INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Plant-Derived Bioactive Compounds Targeting Molecular Mechanisms of Type 2 Diabetes and its Associated Complications: Evidence from Experimental Studies

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ARTICLE INFO

Published: 08 July 2026

Keywords:

Type 2 diabetes mellitus, bioactives, mechanistic validation, phytochemicals, diabetic complications, Plant-based extract

DOI:

10.5281/zenodo.21267536

ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a progressive metabolic syndrome, which is insulin resistant, pancreatic dysfunction of beta cells, chronic inflammation, and oxidative stress, culminating in disastrous microvascular and macrovascular complications. Although there is a variety of antidiabetic medications, long-term treatment is frequently constrained due to adverse responses, progressive failure and poor management of subsequent complications. Plant-derived bioactive compounds have been of special interest in recent years as a therapeutic option because of their multitargets, safety, and pharmacological properties as illustrated in experimental research. The review aims to highlight the molecular pathways involved in the antidiabetic actions of plant bioactives, such as the regulation of insulin signalling pathways (IRS-1/PI3K/Akt/GLUT4), activation of the AMP-activated protein kinase (AMPK), the pro-inflammatory mediators, e.g., NF-kB, TNF-a and IL-6. Moreover, the protective effects of such bioactives in ameliorating diabetic complications which include nephropathy, neuropathy, cardiovascular dysfunction and compromised wound healing are discussed using evidence of in vitro and in vivo experimental models. Even though the preclinical evidence is encouraging, there are shortcomings such as standardization, mechanistic validation, and poor clinical translation, which are a challenge. Further studies must focus on molecular studies, standardized extract preparations, and properly structured clinical trials in order to foster application of plant-based extracts in control of diabetes.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive and multifactorial metabolic condition that is associated with the persistent hyperglycaemia due to insulin resistance, insulin inadequate secretion, or both [1]. The incidence of T2DM over the last few decades has been rising at alarming rates, with most of the blame resting on sedentary lifestyle habits, rising cases of obesity and an ageing world

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

population [2,3]. This has led to T2DM being one of the most urgent international health issues of concern [2]. In addition to the disruption of glucose homeostasis, the disease is also accompanied by severe changes in lipid metabolism, redox balance, and the inflammatory signalling all of which further propagate the disease and also lead to the advancement of the long-term complications [4,5].

The morbidity and death caused by T2DM still remain the major problems. These are microvascular complications (diabetic nephropathy, neuropathy and retinopathy) and macrovascular manifestations (cardiovascular disease and wound repair impairment) [5]. There is increasing evidence that the pathogenesis of these complications is in the oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, and accumulation of advanced glycation end products (AGEs). There is a collective effect on the molecular disturbances, which worsen insulin resistance, induce cellular damage, and disrupt normal tissue repair mechanisms [6-8].

Although there are a few types of synthetic antidiabetic drugs: biguanides, sulfonylureas, thiazolidinediones, and incretin-based therapy, it is still difficult to achieve long-term glycaemic control and avoid the emergence of long-term complications [9]. A lot of these drugs come with side effects that include; hypoglycaemia, weight gain, gastro intestinal disturbances and in some individual instances, secondary failure of the therapy. In addition, the majority of the traditional treatments are mainly geared towards the maintenance of glycaemic control without sufficient attention to the multifactorial pathways of diabetic complications [4,9]. Such constraints can highlight the need to implement safer and more holistic treatment measures that would have the ability to address several pathogenic pathways in a single setting.

Plant- derive bioactive compounds have received a lot of interest in this regard as a potential adjunct or alternative in diabetes management [10,11]. The phytoconstituents of medicinal plants are abundant in flavonoids, polyphenols, alkaloids, terpenoids and glycosides and they have antidiabetic action due to multiple and interrelated mechanisms [10,12]. It is experimentally indicated that these compounds regulate insulin signalling pathways, activate AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma (PPAR-g), endogenous antioxidant systems, and prevent pro-inflammatory intermediates [12,14]. It is worth noting that a large number of phytochemicals exhibit multitargeted activities that have relatively favourable safety profiles in preclinical studies [11,13].

In vitro studies and animal models, especially streptozotocin-induced and high-fat diet-induced diabetic rodents, have helped in gaining a substantial insight on the molecular underpinning of phytotherapeutic interventions [15]. All these findings indicate that plant-compounds that do not require conversion into drugs can be used to positively influence glycaemic parameters, as well as offer organ-protective benefits by reducing oxidative stress, altering the inflammatory pathways, and suppressing tissue-specific pathological alterations [12-14].

Subsequently, the current review is a critical synthesis of the available experimental data on plant-derived bioactive compounds that inhibit major molecular pathways involved in T2DM and related complications. Specific stress is laid on mechanistic pathways, experimental models, and therapeutic outcomes. Also, limitations and gaps in research are also addressed to narrow the future perspectives and improve the translational opportunities of phytotherapeutic treatments in the management of diabetes.

TYPE 2 DIABETES MELLITUS PATHOPHYSIOLOGY

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disease that develops as a result of interplay between genetics and the environment, such as obesity, sedentary lifestyles, and inappropriate nutritional habits [16,17]. It does not emerge due to a single aberration but instead occurs as a combination of interrelated imbalances that are mainly insulin resistance and progressive b-cell dysfunction in the pancreas [18]. These fundamental aberrations are further augmented with persistent oxidative stress and low-grade inflammation, which finally impairs glucose homeostasis and leads to people being predisposed to long-term complications [19,20].

Insulin Resistance

Insulin resistance is also a hall mark of T2DM and is a state of decreased sensitivity of the peripheral tissues especially skeletal muscle, fat tissue and the liver to circulating insulin [18,21]. The insulin receptor binding under normal physiological conditions triggers a tightly-controlled insulin-receptor-initiated signalling pathway involving insulin receptor substrates (IRS-1 and IRS-2), which is then followed by the activation of phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). This signalling pathway facilitates the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane that enables the cells to absorb glucose efficiently [21].

Several defects in this pathway disrupt this pathway in T2DM. Enhanced serine phosphorylation of IRS proteins, decreased activation of PI3K/Akt and changes in receptor signalling, all inhibit GLUT4 translocation and result in impaired glucose uptake in peripheral tissues [21,22]. The resistance to insulin in the liver is unable to inhibit the processes of gluconeogenesis, hence the high production of hepatic glucose and additional complications of hyperglycaemia [18,22].

Pancreatic Dysfunction of Beta Cells

At the initial phases of insulin resistance, a pancreatic b-cells response involves supplementing insulin secretion to create a condition of hyperinsulinemia [23]. This compensatory mechanism is not however sustainable. Extended glucose and lipid conditions that are often called glucotoxicity and lipotoxicity exert metabolic strain on b-cells [24]. Additional effects of oxidative stress and endoplasmic reticulum stress are a decline in insulin production and release [19,25].

In the long term, chronic metabolic stress will stimulate b-cell apoptosis and lower functional b-cell mass [23,25]. With decreasing insulin secretion capacity, there is a lowering of the body to glycaemic regulation levels, and one passes through compensated insulin resistance to overt diabetes.

Role of Oxidative Stress

Oxidative stress also plays a central role in the development and the course of T2DM [19,26]. Continued hyperglycaemia increases the formation of the reactive oxygen species (ROS) by including increased superoxide production within the mitochondrion, glucose autoxidation, and polyol activation of the polyol pathway. Cellular redox imbalance occurs when the production of ROS surpasses the capacity of the endogenous antioxidant mechanisms, such as superoxide dismutase (SOD), catalase and reduced glutathione (GSH) [26].

Oxidative stress in excess causes lipids, proteins and nucleic acid damage, disrupts insulin signalling, and endothelial dysfunction. These do not only increase insulin resistance but they also stimulate tissue damage in organs where diabetic complications usually occur.

Chronic Inflammation

T2DM is becoming a metabolic disease having a powerful inflammatory factor [20,28]. Expanded adipose tissue is an active endocrine organ that produces pro-inflammatory cytokines in obesity, including tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6) and resistin [28,29]. Such cytokines interfere with insulin signalling pathways and increase the process of serine phosphorylation of IRS proteins, which worsens insulin resistance [21,29].

Transcription factors like nuclear factor kappa B (NF-kB) also increase inflammatory reactions, which forms a self-perpetuating loop of metabolic and immune dysregulation [20,28]. Chronic inflammation is also known to contribute to b-cell dysfunction as well as vascular and neural damage in diabetic complications in addition to accelerating them [27].

Advanced Glycation End Products (AGEs) and Related Metabolism

Prolonged hyperglycaemia favours non-enzymatic glycation of proteins and lipids giving rise to advanced glycation end products (AGEs) [8]. These molecules bind to their receptor (RAGE) eliciting oxidative stress and an inflammatory signalling cascade [8,30]. The AGE-RAGE axis is closely involved with the development of endothelial dysfunction and the development of diabetic complications [30].

Moreover, hyperglycaemia elevates metabolic flux by other biochemical pathways, such as the polyol pathway, protein kinase C (PKC) activation and hexosamine biosynthetic pathway [27,31]. These metabolic imbalances also worsen the functioning of cells and are major factors in the emergence of microvascular and macrovascular complications [27].

MOLECULAR PATHWAYS MEDIATED BY PLANT-DERIVED BIOACTIVE COMPOUNDS

The antidiabetic action of plant-derived bioactive compounds is a result of coordinated annual regulation of several molecular pathways involved in the regulation of glucose metabolism, lipid homeostasis, oxidative stress and inflammation [32,12]. Contrary to the single-target synthetic agents, most of the phytochemicals exhibit pleiotropic effects, which allow them to respond to the multifaceted and interdependent disruptions that are the root causes of T2DM [12,14]. Investigations experimental studies have repeatedly demonstrated that these compounds affect important signalling cascades that mediate the effects of insulin resistance, b-cell dysfunction and tissue injury, thus enhancing glycaemic regulation and decreasing diabetic complications [11,33].

Insulin Signalling Pathway Modulation

There is a pivotal role in insulin signalling cascade in the homeostasis of glucose. In a normal physiological state, insulin binding with its receptor causes phosphorylation of IRS-1 and IRS-2, and then activation of phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). Stimulated Akt promotes the translocation of glucose transporter 4 (GLUT4) to the plasma membrane in skeletal muscle and adipose tissue facilitating the efficient uptake of glucose [21].

In insulin resistant conditions, malfunctioning of this pathway hinders the use of glucose [22]. A range of bioactives in plants, especially flavonoids and polyphenols, have been demonstrated to increase insulin receptor sensitivity, reinstate IRS function, and PI3K/Akt signalling [33,34]. These effects enhance more GLUT4 expression and membrane translocation in the long-term which ultimately leads to improved peripheral glucose disposal [34]. Phytochemicals directly reverse one of the major pathophysiological pathologies of T2DM, by repairing abnormalities in this pathway [11,12].

AMPK activation

AMP-activated protein kinase (AMPK) is one of the important cellular messengers that mediate metabolic homeostasis [35]. Its stimulation increases the uptake of glucose, fatty acid oxidation, mitochondrial biogenesis and reduces hepatic gluconeogenesis and lipogenesis [35,36].

There is an emerging literature of experimental data on the fact that many of the plant-based compounds stimulate AMPK in diabetic models [37]. Notably, the AMPK-mediated glucose uptake uses no insulin signalling, and so this pathway will be especially useful in insulin-resistance situations [36]. Moreover, AMPK activation decreases the ectopic lipid deposition and increases metabolic flexibility thereby alleviating lipotoxic stress and improving overall metabolic efficiency [37].

Peroxisome proliferator-activated receptor gamma (PPAR- gamma) regulation

Peroxisome proliferator-activated receptor gamma (PPAR-g) is a nuclear receptor known to regulate the adipogenesis, lipid storage, and insulin sensitivity [38]. Despite the advantages of the pharmacological PPAR-g agonists in glycaemic control, adverse effects tend to limit their application over time [39].

Most intriguingly, some plant bioactives can act as natural regulators of the PPAR-g activity [40]. These compounds can promote the secretion of adiponectin, reduce free fatty acids in the blood, and increase peripheral tissue insulin responsiveness by partial or balanced stimulation of this receptor [40,41]. These modulations could have comparable metabolic advantages to synthetic agonists and may have reduced adverse effects [41].

Increase in Antioxidant Defence Mechanisms

The role of oxidative stress in the pathogenesis of insulin resistance, b-cell dysfunction, and development of diabetic complications has become a central point in the evolution of the disease [19,26]. High concentrations of reactive oxygen species (ROS) may disrupt cellular signalling and lead to the damage of important biomolecules [26].

Several phytochemicals have inherent antioxidant activities and also enhance endogenous defence mechanisms [42]. It has been experimentally proven that the roles of plant-derived compounds are to augment the action of antioxidant enzymes, i.e., superoxide dismutase (SOD), catalase, and glutathione peroxidase and to diminish lipid peroxidation indicators, i.e., malondialdehyde (MDA) [42,43]. Through the restoration of the redox balance, these agents provide pancreatic b-cell protection and tissue integrity in organs that are prone to diabetic damages [11,43].

Immunomodulation Of Inflammatory Processes

T2DM is characterized by chronic low-grade inflammation that plays an important role in the progression of insulin resistance and vascular damage [20,28]. The continued stimulation of the inflammatory signalling pathways disrupts metabolic homeostasis and speeds up the tissue dysfunction [28].

Experimental model evidence indicates that plant bioactives have a significant inherent ability in anti-inflammatory effects [44]. Nuclear factor kappa B (NF-kB) is a major transcription factor that empowers the expression of genes involved in inflammation, and it is also inhibited by a great number of phytoconstituents [44,45]. Damping of NF-kB signalling decreases the expression of the pro-inflammatory cytokine tumour necrosis factor-a (TNF-a) and interleukin-6 (IL-6) [45]. Phytochemicals also enhance insulin sensitivity and prevent the development of diabetic complications through the attenuation of inflammatory cascades [11,44].

Inhibition of AGE Formation and Related Metabolic Dysfunction

The AGEs are important factors which contribute to the development of diabetic complications through enhancing oxidative stress, inflammation, and vascular dysfunction [8,30]. Continuous hyperglycaemia enhances the formation of AGE by non-enzymatic glycation reactions [8].

Some compounds that are produced by plants have been reported to prevent the formation of AGEs and lower their concentration in the tissues [46]. Moreover, phytochemicals can also regulate the metabolic pathways induced by hyperglycaemia such as polyol pathway and protein kinase C (PKC) activation, thus alleviating cellular damage downstream [31,46]. Plant bioactives have the potential to prevent microvascular and macrovascular complications through the targeting of these linked mechanisms [46].

ROLE OF PLANT BIOACTIVES IN DIABETIC COMPLICATIONS

Sustained oxidative stress, low-grade inflammation and cellular signalling imbalance are the result of a cascade of metabolic disruptions, triggered by chronic hyperglycaemia in T2DM [6,27]. With time, these changes lead to progressive structural and functional impairment of a variety of organ systems with the ultimate result being microvascular, as well as, macrovascular complications [4,27]. There is increasing experimental data to the effect that plant-based bioactive compounds have a protective effect on these complications via a combination of antioxidant, anti-inflammatory, and cytoprotective effects [47,48].

Diabetic Nephropathy

One of the most severe long-term effects of T2DM is diabetic nephropathy that is a major cause of end-stage renal disease in the entire globe [49]. It is pathologically defined by hypertrophy of the glomeruli, mesangial muscular expansions, thickening of the glomerular basement membrane, proteinuria, and renal fibrosis progression [49,50]. Constant hyperglycaemia fosters oxidative stress, advanced glycation end product (AGEs) buildup, and inflammatory and profibrotic signalling, which lead to renal damage [50,8].

Bioactives in plants have also shown significant Reno protective effects in diabetic nephropathy experimental models [51]. These are compounds that decrease oxidative stress through an increase in endogenous antioxidant defences and a restriction of lipid peroxidation [51,52]. Moreover, inhibition of nuclear factor kappa B (NF-kB) signalling inhibits inflammatory responses, whereas sustained down-regulation of profibrotic mediators, including transforming growth factor-b (TGF-b) prevents excessive deposition of extracellular matrix [52,53]. Biochemical markers, such as serum creatinine, blood urea nitrogen (BUN), and urinary excretion of albumin, and positive histopathological results, are further evidence of the potential of phytochemicals to enhance renal function [51,53].

Diabetic Neuropathy

Diabetic neuropathy is a disabling complication and is typified by residual peripheral nerve damage that transpires as a result of extended hyperglycaemia, microvascular weakness, and metabolic instability [54]. The amplified flow via the polyol route results in sorbitol buildup, which is one of the causes of osmotic stress and neuronal malfunction [54,55]. At the same time, nerve injury is worsened by mitochondrial impairment, oxidative damage, and release of inflammatory mediators [55].

The experimental results suggest that the plant-based compounds have neuroprotective effects due to several different mechanisms [56]. These agents stabilize neuronal integrity by decreasing the production of reactive oxygen species and increasing the activity of the antioxidant enzymes [56,57]. Enhancement of endoneurial blood circulation and preventive effect of pro-inflammatory cytokines also help in functional recovery [57]. The positive effects of phytochemicals in the neuropathic phenomenon are highlighted by reports of enhanced nerve conduction velocity, alleviating thermal hypersensitivity, and maintaining neuronal architecture in the diabetic animal models with the therapy [56,57].

Cardiovascular Complications

The major cause of death among patients with T2DM is cardiovascular disease [58]. Oxidative stress caused by hyperglycaemia, dyslipidaemia, endothelial dysfunction, and chronic inflammation all favour atherosclerosis, diabetic cardiomyopathy, and vascular impairment [58,59].

Bioactives of plant origin have demonstrated cardioprotective effects in animals [60]. These substances have better lipid profiles as they lower total cholesterol, triglycerides and low-density lipoproteins and increase high density lipoprotein levels [60,61]. Also, the increase in the bioavailability of endothelial nitric oxide enhances the vascular activity, and the elimination of oxidative and inflammatory signaling downplay the myocardial and vascular damage [59,61]. AMP-activated protein kinase (AMPK) and decrease in lipid peroxidation activation also play a role in protecting cardiac structure and cardiac function in diabetic models [60,61].

Impaired Wound Healing

Wound healing is a common and clinically relevant complication of diabetes which in most cases occur and result to chronic wound ulcers and secondary infections. Hyperglycaemia interferes with the usual angiogenesis, inhibits collagen synthesis, and affects the immune cell activity. Constant oxidative stress and inflammation also slow down tissue repair and remodelling [62].

The plant-derived bioactives have shown therapeutic effects in diabetic wound models in terms of the promotion of angiogenesis, fibroblast proliferation and increased collagen deposition. Antimicrobial effects and strong antioxidant effects are also common with many phytochemicals, which present a favourable microenvironment to promote tissue regeneration. Accelerated wound contraction, enhancement in the amount of hydroxyproline, enhanced the formation of granulation tissue, and minimization of inflammatory infiltration are frequently reported in experimental results that have been obtained after applying plant extracts. Such multifactorial processes emphasize how phytotherapeutic agents can be used to solve the complicated pathophysiology of diabetic wound impairment [63,64].

PRECLINICAL EVIDENCE OF EXPERIMENTS

Our present knowledge regarding the antidiabetic and organ-protective activity of bioactive compounds of plant origin is based on preclinical research [65,66]. The combination of in vitro studies and animal research has enabled researchers not only to investigate the glucose-lowering properties of phytochemicals but also to reveal the underlying mechanisms of the protective action of phytochemicals against diabetic complications [66]. These experimental models give important mechanistic and translational data prior to the clinical assessment [65].

In Vitro Experimental Models

Molecular events of plant bioactives are studied at a considerable extent in cell-based systems [19]. Common models used are pancreatic b-cell lines, skeletal muscle cells, adipocytes, hepatocytes, endothelial cells either exposed to hyperglycaemic, lipotoxic, or oxidative stress conditions to model diabetic conditions [19,67].

The results of these investigations all confirm that phytochemicals produce an augmentation in insulin signalling cascades, translocation of GLUT4, activation of AMP-activated protein kinase (AMPK), and elevation of glucose uptake in cells [68,69]. Besides enhancing metabolic signalling, most plant-derived compounds inhibit the formation of intracellular reactive oxygen species (ROS), the expression of pro-inflammatory mediators and reduce apoptosis in pancreatic b-cells and other insulin-sensitive tissues [69,70]. This mechanistic evidence underscores the capacity of the phytotherapeutics to act on numerous intracellular targets of interest in the pathophysiology of T2DM [68].

In Vivo Experimental Models

In vitro methods provide an understanding of mechanisms, but in vivo models need to be used to determine the full impact of plant bioactives on the body and the specific effects in the organ [15]. Different experimental models have been simulated to model various aspects of T2DM:

a) Models induced using streptozotocin (STZ) without or with a high-fat diet to simulate insulin resistance and partial b-cell dysfunction [71].

b) The models of high-fat diet (HFD) reflecting the metabolic disruptions associated with obesity [72].

c) There exist genetic models including db/db mice that have severe insulin resistance and hyperglycaemia [73].

These models allow the full evaluation of glycaemic control, insulin sensitivity, lipid metabolism, the level of oxidative stress, and the emergence of organ-specific complications [15]. Plant-derived compounds treatment in these models has often led to large decreases in fasting blood glucose levels, enhanced glucose tolerance, increased insulin responsiveness, and regeneration of antioxidant capacity [74]. Also, the histopathological architecture enhancement of pancreatic, renal, cardiac, and neural tissues is another example that they can protect [74,75].

Evaluated Parameters and Biomarkers

Preclinical studies can determine therapeutic efficacy by assessing a broad spectrum of biochemical, molecular, and histological markers. Categories of parameters that are commonly measured are:

a) Glycaemic indices: Fast blood glucose, glycated haemoglobin (HbA1c), serum insulin.

b) The markers of oxidative stress include superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and malondialdehyde (MDA) [76].

c) Mediators of inflammation: tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6) and nuclear factor kappa B (NF-kB) [77].

d) Parameters of lipid profiles: Triglycerides, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) [78].

e) Markers of renal functions: Serum creatinine, blood urea nitrogen (BUN) and urinary albumin excretion [49].

f) Histopathological evaluation**:** Structural examination of pancreas, kidney, heart, and nerve tissues [75].

The upgrading of these parameters tends to follow the mechanistic pathways mentioned above, which supports the idea that plant-based compounds have multitargeted effects. Together, the preclinical data can be used to assess the therapeutic potential of phytochemicals in reducing hyperglycaemia, as well as against tissue trauma associated with diabetes [66,74].

Together, it has been suggested during preclinical investigations that plant bioactives have antidiabetic effects which can be classified as restoration of insulin signalling pathways, AMPK activation, PPAR-g modulation, antioxidant defence enhancement, and inhibitory effects on inflammatory cascades [68,69]. Also, the compounds have protective effects against diabetic nephropathy, neuropathy, cardiovascular damage, and wound healing impairment [74,75].

A summary of the representative studies including plant sources, experiment models, molecular mechanisms, biomarkers, and significant findings is compared in a table (Table 1).

Table 1: Experimental Evidence of Plant-Derived Bioactives in T2DM and Its Complications

Plant/ Bioactive Compound	Plant Part/ Compound Type	Experimental Model	Dose & Duration	Molecular Mechanism Targeted	Biomarkers Assessed	Major Outcomes	Reference
Curcumin (*Curcuma longa*)	Rhizome polyphenol	STZ-induced diabetic rats	100–200 mg/kg, 4 weeks	AMPK activation, anti-inflammatory signalling	Fasting blood glucose, insulin, TNF-α, lipid profile	Reduced hyperglycaemia and improved insulin sensitivity	Aggarwal et al., 2013 [79]
Berberine (*Berberis vulgaris*)	Isoquinoline alkaloid	HFD + STZ diabetic rats	100 mg/kg, 8 weeks	AMPK activation and inhibition of hepatic gluconeogenesis	Fasting glucose, TG, LDL, insulin	Improved glucose metabolism and lipid profile	Zhang et al., 2008 [80]
Resveratrol (*Vitis vinifera*)	Polyphenolic stilbene	db/db diabetic mice	20 mg/kg, 12 weeks	SIRT1-AMPK pathway activation	Blood glucose, adiponectin, oxidative	Improved insulin sensitivity and reduced oxidative stress	Baur et al., 2006 [81]

					stress markers		
Quercetin (*Allium cepa*)	Flavonoid	STZ-induced diabetic rats	50 mg/kg, 6 weeks	PI3K/Akt pathway activation	Glucose, insulin, GLUT4 expression	Enhanced glucose uptake and reduced hyperglycaemia	Kobori et al., 2011 [82]
Epigallo-catechin gallate (EGCG) (*Camellia sinensis*)	Catechin polyphenol	HFD-induced diabetic mice	50 mg/kg, 8 weeks	AMPK activation and improved insulin signalling	Glucose tolerance test, lipid profile	Improved insulin sensitivity and reduced body weight	Wolfram et al., 2006 [83]
Mangiferin (*Mangifera indica*)	Xanthone polyphenol	STZ diabetic rats	40 mg/kg, 4 weeks	Antioxidant and anti-inflammatory pathways	SOD, MDA, blood glucose	Reduced oxidative stress and hyperglycaemia	Imran et al., 2017 [84]
Naringenin (*Citrus paradisi*)	Flavanone	HFD-induced insulin-resistant mice	50 mg/kg, 8 weeks	Regulation of lipid metabolism via PPAR-α	Glucose, triglycerides, cholesterol	Improved insulin sensitivity and lipid metabolism	Mulvihill et al., 2010 [85]
Genistein (*Glycine max*)	Isoflavone	STZ diabetic rats	10 mg/kg, 4 weeks	Activation of cAMP/PKA signalling	Insulin secretion, glucose levels	Enhanced β-cell function and insulin secretion	Fu et al., 2010 [86]
Diosgenin (*Trigonella foenum-graecum*)	Steroidal saponin	STZ-induced diabetic rats	50 mg/kg, 30 days	Modulation of glucose metabolism enzymes	Blood glucose, glycogen, insulin	Reduced blood glucose and improved glycogen storage	Kalailingam et al., 2014 [87]
Ginsenoside Rb1 (*Panax ginseng*)	Triterpenoid saponin	HFD-induced diabetic mice	10 mg/kg, 6 weeks	Activation of PI3K/Akt pathway	Insulin sensitivity markers, glucose	Improved insulin signalling and glucose homeostasis	Xie et al., 2005 [88]
Gymnemic acids (*Gymnema sylvestre*)	Triterpenoid saponins	STZ diabetic rats	200 mg/kg, 6 weeks	Pancreatic β-cell regeneration	Blood glucose, insulin	Reduced hyperglycaemia and restored β-cell function	Shanmuga-sundaram et al.,1990 [89]
Trigonelline (*Trigonella foenum-graecum*)	Alkaloid	HFD diabetic mice	50 mg/kg, 8 weeks	AMPK pathway activation	Fasting glucose, insulin resistance	Improved glucose tolerance and insulin sensitivity	Zhou et al., 2012 [90]
Baicalein (*Scutellaria baicalensis*)	Flavone	STZ diabetic mice	50 mg/kg, 6 weeks	Anti-inflammatory and antioxidant pathways	IL-6, TNF-α, glucose	Reduced inflammation and hyperglycaemia	Li et al., 2011 [91]
Hesperidin (*Citrus sinensis*)	Flavonoid glycoside	STZ diabetic rats	100 mg/kg, 6 weeks	Antioxidant and lipid metabolism regulation	MDA, SOD, glucose	Improved oxidative stress and lipid profile	Pari et al., 2015 [92]
Chlorogenic acid (*Coffea arabica*)	Phenolic acid	HFD-induced diabetic mice	50 mg/kg, 8 weeks	Inhibition of glucose-6-phosphatase	Fasting glucose, insulin	Reduced hepatic glucose production	Ong et al., 2013 [93]

SHORTCOMINGS OF THE EXISTING EXPERIMENTAL STUDIES.

Despite the mounting evidence in support of the antidiabetic properties of the bioactive compounds that are produced by plants, a number of methodological and translational constraints limit their extraction of the bench to the bedside [94]. These gaps must be filled in to enhance the progress of phytotherapeutics to clinical relevance.

One of the main weaknesses is the excessive use of preclinical models. Most available data is in vitro experiments or animal experiments, especially streptozotocin-induced and high-fat diet induced diabetic rodents. Although these models are effective in replicating some of the metabolic disturbances found in T2DM, they are unable to fully explain the chronic and progressive, and multifactorial nature of human diabetes [15]. The evolution of the disease in the long term, the genetic variation, lifestyle factors, and multi-comorbidity are not easily replicated in the experimental animals. As a result, positive results in preclinical studies do not always have similar clinical advantages.

The other major challenge is that plant extracts are not standardized. The differences in species of the plants, geographical origin, culture, time of harvesting, and methods of extraction may have significant impact on the phytochemical composition [95]. Numerous studies do not adequately characterize or measure active constituents, which makes it difficult to recreate them and compare findings and results across studies. The standardized preparations and clear chemical profiling are needed so that the therapeutic efficacy could be established at all.

The discrepancies of dose choice and duration of treatment make the interpretation of experimental results even more difficult. The choice of doses is frequently arbitrary and not based on human-equivalent dosing approaches or even the justification of dosing. Furthermore, numerous studies focus on short-term, but not on long-term efficacy, safety, and toxicity measures. Such chronic metabolic diseases like T2DM need long-term control, thus, long-term data will be essential to assess the viability of the treatment.

In many studies, mechanistic exploration is also yet to be covered. Although antioxidant and anti-inflammatory effects are commonly described, very little is often elucidated on particular molecular targets, signalling pathways, and changes in gene expression. State of the art investigative tools, such as molecular docking, transcriptomic and proteomic studies, and pathway-oriented mechanistic studies are relatively under-used. The increased mechanistic knowledge would contribute to the scientific validation and contribute to reasonable drug development [96].

The clinical evidence in this area remains quite insufficient. Randomized controlled clinical trials on bioactivity of plant-derived bioactives in people with T2DM are not very common. Furthermore, there are difficulties associated with bioavailability, pharmacokinetics, herb-drug interactions, regulatory approval, which pose an obstacle to clinical translation. Complete safety data, especially those involving long-term use and use with traditional antidiabetic drugs are usually unavailable.

Finally, the fact that phytochemical mixtures are complex may be considered both the strength and a weakness. Although the interaction of constituents can enhance the effects of that treatment, it complicates isolating the active constituents and setting up a standard dose. Consequently, the development of formulations, quality control and mechanistic clarity becomes hard to attain due to this complexity.

Combined, these difficulties suggest the need to standardize approaches, carry out mechanistic research, and conduct solid clinical trials to exhaust the promise of plant-derived bioactives in the treatment of T2DM.

FUTURE PERSPECTIVES

The growing experimental evidence on the supporting effects of plant-derived bioactive compounds on the antidiabetic effect as well as organ-protective effects can serve as a good area to be investigated in the future. However, these promising results need to be translated into clinically practical curative measures with more organised, rigorous, and multidisciplinary research [95].

One of the priorities is to standardize plant materials and phytoconstituents. Further research is required on systematic identification of active compounds, detailed phytochemical profiling and rigid quality control that would provide consistency between batches. The use of sophisticated analytical methods like the HPLC, mass spectrometry and metabolomic profiling techniques can greatly enhance the characterization of compounds and enhance reproducibility of studies. Regulatory acceptability as well as clinical reliability will depend on standardization [97].

More importantly, more mechanistic exploration is required. Even though the antioxidant and anti-inflammatory effects are frequently reported, the exact framework of the interaction between the selected molecules is not always clear. A combination of omics-based technologies such as genomics, proteomics, and metabolomics, with molecular docking and pathway specific studies would give a global understanding of the effects of phytochemicals on major molecular targets of insulin signalling, mitochondrial activity, redox, and inflammatory cascades. These can also be used to discover new therapeutic targets.

The other research priority is to enhance the pharmacokinetic behaviour of plant bioactives. Phytochemicals in many cases are poorly bioavailable and metabolized or unstable thereby interfering with therapeutic action. Advanced drug delivery systems like nano formulations, liposomal carriers and polymer-based nanoparticles have provided possible means to improve absorption, inhibit active compound degradation and delivery to a specific tissue region [98].

It is equally important that there should be robust clinical evaluation. Randomized controlled trials should be carefully designed to establish safety, efficacy, optimum dosage, and long-term effects on individuals with T2DM. Long-term follow-up time must evaluate the effect of phytotherapeutics on diabetic complications and the possible herb drug interactions in its combination with the traditional antidiabetic drugs. Intensification of regulatory mechanisms and creation of standardized rules of herbal therapeutics will also contribute to their introduction into the evidence-based practice.

It also requires the need to investigate further polyherbal formulations and possibilities of synergistic combinations. Considering the multifactorial concept of T2DM, the phytochemicals acting on complementary molecular pathways when combined in different combinations can have an additive or synergistic effect. Such combinations can be systematically evaluated as combinations with a so-called systematic evaluation, which is supplemented with a mechanistic validation, potentially providing more comprehensive metabolic control.

Finally, an evidence-based complementary therapy of phytotherapeutics with conventional pharmacotherapy can contribute to improved disease and glycaemic control and prevents the occurrence of side effects. Further cooperation between pharmacologists, clinicians, phytochemists, and regulatory agencies will be required to grant the complete potential of plant-derived bioactive compounds in the treatment of diabetes.

CONCLUSION

Bioactive compounds of plant origin have become attractive players in terms of finding more holistic treatment approaches to type 2 diabetes mellitus (T2DM) and its related complications. There is extensive experimental evidence that these phytochemicals have a positive impact on coordinated changes in a number of molecular pathways. Plant bioactives address many of the fundamental derangements of the pathophysiology of T2DM by modulating insulin signalling, activating AMP-activated protein kinase (AMPK), controlling peroxisome proliferator-activated receptor gamma (PPAR-g), enhancing endogenous antioxidant defences, suppression of inflammatory responses, and inhibition of advanced glycation end product (AGEs) formation. Notably, they go beyond glycaemic regulation and provide protection to nephropathy, neuropathy, cardiovascular dysfunction, and wound healing impairment in experimental studies.

Such promising results notwithstanding, there are still major obstacles that phototherapeutics must overcome before it can be implemented into the mainstream of clinical practice. The lack of uniformity in extract composition, as well as non-standardized procedures, inconsistent dosage, and minimal clinical evidence over the long term, are still slowing the pace of translational research. In addition, as mechanistic understanding continues to grow, it would still take more sophisticated procedures with sophisticated molecular and systems-level studies to enhance the scientific validation.

In general, plant-based compounds have significant potential in the use as a complementary/alternative method in the management of diabetes. The therapeutic potential of these drugs will solely be achieved through stringent standardization, sound mechanistic clarification and properly designed clinical trials. As a result of a long-lasting interdisciplinary research and regulatory streamlining, phototherapeutics can become a part of the current antidiabetic treatment, just like the experimental intervention.

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HOW TO CITE: Sagar Pradhan, Kusu Susan Cyriac, Plant-Derived Bioactive Compounds Targeting Molecular Mechanisms of Type 2 Diabetes and its Associated Complications: Evidence from Experimental Studies, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 1824-1840. https://doi.org/10.5281/zenodo.21267536