**Advances in understanding cellular mechanisms of cardiovascular complications and retinopathy in diabetes: Therapeutic potential of phytochemicals**

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**Summary**

The comprehensive knowledge of the pathophysiology, aetiology, and clinical discourse of diabetes mellitus is paramount to prognosticating its cardiovascular and ocular complications. This study investigated the mechanisms and processes governing the progressive development of cardiovascular complications and retinopathy in patients with diabetes. It also aimed to determine the diabetes prevention/management potential of multimodal treatments (including phytochemical methods). One hundred and thirty-four research articles were explored and analysed to unravel the pathophysiology, cellular mechanisms, and biomarkers associated with cardiovascular/ocular complications of diabetes. The data sources included PubMed Central, Web of Science, and JSTOR as shown in **Figure 1**. The 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 diabetes complications were extracted for this updated review. The predominant causes of diabetic retinopathies and diabetic macular oedema include haemorrhage and retinal capillary aneurysms. The type of diabetes, age at diagnosis, and race are independent predictors of the risk and incidence of non-proliferative/proliferative diabetic retinopathy (NPDR/PDR). In addition, 75% of diabetes-related deaths 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 utilisation in adjuvant treatments. In addition, comprehensive knowledge of the pathophysiology/cellular mechanisms of diabetes is paramount to improving treatment outcomes. Future studies should investigate the medicinal value of various plant extracts, including their phytochemicals to transform the therapeutic landscape of diabetes management.

**Keywords:** Diabetes, NPDR, PDR, retinopathies, cardiovascular, phytochemicals, Rutin

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1. **Introduction to diabetic retinopathy**

Patients with diabetes remain predisposed to life-threatening complications including cardiac arrest, coronary artery disease, myocardial infarction, and stroke (Cheung & Wong, 2008) (**Figure 1**). Currently, 4.2 million or 28.5% of individuals with diabetes (age ≥40 years) experience retinopathy; possibly, this complication will impact 93 million or 34.6% of people across the globe by 2050. Of note, 80% of patients with >20 years of diabetes history develop retinopathy (Kertes & Johnson, 2007). Evidence reveals the possibility of preventing >90% incidence of diabetic retinopathy with proper monitoring and treatment of ocular disease (Francois & Little, 2015). Findings from several studies indicate that a long-term history of diabetes increases the risk and incidence of diabetic retinopathy (Low et al., 2015). At least 12% of patients with diabetic retinopathy develop blindness annually in the United States; retinopathy in diabetes is the primary contributor to blindness in patients of age 20-64 years (Engelgau et al., 2004). Retinal degeneration-related microvascular breakdown is the primary outcome of diabetic ischemic maculopathy; the affected patients experience a high risk of developing central vision loss (Congdon et al., 2012; Jones & Edwards, 2010). Diabetic retinopathy is classified by neovascularization in the interconnected vascular lesions; it is categorized into proliferative and non-proliferative subtypes (Das et al., 2015). The ocular inflammation and oedema are the outcomes of liquified collections in the retinal fovea or macula lutea (Ford et al., 2013). The findings of the Diabetes Control and Complications Trial (DCCT) indicate improved treatment outcomes in patients with diabetes who received critical care and achieved glycaemic control via metabolic memory phenomenon or legacy effect (Madsen-Bouterse et al., 2010; Santos & Kowluru, 2011; Tewari et al., 2012). Findings from clinical studies reveal the incidences of pericyte disintegration and mortality based on the disintegration of endothelial cells due to advanced glycation end products (AGEs), oxidative stress, and hyperglycaemia (Miloudi et al., 2019). Patients with diabetic retinopathy usually do not develop reportable symptoms during its initial stages; however, progressive disease (in its advanced stage) triggers ocular complications. Diabetic retinopathy impacts the vascular supply of both eyes and induces retinal vasculitis. It further leads to retinal microaneurysms and macular oedema and inflammation. The complications include bilateral complete vision loss, the appearance of eye floaters or black spots (hindering the vision), poor night vision, drusen or white spots on the retina, colour vision deficiency/colour blindness, and eyesight issues (Frank, 2004).



**Figure 1:** **Bibliometric analysis of the keywords in publications of diabetes and its complications**. Co-occurrence of keywords. The size of nodes indicates the frequency of occurrence. The curves between the nodes represents their co-occurrence in the same publication. The shorter the distance between two nodes, the larger 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.*

1. **Pathophysiology of diabetic retinopathy**

The 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 vascular endothelial growth factor (VEGF) expression (Caldwell et al., 2005; Du et al., 2003). 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 (Fong et al., 2004; Miloudi et al., 2019). Diabetic retinopathy further develops due to hyperglycaemia-induced metabolic stress, leading to vascular damage and neuralgia. The leaking and fragile blood vessels replace the damaged vessels following noticeable degeneration in the retinal endothelial cells (Lechner et al., 2017). The nonreceptor protein tyrosine kinase (Src) is regulated upstream by pericyte-induced angiopoietin 1, which interacts with TIE2 endothelial cell receptor. The induction of angiopoietin 1 and TIE 2 activate the platelet-derived growth factor and transforming growth factor signals in the endothelial cells (Whitehead et al., 2019). In addition, the proinflammatory cytokines interleukin (IL)-17A, IL-6, tumour necrosis factor (TNF), and monocyte chemoattractant protein (MCP)-1are the potential markers of diabetic retinopathy based on their attribution to endothelial cell death and vascular leakage.

1. **Biochemical and cellular pathways responsible for diabetic retinopathy**

The contemporary literature to date does not elaborate on viable mechanisms and pathways with their attributions to retinal deterioration in diabetes, which is predominantly the outcome of poor glycaemic 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 (Lindstrom et al., 2019).Diabetic retinopathy progresses with mitochondrial dysfunction and ROS activation, induced by nicotinamide adenine dinucleotide phosphate (NADPH) stimulation (Brownlee, 2001; Kowluru & Chan, 2007). The vicious cycle of ROS induction is prolonged by the continuous damage of mitochondrial cells under the impact of superoxide radicals from the mitochondrial electron transport chain (ETC) (Giacco et al., 2010; Kowluru et al., 2014). Patients with diabetes develop high levels of metabolic disruptions, in addition to hormonal imbalances and hyperglycaemia. The inflammatory processes in diabetes are governed by adhesion molecules, elevated capillary density, increased blood flow, neurotrophic factors, inflammatory compounds, vasoactive agents, and chemokines (Murphy, 2008). The early stages of diabetic retinopathy are also associated with angiogenesis, apoptosis, and vascular permeability.

1. **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 haemoglobin (HbA1C) evaluation ("Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes," 2008). It is important to measure glycaemic control by knowing the HbA1C level, which is also a marker of cardiovascular disease in diabetes (Patel & Macerollo, 2010; Selvin et al., 2014). Other diagnostic biomarkers for diabetes include glycated albumin and fructosamine (Li et al., 2016). Findings from recent studies indicate an uncertainty or standard deviation of ±7.8mmol/L in determining glycaemic control by assessing fructosamine levels. In addition, the overall serum lipid and serum protein levels appear to confound the outcomes from the fructosamine assessment test (Selvin et al., 2014). Recent evidence reveals a high concentration of glycated albumin in patients with poor glycaemic control (Lind et al., 2009). Compared with 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 (Bhonsle et al., 2012). The total glycaemic control in diabetes is best determined by PPG based on its greater correlation with HbA1C. In addition, a comparison of HbA1C with fructosamine indicates its minimal (+) association with the mean glucose profiles of patients with type 2 diabetes. These results negate the notion concerning the overall glycaemic control prediction capacity of HbA1C in diabetes (Rosediani et al., 2006; Tahara & Shima, 1995). Overall, HbA1C is not a strong clinical indicator of glycaemic control. **Table 1** depicts the prognostic indicators/novel biomarkers of diabetic retinopathy. 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 | * Age
* Type of diabetes
* Duration of diabetes
* Family history
* Lifestyle
* Obesity
* High blood pressure
* Pulse wave analysis
* SAF
* AGEs
 |
| Clinical (ocular) biomarkers | * Stage of retinopathy
* Retinal vessel calibre
* CRM
* ERG
 |
| Biochemical biomarkers | * Glycemia (HBA1c level)
* Serum creatinine
* eGFR
* 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 | * SNPs
* Histone modifications
	+ DNA methylation
	+ Histone deacetylation
	+ Histone acetylation
* Non-coding RNAs/MicroRNAs
* Metabolomics
* Lipidomics
* Glycomics
	+ Study of modified glucose/lipids/proteins
 |

1. **Diagnosis of diabetic retinopathy**

Routine ophthalmic assessments are paramount to diagnosing retinopathy in diabetes; the repeat examinations facilitate the early diagnosis (i.e., assessment of the condition at the initial stage of the disease) ("Executive Summary: Standards of Medical Care in Diabetes—2010," 2010; Narbonne et al., 2001). Patients with diabetes require annual or biannual assessments to determine their risk of retinopathy ("Standards of Medical Care in Diabetes—2009," 2009). The diagnostic work-up is guided by the symptomatology, including signs and clinical manifestations. The differential assessments for advanced eye disease, moderate/severe non-proliferative retinopathy, and maculopathy in diabetes are paramount to improving medical decision-making. **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 | * Microaneurysm
* Hard exudates
* Renal oedema/thickening
* Retinal haemorrhage
 |
| Maculopathy | * Oedema/thickening in the macular retina
 |
| Chronic non-proliferative diabetic retinopathy | * Cotton wool spots
* Vascular abnormalities
* Venous bleeding
* IRMA
 |
| Proliferative diabetic retinopathy | * NVD
* NVD elsewhere
* Vitreous haemorrhage
 |
| Advanced eye disorder | * Vitreous haemorrhage
* Pre-retinal fibrosis
* Retinal detachment
 |

1. **Cardiovascular complications**

Cardiovascular disease is the independent predictor of morbidity and mortality in patients with diabetes; more than 30% of patients with diabetes experience cardiovascular complications across the globe (Einarson et al., 2018; "Executive Summary: Standards of Medical Care in Diabetes—2010," 2010). The predominant cardiovascular complications in diabetes include cardiac dysfunction, stroke, myocardial infarction, and premature atherosclerosis (Groop et al., 2009; Haffner et al., 1998; Laing et al., 2003; Prince et al., 2007). The risk factors including persistent blood pressure elevation, poor glycaemic control, and dyslipidaemia predict the early onset of cardiovascular disease in diabetes. The disintegration of complex atherosclerotic plaques in the arteriovenous system results in strokes, unstable angina, and myocardial infarction; however, the etiopathology of these episodes is not yet determined (Drury et al., 2010). The binding of T lymphocytes and other macrophages to the walls of the arteries leads to localised abnormalities, including atherogenesis (Okon et al., 2005). Diastolic dysfunction marks the onset of coronary artery disease in asymptomatic patients with myocardial damage; the diagnostic workup relies on echocardiography (O’Brien et al., 1996; Rakowski et al., 1996). In addition, hyperglycaemia in diabetes activates the inflammatory, migratory, and proliferative attributes of the dormant noncontractile vascular smooth muscle cells. These processes eventually develop the proatherogenic environment, thereby increasing systemic/tissue-specific insulin resistance (**Figure 2**).

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**Figure 2:** Novel biomarkers for diabetes-related retinopathy complications

illustrates the pathogenesis of hyperglycaemia (in diabetes) and its attribution to cardiovascular manifestations (Kannel et al., 1974). The severity of clinical complications in 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 mobilisation, ketonuria, weight loss, increased appetite, and urinary frequency. Other potential complications of diabetes include vaginal infections, skin infections, dental abscesses, blurry vision, irritability, fatigue, and non-healing wounds.

1. **Cellular and biochemical mechanisms of cardiovascular complications in diabetes**

The cardiovascular complications in diabetes are caused by insulin resistance and hyperglycaemia. The onset and progression of diabetes trigger the accumulation of ROS, which eventually disrupts the cellular function and the vascular system’s homeostatic regulation, leading to cardiovascular pathology (Reddy et al., 2016).Findings from the 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. The current data indicating cardiovascular complications in diabetes do not elaborate on 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 are majorly derived from cell culture experiments, with limited reliability (McGuire & Marx, 2014). The predominant crosstalk mechanisms governing atherosclerosis development in diabetes impact the normal function of the liver, visceral fat, bone marrow, phagocytic cells, smooth muscles, endothelial cells, and inflammatory mediators (Ramasamy & Goldberg, 2010). Several clinical studies suggest the possible association of cardiovascular disease in diabetes with the polyol/sorbitol pathway (Burchfield et al., 2013). Findings from a preclinical study in the apolipoprotein E knockout mice indicate the exacerbation of atherosclerosis due to aldose reductase overexpression (Vedantham et al., 2011). The outcomes from a preclinical study revealed comparable atherogenesis and endothelial inflammation in non-diabetic apolipoprotein deficient and glyoxalase-1 inhibitor-induced diabetic mice (Vedantham et al., 2014).In addition, clinical studies indicate the association of plaque accumulation/rupture with the activity/levels of matrix metalloproteinase (MMP)-9, monocyte chemoattractant protein (MCP)-1, and IL-8. The findings also reveal the accumulation of cleaved caspase-3 and MG-H1 in macrophages around the centre of necrotic lesions in diabetes (Tikellis et al., 2014). In addition, heart diseases and associated mortality in diabetes correlate with the increased levels of cyclooxygenase (COX)-1 isoform (Hanssen et al., 2014). Other causative factors include AGE activation, protein kinase C induction, and secondary reduction in nicotinamide-adenine-dinucleotide (NAD)+/NADPH. In addition, ROS elevation and activity of AGE receptors increase the risk of cardiovascular complications in patients with diabetes. A significant increase in COX-2 abundance in the coronary vasculature of diabetic mice was reported by the preclinical study of Guo et al. (Verma et al., 2016).The findings reveal the impact of hyperglycaemia on the renal function of the diabetic mice, indicated by the interaction between prorenin receptor and renin/prorenin and eventual decline in the glomerular filtration rate (Guo et al., 2005).

1. **Biomarkers indicating cardiovascular complications in diabetes**

Several biomarkers independently predict coronary heart disease in patients with type 2 diabetes (Kellogg et al., 2008). They also help determine the pathological pathways of diabetes in skeletal muscles, coronary arteries, kidneys, and myocardium; the significant biomarkers include galectin-3, cardiac troponins, soluble suppressor tumorigenicity-2, and natriuretic peptides. The guidelines of 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) (Ponikowski et al., 2016; Sarhene et al., 2019; Yancy et al., 2017).

1. **Diagnostic workup to evaluate cardiovascular complications in diabetes**

The contemporary literature does not specify any standardized approach to evaluate dilated cardiomyopathy in diabetes. Accordingly, clinical correlation based on symptomatology and disease progression, predicted by imaging and biochemistry assessments strengthens medical decision-making. The doppler/echocardiography imaging is the gold standard to evaluate diastolic dysfunction in diabetes; patients with early-stage dilated cardiomyopathy may develop diastolic heart failure despite a normal ejection fraction (Araz, 2016). Literature results reveal a 75% incidence rate of dilated cardiomyopathy in asymptomatic patients with diabetes (Tarquini et al., 2010). The left ventricular function in diabetes is impacted by a range of factors including, calcium cycling, excitation-contraction coupling, left ventricular hypertrophy, and myocardial fibrosis (Chow et al., 2017; Lichtenauer et al., 2021).Magnetic resonance imaging (MRI) is a standard approach to evaluate the structure/function and motility of the left ventricle in diabetes (Wong & Tse, 2021). In addition, elevated HbA1C and high blood glucose levels are the potential serological biomarkers indicating the development of diabetes. However, cellular damage/necrosis and resultant cardiovascular complications are predicted by the increased troponin levels. The onset and progression of fibrosis in diabetes are indicated by the abundance of MMP9 (Berezin & Berezin, 2020). Cardiovascular disorder in diabetes is further determined by a clinically significant decline in metalloproteinases (TIMPs) tissue inhibitors; the progression of dilated cardiomyopathy is predicted by marked elevations in O-linked beta-N-acetylglucosamine levels (Achenbach et al., 2001; Boyer et al., 2004; Cosson & Kevorkian, 2003). The possible biomarkers for cardiac biochemical stress, cardiac myocyte necrosis, inflammation, fibrosis, myocardial hypertrophy, and extracellular matrix modelling in diabetes (Jones, 2005; Lunde et al., 2012; Maisch et al., 2011). The assessment of these pathogenic states is the key to determining potential cardiovascular complications in patients with prediabetes or type 2 diabetes.

1. **The therapeutic significance of routine oral hypoglycaemic agents in diabetes**

The improvement in glycaemic control is the key to minimising cardiovascular complications in patients with diabetes. The evidence-based treatments focus on normalising blood glucose levels and decreasing the risk of clinical complications (Zachara, 2012). The increased production of oral hypoglycaemic drugs in the recent decade has revolutionised the treatment landscape of type 2 diabetes by improving glycaemic control and reducing the incidence of preventable complications. The dosages of the hypoglycaemic drugs are determined by the treatment goals based on symptomatology and clinical complications. The primary goal of these oral hypoglycaemics is to lower the HbA1C levels below 7.0% to enhance glycaemic control ("Guía ESC 2019 sobre diabetes, prediabetes y enfermedad cardiovascular, en colaboración con la European Association for the Study of Diabetes (EASD)," 2020). They also activate beta cells of the pancreas to improve insulin production and concomitantly lower 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. However, the potential complications/adversities associated with oral hypoglycaemic drugs include hypoglycaemia, increased appetite, tachycardia, confusion, irritability, shakiness, weight gain, and sweating. While sulfonylureas impact ischaemic preconditions, pioglitazone adds to the risk and incidence of heart failure. The utilisation of gut hormones (incretin mimetics) also assists in lowering blood glucose levels based on improvements in digestive processes. However, incretin administration adds to the risk of diarrhoea, vomiting, nausea, and arrhythmia in non-responders (Scheen & Charbonnel, 2014). The recommended treatments for hyperglycaemia in diabetes include sodium-glucose cotransporter 2 inhibitors, α-glucosidase inhibitors, peroxisome proliferator-activated receptor agonists, biguanides, and sulfonylureas (Lee & Chou, 2003). These drugs may be administered as monotherapies or combination therapies with other hypoglycaemics. However, uncontrolled/persistent hypoglycaemia lowers the treatment efficacy, increases the risk of weight gain, and adds to the incidence of metabolic complications (Chaudhury et al., 2017). The potential challenges to the effective management of diabetes include long-term glycaemic control and lowering of treatment-emergent adverse events (Feingold, 2000).Contemporary therapies aim to optimise glycaemic goals and increase the quality-adjusted life years of the treated patients ("ACOG Practice Bulletin No. 201: Pregestational Diabetes Mellitus," 2018; Gatwood et al., 2018; Tan et al., 2019; Wang & Perri, 2018). The aim of quantifying the dosages of oral hypoglycaemic monotherapies or combination therapies is to improve clinical outcomes and reduce safety events (Bijnsdorp et al., 2011; Ganesan et al., 2022; Levetan, 2007; Maharjan et al., 2017; Refuerzo, 2011). In addition, the choice of second therapy relies on the selection, characteristics, and outcomes of the primary treatment. Evidence-based guidelines recommend several drug combinations to improve treatment outcomes and reduce preventable adversities in patients with diabetes. The commonly used combinations include 1) Thiazolidinediones with glucosidase inhibitors and metformin, 2) Metformin with repaglinide, 3) Thiazolidinedione with sulfonylurea, 4) Alpha-glucosidase inhibitor with sulfonylurea, and 5) Metformin with sulfonylurea (Loewe, 1953).The advantages of these combination therapies include their synergistic efficacy at reduced dosages, low risk of refractory disease, and reduced incidence of toxicity (Wagner & Ulrich-Merzenich, 2009).

1. **Diabetes management via herbal remedies**

The ongoing innovations in integrative medicine have increased the scope of using herbal remedies with routine treatment modalities for diabetes management (Prabhakar et al., 2014). The herbal extracts derived from plants are utilised for treating diabetes complications based on their medicinal properties. They are administered orally or by topical route in concordance with the treatment goals. Literature reveals the capacity of herbal medications to influence and modify the human body’s physiological processes (Kumar et al., 2021).The pharmacological properties of their bioactive ingredients help improve the body’s immunity and capacity to cope with type 2 diabetes. These ingredients are extracted from flowers, fruits, roots, stems, and leaves. Countries including India, China, and Tibet continue to practice herbal remedies against various disease processes for ages. The recent decade has witnessed unprecedented advancements and transformations in herbal practices across the globe. Evidence suggests the capacity of the herbal system of treatments to prevent and control chronic disease conditions including heart diseases, obesity, diabetes, asthma, hypertension, and autoimmune diseases. However, most advancements in herbal practices are supported by anecdotal evidence. The scarcity of preclinical and clinical studies to support the medicinal value of various herbs and their bioactive compounds restrict their evidence-based utilisation by the scientific community. Since none of the currently practised drugs/treatments provides a complete cure for diabetes and its fatal complications, future studies should investigate the diabetes management potential of herbal medicines. The studies should also examine the safety profiles and cost-effectiveness of herbal medicines in the setting of type 2 diabetes. Human history reveals a wide range of benefits of traditional ailments and ongoing studies should accordingly investigate their clinical outcomes in chronic conditions (Dixit et al., 2006). World Health Organization (WHO) has listed 21,000 plants based on their medicinal value and potential to manage complications of a range of chronic diseases. 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 for determining their efficacy and safety outcomes (Tran et al., 2020). The 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 grounded on anecdotal information (Chen et al., 2017; Kumar et al., 2021; Xiao, 2015). Few studies have demonstrated the possibility of preventing diabetes and its complications by including a range of phytochemical compounds in dietary regimens. These phytochemicals include flavonoids, alkaloids, coumarins, lignans, stilbenes, terpenoids, and monoterpenes. Clinical trials have demonstrated the role of various plant species in increasing insulin secretion and minimising 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), Enicostemma littorale (Chhota chirayata), Coccinia indica, Cinnamomum tamala (Indian Bay Leaf), Clerodendron phlomoides (Aarni),* and *Allium cepa (Onion)* (Wu et al., 2017).

The 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/muscle tissues, and minimising the production of endogenous glucose(M. Jung et al., 2006). The improved regulation of lipid and glucose metabolism improves the prevention and treatment of diabetes in high-risk patients. Findings from past studies indicate the possible role of flavonoid-based foods in improving diabetes symptoms and complications (Modak et al., 2007). In addition, the regular consumption of these diets minimises the risk and incidence of diabetes. Plant phytochemicals may prove to be novel therapies based on their promising role in controlling diabetes onset and potential complications (Jarald et al., 2008). Some of the commercially available antidiabetic products, which are sourced from natural herbs, include voglibose, miglitol, acarbose, and Pycnogenol. The bioactive ingredients of medicinal herbs improve glycaemic control by reducing the activities of protein tyrosine phosphatase 1B, alpha-amylase, and alpha-glucosidase. Several pharmaceutical companies are in the process of designing novel treatment molecules based on herbal extracts for diabetes management due to the low risk of adverse events. The herbal extracts can also minimise 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 (Xiao et al., 2015; Xiao et al., 2014).

1. **The medicinal properties of phytochemicals in managing diabetes complications**

The extraction of phytochemicals from medicinal herbs requires a range of complex procedures and mechanisms (Liu et al., 2014). The non-nutrient biomolecules incorporate phytochemicals based on their capacity to prevent and manage a range of chronic diseases (Altemimi et al., 2017). However, these biomolecules are not routinely needed by the human body for maintaining its normal physiology. The potential antidiabetic properties of the phytochemicals make them the most effective substances against type 2 diabetes and its 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 (Kennedy & Wightman, 2011). 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 studies should investigate the mechanism of action, pharmacokinetics, and pharmacodynamics of the potential phytochemicals including saponins, terpenoids, amino acids, glycosides, alkaloids, and polyphenols. The molecules passing the final testing will be able to enhance the metabolic processes and delay fatal complications of diabetes in the treated patients. Furthermore, clinical studies must compare the therapeutic outcomes, safety profile, and synergism of these phytochemical-based herbal remedies with synthetic drugs to effectively transform the diabetes treatment landscape. Recent evidence demonstrates the role of phytochemicals in altering the biochemical pathways and activities of dipeptidyl peptidase-4, α-glucosidase, and α-amylase. In-vivo and in-vitro (preclinical) studies also reveal several other phytochemicals that require testing to determine their diabetes treatment/prevention capacity in real-time scenarios.

1. **Predominant phytochemicals against diabetes complications**

Recent studies have investigated the efficacy and safety of flavonoids in a variety of chronic diseases, including diabetes, heart diseases, neurological disorders, and cancers (**Figure 3**). The efficacy/safety of these flavonoids is 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 indicates the role of flavonoids in minimising insulin resistance by enhancing endothelial function and improving vasodilation in blood vessels. They actively interact with the vascular smooth muscle cells and increase their vasorelaxation capacity by inducing the BKCa channels. The improved physiological regulation of intracellular calcium, membrane voltage, and neurotransmitter release eventually enhances endothelial function and glycaemic control. Phytochemicals also disrupt potential alterations in endothelial function that eventually delays the development of atherosclerotic lesions and associated cardiovascular complications in patients with diabetes.

**Figure 3:** The therapeutic molecular targets of phytochemicals and the diseases they prevent.

Findings in the contemporary literature reveal the possible role of phytochemicals in minimising the accumulation of ROS and nitric oxide, which eventually results in vasodilation and reduction in systolic blood pressure in diabetes. Phytochemicals also facilitate the translocation of glucose transporter type 4 across the plasma membrane, which subsequently improves the absorption of glucose across adipose tissues and skeletal muscles (Modak et al., 2007). Clinical studies also signify the role of flavonoids in improving hepatic function by controlling the function of genes responsible for gluconeogenesis. The reduced glucose synthesis in the liver eventually lowers the serum blood glucose levels and increases glycaemic control. Additionally, flavonoids improve the intestinal absorption of glucose by delaying the breakdown of complex carbohydrates. They also elevate insulin production, enhance cell vitality, and reduce the oxidative stress in the beta cells of pancreas (Kim et al., 2011). **Table 3** summarises therapeutic effects of flavonoids on retinopathy and cardiovascular complications in diabetic mice and 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

|  |
| --- |
| IN-VIVO MODELS |
| Animal | **DM** | **Model** | **Treatment** | **Results** | **Effect** |
| DIABETIC RETINOPATHY COMPLICATIONS |
| Rat | T1DM | STZ | Catechin 50–200 mg/kg/day 8 weeks | Modulation NF-κB pathway ↓ IL-1β, IL-6, and TNF-α | Anti-inflammatory |
| Rat | T1DM | STZ | Biochanin A 10–15 mg/kg/day. 6 weeks | ↓ TNFα, IL-1β, 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-1β; ↑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 ↓ TNFα, IL-1β and IL-6 ↓p65, IκB 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-κBsignaling pathway | Cardioprotective and anti-inflammatory |
| Rat | T1DM | STZ | Apigenin 100 mg/kg/day 7 months | ↓ cardiomyocyte enlargement; ↑SOD and GPx ↓ NF-κB/p65 signaling pathway activation ↓ Col-I, Col-III, CTGF, TGFβ | 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 | Isoquecertin 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 |

1. **Diabetes treatment potential of phytochemicals**
	1. **Rutin**

The flavonoid phytochemical ‘rutin (sophorin/quercetin-3-O-rutinoside)’is extracted from limes, lemons, apples, ginkgo, St. John’s wort, buckwheat, eucalyptus, and citrus fruits (Kreft et al., 1999; Wang et al., 2019). The primary role of rutin is to improve glycaemic control by controlling ROS accumulation and minimising oxidative stress in the pancreas. It also enhances insulin secretion by preserving the beta cells of the pancreas and reduces gluconeogenesis. In addition, it minimises the absorption of glucose in the small intestine. Rutin effectively challenges the accumulation of free radicals, which further reduces oxidative stress and minimises life-threatening complications in diabetes. Rutin induces significant reductions in IL-6, sorbitol, and AGEs; it also alters the signalling cascades that eventually reduce the risk of clinical complications in diabetes (Huang et al., 2012). The intraperitoneal/oral administration of 50-100 mg/kg rutin to mice with streptozotocin-induced type 1 diabetes leads to improvements in their fasting blood glucose and glycated haemoglobin levels (Ghorbani, 2017).In addition, rutin activates hexosamine pathways that eventually minimise gluconeogenesis and organ system complications in diabetes (Prince & Kamalakkannan, 2006).Rutin also maintains the levels of albumin and blood urea nitrogen, in addition to controlling oxidative stress and reducing blood glucose concentration (Niture et al., 2014). It effectively activates anti-apoptotic molecules (including B-cell lymphoma 2) and reduces the concentration of caspase 3, which eventually minimises cell death processes in various organ systems.

* 1. **Quercetin**

Quercetin dihydrate (3,3,4,5,7-pentahydroxyflavone or C15H14O9) or quercetin is a bioactive phytochemical, known for its antimicrobial, antioxidant, anti-inflammatory, and anti-diabetic properties; it is derived from red wine, green tea, berries, tea, onions, and apples (Prince & Kannan, 2006). 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 (Hao et al., 2012; Ola et al., 2015). The outcomes from a recent systematic review and meta-analysis indicate the capacity of quercetin to minimise fasting glucose levels in laboratory animals within the dose range of 10mg/kg, 25mg/kg, and 50mg/kg body weight (Parasuraman et al., 2016). 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/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 (Haddad & Eid, 2017; Hollman et al., 1995). Results from the preclinical studies also indicate improvements in the pancreatic beta cell structure/function, glucose metabolism, inflammatory processes, and oxidative state in streptozotocin-induced diabetic mice(Yao et al., 2018). Quercetin effectively modulates the activity of nuclear factor kappa B, which eventually improves insulin secretion and glycaemic control (Bule et al., 2019; Fang et al., 2008).

* 1. **Hesperidin**

The saturated aglycon derivative ‘hesperidin’ is a bioflavonoid, derived from sweet oranges, lemons, gooseberry, cranberry, and raspberry. Clinical studies indicate the medicinal value of hesperidin against a range of conditions, including diabetes, inflammation, memory impairment, allergies, and neurological disorders (Eid et al., 2010). Its neuroprotective, antioxidant, and anti-inflammatory properties add value to its pharmacological profile against chronic disease conditions. Preclinical studies indicate the role of hesperidin supplements in reducing blood glucose levels by regulating the function of glycolytic liver enzymes and controlling the process of gluconeogenesis (Visnagri et al., 2014). It also induces lipolysis, reduces the activity of lipid-metabolising hepatic enzymes, and enhances the faecal excretion of triglycerides (Jung et al., 2004). 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 10g/kg of hesperidin in reducing the accumulation of glucose-6 phosphate and glucose levels in streptozotocin-induced diabetic mice (U. J. Jung et al., 2006). In addition, it also improves glycaemic control by regulating lipolysis and carbohydrate metabolism. Findings from several preclinical studies also indicate hesperidin’s potential to reverse liver and kidney damage by upregulating the klotho and fibroblast growth factor 23 pathway in streptozotocin-induced diabetic mice (Akiyama et al., 2009; Akiyama et al., 2014; Das et al., 2014).

* 1. **Resveratrol**

The stilbenoid ‘resveratrol’ is a natural food ingredient, which is derived from plants across the globe based on its medicinal value (Zordoky et al., 2015). The pharmacological properties of resveratrol assist in treating several disease conditions including, Alzheimer’s disease, diabetes, heart diseases, and cancers. The cardioprotective role of resveratrol is based on its potential to control systolic and diastolic blood pressures. 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. The vasodilation property of resveratrol is due to its capacity to block diacylglycerol and inositol triphosphate signalling pathways (Cao et al., 2014; Shen et al., 2013). Resveratrol also suppresses triglycerides and the expression of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, thereby lowering serum cholesterol. In addition to its synergism with metformin, resveratrol also reduces apoptosis and upregulates glucose transporter 4 translocation in diabetes (Lekli et al., 2008).

* 1. **Other phytochemicals**

The isoquinoline alkaloid ‘berberine’ effectively reduces the risk of cognitive impairment, enhances insulin resistance, maintains total cholesterol, and reduces blood glucose levels (Ye et al., 2021). The flavonoid ‘naringenin’ is recognized in scientific literature for its cardioprotective, antiadipogenic, anti-inflammatory, antibacterial, antiviral, antitumor, and antioxidant properties (Salehi et al., 2019). The predominant flavonoid aglycone ‘kaempferol’ is known for its antidiabetic, neuroprotective, cardioprotective, antitumor, antioxidant, anti-inflammatory, and antimicrobial potential (Imran et al., 2019). The therapeutic implications of the natural phenol ‘chrysin’ are observed in neurodegenerative diseases, diabetes, and cancers. It also helps reduce inflammation and oxidative stress in diabetes complications (Stompor-Gorący et al., 2021). Similarly, scutellarin is a potential phytochemical with a promising mechanism of action against diabetes (vascular complications), Helicobacter pylori infection, Alzheimer’s disease, cerebral ischemia, and cardiovascular complications (Chledzik et al., 2018). Future studies should re-examine the treatment profile of these phytochemicals against retinopathy and cardiovascular disease in diabetes.

**Conclusion**

The progressive clinical manifestations of diabetes reciprocate with inflammatory processes and an increase in oxidative stress. Phytochemicals may prove to be promising therapeutic modalities against diabetes due to their anti-hyperglycaemic, antioxidant, and anti-inflammatory properties. Their interaction and interference with the cellular metabolites and pathological processes in retina may challenge the onset/progression of diabetic retinopathy. Similarly, their cholesterol lowering capacity may assist in reducing the incidence of hyperlipidaemia, thereby minimising the risk of cardiovascular diseases in diabetes. The therapeutic utilisation of phytochemicals is currently limited due to their low bioavailability and tissue assimilatory capacity. Future studies should accordingly determine robust tools and techniques to enhance the bioavailability of phytochemicals and re-evaluate their efficacy and safety in diabetes. It is also important to standardise the dosages of the crude extracts of phytochemicals based on their medicinal value and diabetes management goals. The adjuvant therapies based on phytochemicals may revolutionise 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

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