is also a marker of cardiovascular disease in diabetes (31,32). Other diagnostic biomarkers of diabetes include glycated albumin and fructosamine. Recent studies indicate an uncertainty or standard deviation of ± 7.8 mmol/L in determining glycemic control by assessing fructosamine levels. In addition, overall serum lipid and protein levels appeared to confound the outcomes of the fructosamine assessment test. Recent evidence has revealed a high concentration of glycated albumin in patients with poor glycemic control. Compared to postprandial glucose (PPG), fasting plasma glucose (FPG) correlates more with HbA1C levels; however, both have a clinically significant association with fructosamine in type 2 diabetes. Total glycemic control in diabetes is best determined by PPG based on its greater correlation with HbA1C. In addition, a comparison of HbA1C with fructosamine indicated a minimal (+) association with the mean glucose profiles of patients with type 2 diabetes. These results negate the notion of the overall glycemic control prediction capacity of HbA1C in diabetes (33). Overall, the HbA1C level is not a strong clinical indicator of glycemic control. **Table 1** depicts the prognostic indicators and novel biomarkers of diabetic retinopathy, such as AGEs, advanced glycation end-products; CRM, corneal confocal microscopy; DNA, deoxyribonucleic acid; eGFR, estimated glomerular filtration rate; ERG, Electroretinogram; NO nitric oxide; PAI-1, plasminogen activator inhibitor 1; PEDF, pigment epithelium-derived factor; RAGE, receptor for advanced glycation end-products; SAF, Skin autofluorescence; SNPs, single-nucleotide polymorphisms; VEGF, vascular endothelial growth factor.

Table 1: Prognostic Indicators/novel Biomarkers of Diabetic Retinopathy

Routine and novel biomarkers of diabetic retinopathy	
Clinical (general) biomarkers	<ul style="list-style-type: none"> • Age • Type of diabetes • Duration of diabetes • Family history • Lifestyle • Obesity • High blood pressure • Pulse wave analysis • SAF • AGEs
Clinical (ocular) biomarkers	<ul style="list-style-type: none"> • Stage of retinopathy • Retinal vessel calibre • CRM • ERG
Biochemical biomarkers	<ul style="list-style-type: none"> • Glycemia (HBA1c level) • Serum creatinine • eGFR

	<ul style="list-style-type: none"> • Urine albumin • Adiponectin • Lipid and lipoprotein • Vitamin D • Homocysteine • Inflammation molecules • Cytokines • Chemokines • AGEs • RAGE • Growth-related factors (VEGF/PEDF) • Endothelin-1 • NO • Fibrinogen • PAI-1
Molecular biomarkers	<ul style="list-style-type: none"> • SNPs • Histone modifications <ul style="list-style-type: none"> ○ DNA methylation ○ Histone deacetylation ○ Histone acetylation • Non-coding RNAs/MicroRNAs • Metabolomics • Lipidomics • Glycomics <ul style="list-style-type: none"> ○ Study of modified glucose/lipids/proteins

V. DIAGNOSIS OF DIABETIC RETINOPATHY

Routine ophthalmic assessments are paramount for diagnosing retinopathy in diabetes; repeat examinations facilitate early diagnosis (i.e., assessment of the condition at the initial stage of the disease). Patients with diabetes require annual or biannual assessments to determine their risk of retinopathy. The diagnostic workup is guided by symptomatology, including signs and clinical manifestations. Differential assessments for advanced eye disease, moderate/severe non-proliferative retinopathy, and maculopathy in diabetes are paramount to improving medical decision-making (34,35). **Table 2** lists the diagnostic parameters for diabetic retinopathy.

Table 2: Diagnostic Parameters for Diabetic Retinopathy

Type of diabetic retinopathy	Diagnostic parameters
Acute non-proliferative diabetic retinopathy	<ul style="list-style-type: none"> • Microaneurysm • Hard exudates • Renal oedema/thickening

	<ul style="list-style-type: none"> • Retinal haemorrhage
Maculopathy	<ul style="list-style-type: none"> • Oedema/thickening in the macular retina
Chronic non-proliferative diabetic retinopathy	<ul style="list-style-type: none"> • Cotton wool spots • Vascular abnormalities • Venous bleeding • IRMA
Proliferative diabetic retinopathy	<ul style="list-style-type: none"> • NVD • NVD elsewhere • Vitreous haemorrhage
Advanced eye disorder	<ul style="list-style-type: none"> • Vitreous haemorrhage • Pre-retinal fibrosis • Retinal detachment

VI. CARDIOVASCULAR COMPLICATIONS

Cardiovascular disease is an independent predictor of morbidity and mortality in patients with diabetes, and more than 30% of patients with diabetes experience cardiovascular complications worldwide. The predominant cardiovascular complications of diabetes include cardiac dysfunction, stroke, myocardial infarction, and premature atherosclerosis (36,37). Risk factors, including persistent blood pressure elevation, poor glycemic control, and dyslipidemia, predict early onset of cardiovascular disease in diabetes. Disintegration of complex atherosclerotic plaques in the arteriovenous system results in strokes, unstable angina, and myocardial infarction; however, the etiopathology of these episodes has not yet been determined. The binding of T lymphocytes and other macrophages to the walls of arteries leads to localized abnormalities, including atherogenesis (38). Diastolic dysfunction marks the onset of coronary artery disease in asymptomatic patients with myocardial damage. The diagnostic workup relies on echocardiography.

Clinical (general)	Clinical (ocular)	Biochemical	Molecular
Age	Stage of retinopathy (e.g., ETDRS, visual acuity, visual fields)	Glycemia (e.g., HbA1c) and glycemic variability)	DNA based (e.g. SNPs)
Type of diabetes	OCT (e.g., retinal thickness, edema, DRIL)	Insulin resistance (e.g., estimated glucose disposal rate (eGDR), adiponectin)	RNA Based
Diabetes duration	Electroretinograms	Lipid / lipoprotein related (e.g., lipids, ApoA1)	Epigenetics (e.g. DNA methylation, acetylation)
Family history	Corneal confocal microscopy (CCM)	Hematologic (e.g., Hemoglobin, EPO)	Proteomics
Body habitus (obesity, in particular central obesity)	Retinal vessel calibre	Nutrition related: e.g., Vitamin D, homocysteine	Metabolomics
Blood pressure	Retinal vessel geometry	Inflammation: (e.g., CRP, Adhesion Molecules, Cytokines)	Lipidomics
Pulse wave analysis	Corneal and lens autofluorescence (AGEs)		Glycomics
Skin autofluorescence / AGEs			

Figure 2: Novel biomarkers for diabetes-related retinopathy complications [36-39]

In addition, hyperglycemia in diabetes activates the inflammatory, migratory, and proliferative attributes of dormant non-contractile muscle cells (39). These processes eventually lead to the development of a proatherogenic environment, thereby increasing systemic/tissue-specific insulin resistance (**Figure 2**). illustrates the pathogenesis of hyperglycemia (in diabetes) and its association with cardiovascular manifestations. The severity of clinical complications of diabetes is indicated by high blood glucose levels. Asymptomatic patients with prediabetes or type 2 diabetes also experience a high risk of clinical complications including fatty acid mobilization, ketonuria, weight loss, increased appetite, and urinary frequency. Other potential complications of diabetes include vaginal and skin infections, dental abscesses, blurry vision, irritability, fatigue, and non-healing wounds.

VII. CELLULAR AND BIOCHEMICAL MECHANISMS OF CARDIOVASCULAR COMPLICATIONS IN DIABETES

Cardiovascular complications in diabetes are caused by insulin resistance and hyperglycemia. The onset and progression of diabetes triggers the accumulation of ROS, which eventually disrupts cellular function and homeostatic regulation of the vascular system, leading to cardiovascular pathology (40,41). Preclinical studies in rodents provide inconclusive evidence concerning a possible correlation between complex plaque rupture and the development of coronary atherosclerosis, heart failure, or fibrosis. Current data indicating cardiovascular complications in diabetes do not elaborate the role of end-stage diabetes in the onset and progression of cardiovascular manifestations. The contemporary literature reveals distinct mechanisms governing the pathophysiology of atherosclerosis, fibrous plaques, plaque rupture, and complex lesions in diabetes. However, these findings were mainly derived from cell culture experiments with limited reliability (42-44). The predominant crosstalk mechanisms governing atherosclerosis development in diabetes affect the normal function of the liver, visceral fat, bone marrow, phagocytic cells, smooth muscles, endothelial cells, and inflammatory mediators (45). Several clinical studies have suggested a possible association between cardiovascular disease in diabetes and the polyol/sorbitol pathway. Findings from a preclinical study in apolipoprotein E knockout mice indicated the exacerbation of atherosclerosis due to aldose reductase overexpression (46). The outcomes of a preclinical study revealed comparable atherogenesis and endothelial inflammation in non-diabetic apolipoprotein-deficient and glyoxalase-1 inhibitor-induced diabetic mice (47). In addition, clinical studies have indicated an association between plaque accumulation/rupture and activity/levels of matrix metalloproteinase (MMP)-9, monocyte chemoattractant protein (MCP)-1, and IL-8. These findings also revealed the accumulation of cleaved caspase-3 and MG-H1 in macrophages around the centre of necrotic lesions in diabetes (48). In addition, heart disease and associated mortality in diabetes correlate with increased levels of the cyclooxygenase (COX)-1 isoform. Other causative factors include AGE activation, protein kinase C induction, and secondary reduction of nicotinamide adenine dinucleotide (NAD)⁺/NADPH (49,50). In addition, ROS elevation and AGE receptor activity increase the risk of cardiovascular complications in diabetic patients. A significant increase in COX-2 levels in the coronary vasculature of diabetic mice was reported in a preclinical study (51). These findings reveal the impact of hyperglycemia on the renal function of diabetic mice, as indicated by the interaction between prorenin receptor and renin/prorenin and eventual decline in the glomerular filtration rate.

VIII. BIOMARKERS INDICATING CARDIOVASCULAR COMPLICATIONS IN DIABETES

Several biomarkers can independently predict coronary heart disease in patients with type 2 diabetes. Significant biomarkers include galectin-3, cardiac troponins, soluble suppressor tumorigenicity-2, and natriuretic peptides in skeletal muscles, coronary arteries, kidneys, and myocardium. The American College of Cardiology (ACC) recommend the inclusion of biomarker analysis in the diagnostic workup to determine the risk of cardiovascular complications in patients with diabetes (type 2 and type 1) (52).

IX. DIAGNOSTIC WORKUP TO EVALUATE CARDIOVASCULAR COMPLICATIONS IN DIABETES

Contemporary literature does not specify a standardized approach for evaluating dilated cardiomyopathy in diabetes. Accordingly, clinical correlation based on symptomatology and disease progression, predicted by imaging and biochemical assessments, strengthens medical decision-making. Doppler/echocardiographic imaging is the gold standard for evaluating diastolic dysfunction in patients with diabetes. Patients with early stage dilated cardiomyopathy may develop diastolic heart failure despite a normal ejection fraction. The literature reveals a 75% incidence rate of dilated cardiomyopathy in asymptomatic patients with diabetes (53,54). Left ventricular function in diabetes is affected by a range of factors, including calcium cycling, excitation-contraction coupling, left ventricular hypertrophy, and myocardial fibrosis. Magnetic resonance imaging (MRI) is a standard approach for evaluating the structure, function, and motility of the left ventricle in patients with diabetes. In addition, elevated HbA1C and high blood glucose levels are potential serological biomarkers for the development of diabetes (55,56). However, cellular damage/necrosis and the resultant cardiovascular complications are predicted by increased troponin levels. The onset and progression of fibrosis in diabetes is indicated by the abundance of MMP9. Cardiovascular disorders in diabetes are further determined by a clinically significant decline in metalloproteinase (TIMPs) tissue inhibitors, and the progression of dilated cardiomyopathy is predicted by marked elevations in O-linked beta-N-acetylglucosamine levels (57-60). Possible biomarkers for cardiac biochemical stress, cardiac myocyte necrosis, inflammation, fibrosis, myocardial hypertrophy, and extracellular matrix modelling in diabetes. Assessment of these pathogenic states is key to determining potential cardiovascular complications in patients with prediabetes or type 2 diabetes.

X. THE THERAPEUTIC SIGNIFICANCE OF ROUTINE ORAL HYPOGLYCAEMIC AGENTS IN DIABETES

Improvement in glycemic control is the key to minimizing cardiovascular complications in patients with diabetes. Evidence-based treatments focus on normalizing the blood glucose levels and decreasing the risk of clinical complications. The increased production of oral hypoglycemic drugs in recent decades has revolutionized the treatment landscape of type 2 diabetes by improving glycemic control and reducing the incidence of preventable complications. The dosages of hypoglycemic drugs were determined by the treatment goals based on symptomatology and clinical complications. The primary goal of these oral hypoglycaemics is to lower HbA1C levels below 7.0% to enhance glycemic control

(61). They also activate pancreatic beta cells to improve insulin production and concomitantly reduce insulin resistance. Metformin is the first-line oral hypoglycaemic drug utilised to lower blood glucose levels. Other hypoglycaemics include GLP-1 agonists, DPP-4 inhibitors, sulfonylureas, and thiazolidinediones (62,63). However, potential complications associated with oral hypoglycemic drugs include hypoglycemia, increased appetite, tachycardia, confusion, irritability, shakiness, weight gain, and sweating. While sulfonylureas affect ischemic preconditions, pioglitazone increases the risk and incidence of heart failure. The utilization of gut hormones (incretin mimetics) also assists in lowering blood glucose levels based on improvements in the digestive processes (64,65). However, incretin administration increased the risk of diarrhoea, vomiting, nausea, and arrhythmia in non-responders. The recommended treatments for hyperglycemia in diabetes include sodium-glucose cotransporter 2 inhibitors, α -glucosidase inhibitors, peroxisome proliferator-activated receptor agonists, biguanides, and sulfonylureas. These drugs may be administered as monotherapy or in combination with other hypoglycemic agents. However, uncontrolled/persistent hypoglycemia lowers treatment efficacy, increases the risk of weight gain, and increases the incidence of metabolic complications. The potential challenges to the effective management of diabetes include long-term glycemic control and the lowering of treatment-emergent adverse events. Contemporary therapies aim to optimize glycemic goals and increase the quality-adjusted life-years of treated patients. The aim of quantifying the dosages of oral hypoglycemic monotherapies or combination therapies is to improve clinical outcomes and reduce adverse events. In addition, the choice of secondary therapy relies on the selection, characteristics, and outcomes of the primary treatment (65,66). Evidence-based guidelines recommend several drug combinations to improve treatment outcomes and reduce preventable adverse events in patients with diabetes. Commonly used combinations include 1) thiazolidinediones with glucosidase inhibitors and metformin, 2) metformin with repaglinide, 3) thiazolidinedione with sulfonylurea, 4) alpha-glucosidase inhibitors with sulfonylurea, and 5) metformin with sulfonylurea (67). The advantages of these combination therapies include synergistic efficacy at reduced dosages, low risk of refractory disease, and reduced incidence of toxicity.

XI. DIABETES MANAGEMENT VIA HERBAL REMEDIES

Ongoing innovations in integrative medicine have increased the scope of using herbal remedies in routine treatment modalities for diabetes management. Herbal extracts derived from plants are used to treat diabetes complications owing to their medicinal properties (68). They are administered orally or via a topical route in accordance with treatment goals. Literature reveals the capacity of herbal medications to influence and modify the physiological processes of the human body. The pharmacological properties of their bioactive ingredients help to improve the body's immunity and capacity to cope with type 2 diabetes. These ingredients are extracted from the flowers, fruits, roots, stems, and leaves. Countries, including India, China, and Tibet, continue to practice herbal remedies against various disease processes (69,70). The last decade has witnessed unprecedented advancements and transformations in herbal practices worldwide. Evidence suggests the capacity of herbal systems to prevent and control chronic disease conditions, including heart diseases, obesity, diabetes, asthma, hypertension, and autoimmune diseases. However, most advancements in herbal practices have been supported by anecdotal evidence. The scarcity of preclinical and clinical studies to support the medicinal value of various herbs and their bioactive compounds

restricts their evidence-based utilization by the scientific community. As none of the currently practiced drugs/treatments provide a complete cure for diabetes and its fatal complications, future studies should investigate the diabetes management potential of herbal medicines. Studies should also examine the safety profiles and cost-effectiveness of herbal medicines in the context of type 2 diabetes. Human history reveals a wide range of benefits of traditional ailments, and ongoing studies should investigate their clinical outcomes in chronic conditions. The World Health Organization (WHO) has listed 21,000 plants based on their medicinal value and potential to manage the complications of a range of chronic diseases (71,72). Approximately 400 herbs have been identified by the WHO based on the therapeutic value of their bioactive compounds against diabetes; however, an insignificant percentage of these plants has been subjected to scientific investigation to determine their efficacy and safety outcomes. Approaches and trends concerning the use of herbal medicines against chronic conditions are rapidly changing, and people are more inclined towards benefiting from these alternative treatments based on their promising safety and efficacy based on anecdotal information. Few studies have demonstrated the possibility of preventing diabetes and its complications by including a range of phytochemical compounds in the diet. These phytochemicals include flavonoids, alkaloids, coumarins, lignans, stilbenes, terpenoids, and monoterpenes (73,74). Clinical trials have demonstrated the role of various plant species in increasing insulin secretion and minimizing insulin resistance by inducing extra pancreatic processes in diabetes. These species include *Syzygium cumini* (Jamun), *Pterocarpus marsupium* (Malabar kino), *Momordica charantia* (bitter melon), *Gymnema sylvestre* (gurmar) leaves, *Ficus bengalensis* (banyan), *Encostemma littorale* (Chhota chirayata), *Coccinia indica*, *Cinnamomum tamala* (Indian Bay Leaf), *Clerodendron phlomoides* (Aarni), and *Allium cepa* (Onion) (75).

Phytochemicals in various plant species effectively regulate lipid and glucose metabolism by activating insulin signal transduction proteins, producing fatty acids, elevating glucose absorption in adipose and muscle tissues, and minimizing endogenous glucose production (76). Improved regulation of lipid and glucose metabolism improves the prevention and treatment of diabetes in high-risk patients. Findings from previous studies indicate the possible role of flavonoid-based foods in improving diabetes symptoms and complications (77). In addition, the regular consumption of these diets minimizes the risk and incidence of diabetes. Plant phytochemicals may prove to be novel therapies based on their promising role in controlling the onset of diabetes and its potential complications. Some commercially available antidiabetic products sourced from natural herbs include voglibose, miglitol, acarbose, and Pycnogenol (78). The bioactive ingredients of medicinal herbs improve glycemic control by reducing the activity of protein tyrosine phosphatase 1 B, alpha-amylase, and alpha-glucosidase. Several pharmaceutical companies are in the process of designing novel treatment molecules based on herbal extracts for diabetes management because of their low risk of adverse events. Herbal extracts can also minimize the incidence of secondary complications in patients with diabetes. Clinical studies continue to investigate the efficacy and safety of several herbal products to improve the prevention and management of diabetes and its deleterious manifestations (79).

XII. THE MEDICINAL PROPERTIES OF PHYTOCHEMICALS IN MANAGING DIABETES COMPLICATIONS

The extraction of phytochemicals from medicinal herbs requires a range of complex procedures and mechanisms. Non-nutrient biomolecules incorporate phytochemicals, based on their capacity to prevent and manage a range of chronic diseases. However, these biomolecules are not routinely required by the human body to maintain a normal physiology (80). The potential antidiabetic properties of phytochemicals make them the most effective substances against type 2 diabetes and its associated clinical complications. The currently available herbal formulations for diabetes treatment/prevention include Syntax, Diabetes, Insulin, DiaCare, Chakrapani, Bitter Gourd Powder, and Pancreas Tonic-Glycoprin-180 CP. The contemporary literature provides strong scientific evidence supporting the diabetes prevention/treatment properties of plant-based phytochemicals. However, future studies should explore potential bioactive compounds for their integration into new treatment formulations against diabetes. It is important to examine drug-drug interactions between various phytochemical-based herbal formulations and identify their cytotoxic properties via rigorous clinical investigation. In addition, the mechanisms of action, pharmacokinetics, and pharmacodynamics of potential phytochemicals, including saponins, terpenoids, amino acids, glycosides, alkaloids, and polyphenols, are discussed. The molecules passing the final testing will be able to enhance metabolic processes and delay the fatal complications of diabetes in treated patients. Furthermore, clinical studies must compare the therapeutic outcomes, safety profiles, and synergism of these phytochemical-based herbal remedies with synthetic drugs to effectively transform the diabetes treatment landscape (81,82). Recent evidence has demonstrated the role of phytochemicals in altering biochemical pathways and activities of dipeptidyl peptidase-4, α -glucosidase, and α -amylase. In vivo and in vitro (preclinical) studies have revealed several other phytochemicals that require testing to determine their capacity for diabetes treatment/prevention in real-time scenarios (83).

XIII. PREDOMINANT PHYTOCHEMICALS AGAINST DIABETES COMPLICATIONS

Recent studies have investigated the efficacy and safety of flavonoids in a variety of chronic diseases, including diabetes, heart disease, neurological disorders, and cancers (**Figure 3**). The efficacy and safety of these flavonoids are based on their strong antioxidant properties; in addition to improving glucose homeostasis, they also strengthen the insulin sensitivity of skeletal muscles, adipose tissues, the liver, and the pancreas. Recent evidence has indicated the role of flavonoids in minimizing insulin resistance by enhancing endothelial function and improving vasodilation in blood vessels. They actively interact with vascular smooth muscle cells and increase their vasorelaxant capacity by inducing BKCa channels. Improved physiological regulation of intracellular calcium, membrane voltage, and neurotransmitter release eventually enhances endothelial function and glycemic control. Phytochemicals also disrupt potential alterations in endothelial function, which eventually delay the development of atherosclerotic lesions and associated cardiovascular complications in patients with diabetes (84,85).

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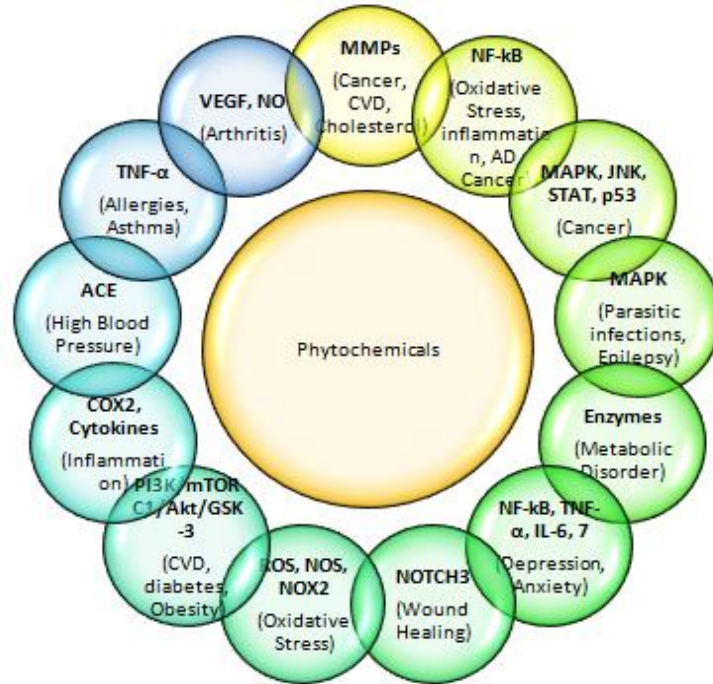


Figure 3: The Therapeutic Molecular Targets of Phytochemicals and the Diseases they Prevent [84-88].

Contemporary literature reveals the possible role of phytochemicals in minimizing the accumulation of ROS and nitric oxide, which eventually results in vasodilation and reduction in systolic blood pressure in diabetes (86,87). Phytochemicals also facilitate the translocation of glucose transporter type 4 across the plasma membrane, which subsequently improves glucose absorption across adipose and skeletal muscles. Clinical studies have also demonstrated the role of flavonoids in improving hepatic function by controlling the function of genes responsible for gluconeogenesis. Reduced glucose synthesis in the liver eventually lowers serum blood glucose levels and increases glycaemic control (88). In addition, flavonoids improve the intestinal absorption of glucose by delaying the breakdown of complex carbohydrates. They also elevate insulin production, enhance cell vitality, and reduce oxidative stress in pancreatic β -cells. **Table 3** summarizes the therapeutic effects of flavonoids on retinopathy and cardiovascular complications in diabetic mice and in human epithelial/endothelial cell lines.

Table 3: Therapeutic effects of flavonoids on retinopathy and cardiovascular complications in diabetic mice and human epithelial/endothelial cell lines

<i>IN-VIVO</i> MODELS					
Animal	DM	Model	Treatment	Results	Effect
DIABETIC RETINOPATHY COMPLICATIONS					
Rat	T1DM	STZ	Catechin 50–200 mg/kg/day 8 weeks	Modulation NF- κ B pathway \downarrow IL-1 β , IL-6, and TNF- α	Anti-inflammatory

Rat	T1DM	STZ	Biochanin A 10–15 mg/kg/day. 6 weeks	↓ TNF α , IL-1 β , and VEGF	Anti- inflammatory and anti- angiogenic
Rat	T1DM	STZ	Trans- Resveratrol 5 mg/kg/day. 2– 4 weeks	↑ Cyp26b1 and Cyp3a9 transcription levels	Anti-oxidant
Rat	T1DM	STZ	Morus alba extract 100 mg/kg/day 16 weeks	↓ Caspase-3, Bax and ↑ Bcl2; ↓TNF- α and IL-1 β ; ↑CAT, SOD, and GPx. ↓VEGF	Anti- apoptotic, anti- oxidant, anti- inflammatory and anti- angiogenic
Rat	T1DM	STZ	Naringenin 50 mg/kg/day 5 weeks	↑GSH; ↓Caspase- 3, Bax and ↑ Bcl2; ↓pro-BDNF and ↑BDNF	Neuroprotective, anti-oxidant and anti-apoptotic
Mouse	T1DM	STZ	Galangin 10 mg/kg/day 30 day	↑Occludin and claudin1; ↓Iba-1 ↓ TNF α , IL-1 β and IL-6 ↓p65, I κ B and IKK phosphorylation	Neuroprotective and anti- inflammatory
Mouse	T2DM	db/db mouse	Chrysin 10 mg/kg/day 10 weeks	Increasing retinoid-binding proteins (RPE65, LRAT, RDH5, and rhodopsin)	Anti-oxidant
CARDIOVASCULAR COMPLICATIONS					
Rat	T2DM	HGI	Rutin 25–50 mg/kg/day 12 weeks	↓ inflammasome pathway in aortic tissue; ↓ROS generation	Anti- inflammatory and anti- oxidant
Rat	T2DM	HFD/STZ	Resveratrol 10 mg/kg/day 8 weeks	↓ TLR4/MyD88/NF- κ Bsignaling pathway	Cardioprotective and anti- inflammatory
Rat	T1DM	STZ	Apigenin 100 mg/kg/day 7 months	↓ cardiomyocyte enlargement; ↑SOD and GPx ↓ NF- κ B/p65 signaling pathway activation ↓ Col-I, Col-III, CTGF, TGF β	Cardioprotective , anti-oxidant, anti- inflammatory and anti-fibrotic

Rat	T1DM	STZ-IRIA	Resveratrol 5 mg/kg/day + Glibenclamide 5 mg/kg/day 6 weeks	↑ Kir6.2 expression (subunit of KATP channel)	Anti-arrhythmic
Rat	T1DM	STZ	Heracleum Persicum 100 mg/kg/day; 8 weeks	↓MDA; ↑GSH, CAT and SOD	Anti-oxidant
Rat	T1D	STZ	Isoquercetin 40 mg/kg/day 45 days	↓ TG, PPL and FFA	Anti-hyperlipidaemic
Rat	T1D	STZ	Galangin 40 mg/kg 45 days	↓ TG, PPL, total cholesterol, and FFA	Anti-hyperlipidaemic
Mouse	T2D	db/db mouse	Scutellarin 25–100 mg/kg 8 week	↑ high-density lipoprotein cholesterol ↓ TG and cholesterol	Anti-hyperlipidaemic
IN-VITRO MODELS					
DIABETIC RETINOPATHY					
Human retinal pigment epithelial cell line	Glucose oxidase	Myricetin 40 µg/mL	Activation of Nrf2 ↑ SOD ↓ NOS2		Anti-oxidant
CARDIOVASCULAR COMPLICATIONS					
Human umbilical vein endothelial cells	HG	Rutin 30–100 µM	↓Nox2 and Nox4		Anti-oxidant
Human aortic endothelial cells	Palmitic acid	Resveratrol 50–100 µM	↓ ROS production via AMPK-mTOR pathway		Autophagia and anti-oxidant

XIV. DIABETES TREATMENT POTENTIAL OF PHYTOCHEMICALS

- 1. Rutin:** The flavonoid phytochemical ‘rutin (sophorin/quercetin-3-O-rutinoside)’ is extracted from limes, lemons, apples, ginkgo, and St. John’s wort, buckwheat, eucalyptus, and citrus fruits. The primary role of rutin is to improve glycemic control by controlling ROS accumulation and minimizing pancreatic oxidative stress. It also enhances insulin secretion by preserving pancreatic beta cells and reducing gluconeogenesis. In addition, it minimized the absorption of glucose in the small intestine. Rutin effectively inhibits the

accumulation of free radicals, which further reduces oxidative stress and minimizes life-threatening complications in diabetes. Rutin induces significant reductions in IL-6, sorbitol, and AGEs and alters the signalling cascades that eventually reduce the risk of clinical complications in diabetes (89). Intraperitoneal administration of 50-100 mg/kg rutin to mice with streptozotocin-induced type 1 diabetes led to improvements in fasting blood glucose and glycated hemoglobin levels (90). In addition, rutin activates hexosamine pathways, which eventually minimize gluconeogenesis and organ system complications in diabetes. In addition to controlling oxidative stress and reducing blood glucose concentration, rutin maintains the levels of albumin and blood urea nitrogen. It effectively activates anti-apoptotic molecules (including B-cell lymphoma 2) and reduces the concentration of caspase 3, which eventually minimizes cell death in various organ systems (91).

- 2. Quercetin:** Quercetin dihydrate (3,3,4,5,7-pentahydroxyflavone or $C_{15}H_{14}O_9$) or quercetin is a bioactive phytochemical known for its antimicrobial, antioxidant, anti-inflammatory, and anti-diabetic properties and is derived from red wine, green tea, berries, tea, onions, and apples. The structure of quercetin is similar to the configuration of other flavonoids, including luteolin, hesperidin, rutin, and naringenin. This phytochemical actively reduces glucose absorption in the intestine, and peripheral glucose utilization eventually improves glucose homeostasis, insulin resistance, and the pharmacological response. The outcomes from a recent systematic review and meta-analysis indicate the capacity of quercetin to minimize fasting glucose levels in laboratory animals within the dose range of 10 mg/kg, 25 mg/kg, and 50 mg/kg body weight (92). Quercetin also activates the adenosine monophosphate protein kinase pathway, which eventually induces glucose transporter type 4 translocation and alters adenosine diphosphate utilisation in mitochondria. The diabetes prevention and management properties of quercetin are indicated by its role in replenishing hepatic glycogen, gluconeogenesis, and phosphoinositide 3-kinase activation in streptozotocin-induced diabetic mice. Findings from a preclinical study reveal the outcomes of the two-week administration of quercetin in streptozotocin-induced diabetic mice; these outcomes include improved cell survival, enhanced serum insulin accumulation, low blood glucose levels, improved hepatic glucokinase activity, enhanced glucose tolerance, and reduced triglyceride/plasma cholesterol levels. Results from preclinical studies also indicate improvements in pancreatic beta cell structure/function, glucose metabolism, inflammatory processes, and oxidative state in streptozotocin-induced diabetic mice. Quercetin effectively modulates the activity of nuclear factor kappa B, which eventually improves insulin secretion and glycemic control (93-95).
- 3. Hesperidin:** The saturated aglycone derivative 'hesperidin' is a bioflavonoid derived from sweet oranges, lemons, gooseberry, cranberry, and raspberry. Clinical studies have indicated the medicinal value of hesperidin in a range of conditions, including diabetes, inflammation, memory impairment, allergies, and neurological disorders. Its neuroprotective, antioxidant, and anti-inflammatory properties add value to its pharmacological profile against chronic diseases. Preclinical studies have indicated the role of hesperidin supplements in reducing blood glucose levels by regulating the function of glycolytic liver enzymes and controlling gluconeogenesis. It also induces lipolysis, reduces the activity of lipid-metabolizing hepatic enzymes, and enhances fecal excretion

of triglycerides. Hesperidin upregulates peroxisome proliferator-activated receptors and glucose transporter type 4 translocation that eventually stabilises the blood glucose levels and improves glycaemic control. Evidence demonstrates the role of 10 g/kg hesperidin in reducing the accumulation of glucose-6 phosphate and glucose levels in streptozotocin-induced diabetic mice (96-101). In addition, it improves glycemic control by regulating lipolysis and carbohydrate metabolism. Findings from several preclinical studies also indicate the potential of hesperidin to reverse liver and kidney damage by upregulating the klotho and fibroblast growth factor 23 pathways in streptozotocin-induced diabetic mice (102).

- 4. Resveratrol:** Stilbenoid ‘resveratrol’ is a natural food ingredient derived from plants across the globe based on its medicinal value. The pharmacological properties of resveratrol assist in the treatment of several diseases, including Alzheimer’s disease, diabetes, heart diseases, and cancer. The cardioprotective role of resveratrol is based on its potential to control systolic and diastolic blood pressure. In addition, resveratrol improves vascular function and muscle contractility by inhibiting the activity of rho-associated protein kinase, adenosine monophosphate-activated protein kinase (myosin light chain phosphorylation by angiotensin II), and myosin phosphatase target subunit 1 (103-105). The vasodilation property of resveratrol is due to its ability to block the diacylglycerol and inositol triphosphate signalling pathways. Resveratrol also suppresses triglyceride levels and the expression of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, thereby lowering serum cholesterol levels. In addition to its synergism with metformin, resveratrol reduces apoptosis and upregulates glucose transporter 4 translocation in diabetes (106,107).
- 5. Other Phytochemicals:** The isoquinoline alkaloid ‘berberine’ effectively reduces the risk of cognitive impairment, enhances insulin resistance, maintains total cholesterol, and reduces blood glucose levels. The flavonoid ‘naringenin’ is recognized in the scientific literature for its cardioprotective, antiadipogenic, anti-inflammatory, antibacterial, antiviral, antitumor, and antioxidant properties (108-110). Kaempferol, the predominant flavonoid aglycone, is known for its antidiabetic, neuroprotective, cardioprotective, antitumor, antioxidant, anti-inflammatory, and antimicrobial potential. The therapeutic implications of the natural phenol ‘chrysin’ are observed in neurodegenerative diseases, diabetes, and cancers (111,112). It also helps reduce inflammation and oxidative stress in diabetic complications. Similarly, scutellarin is a potential phytochemical with promising mechanisms of action against diabetes (vascular complications), *Helicobacter pylori* infection, Alzheimer’s disease, cerebral ischemia, and cardiovascular complications. Future studies should re-examine the treatment profile of these phytochemicals against retinopathy and cardiovascular diseases in diabetes (113,114).

XV. CONCLUSION

The progressive clinical manifestations of diabetes reciprocate with inflammatory processes and increase in oxidative stress. Phytochemicals may prove to be promising therapeutic modalities against diabetes because of their antihyperglycemic, antioxidant, and anti-inflammatory properties. Their interaction and interference with cellular metabolites and pathological processes in the retina may challenge the onset and progression of diabetic

retinopathy. Similarly, their cholesterol-lowering capacity may assist in reducing the incidence of hyperlipidaemia, thereby minimizing the risk of cardiovascular disease in diabetes. Therapeutic utilization of phytochemicals is currently limited owing to their low bioavailability and tissue assimilation capacity. Future studies should determine robust tools and techniques to enhance the bioavailability of phytochemicals and reevaluate their efficacy and safety in diabetes. It is also important to standardize the dosages of crude extracts of phytochemicals based on their medicinal value and diabetes management goals. Adjuvant therapies based on phytochemicals may revolutionize the therapeutic landscape of diabetes and transform its medical management/prevention and serious complications. Finally, the combination treatments based on routine drugs and phytochemicals may reduce the prevalence of diabetes manifestations and the incidence of safety events, and add to the quality-adjusted life years of the treated patients.

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ABBREVIATIONS

AGEs: advanced glycation end products

CRM: corneal confocal microscopy

DNA: deoxyribonucleic acid

eGFR: estimated glomerular filtration rate

ERG: Electroretinogram

NO: nitric oxide

PAI-1: plasminogen activator inhibitor 1

PEDF: pigment epithelium-derived factor

RAGE: receptor for advanced glycation end products

SAF: Skin autofluorescence

SNPs: single-nucleotide polymorphisms

VEGF: vascular endothelial growth factor

IRMA: intraretinal microvascular abnormality

NVD: neovascularization on the disc