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Review

Epigenetic Modulation of Diabetes Mellitus by Plant-Derived Polyphenols: Mechanistic Insights and Therapeutic Prospects

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Abstract

Diabetes mellitus is a complex metabolic disease characterised by chronic hypoglycemia, which results from the insulin secretion, insulin resistance or both. In recent times, evidence has proven the significant role of epigenetic modulations, particularly DNA methylation and histone modifications, in the progression and long-term persistence of diabetes. These modifications influence the gene expression associated with insulin signaling, glucose metabolism, and β -cell function and inflammatory pathways, which result in the contribution of metabolic dysfunction. Plant-derived polyphenols like curcumin and rutin exhibit antioxidant, anti-inflammatory and antidiabetic properties. Moreover, these compounds have remarkable potential to modulate the epigenetic mechanisms that ultimately lead to beneficial changes in gene expression. This review highlights the epigenetic mechanisms through which curcumin and rutin exert their therapeutic potential in diabetes mellitus, identifying the challenges in ongoing research and future scope in this field.

Keywords: diabetes mellitus; epigenetic modulations; DNA methylation; histone modifications; curcumin; rutin

1. Introduction

Diabetes mellitus is a chronic metabolic disorder that represents a complex disease with many different complications, and it is characterised by hyperglycemia arising from severe defects in insulin secretion, the action of the insulin or a combination of both (Powers, A. C.2021). The persistent increase in blood glucose level leads to damage of multiple organ systems, which include cardiovascular, renal, neural, and retinal tissues (Tomic et al. 2022). Despite advances in pharmacological management, the available antidiabetic therapies primarily target glycemic control and fail to address the underlying molecular dysregulation responsible for disease progression and other complications (Wu et al. 2023).

Recent findings indicate that diabetes mellitus is not only governed by genetic predisposition and imbalance in metabolism but is strongly influenced by epigenetic modifications (Rönn et al. 2023). Epigenetic modifications, including DNA methylation, histone modifications, and regulation by non-coding RNAs, play a key role in controlling gene expression without changing the existing DNA sequence (Cheng et al. 2018). In conditions like diabetes, persistent hyperglycemia induces abnormal epigenetic alterations that would promote insulin resistance, inflammation, oxidative stress and beta-cell dysfunction (Rönn et al. 2023). These abnormalities or changes can persist even after

normalisation of blood glucose levels; this is a phenomenon known as “metabolic memory”, which contributes to the persistent risk of diabetes and its complications (Chen et al. 2016).

Epigenetic dysregulation in diabetes is mainly caused by oxidative stress and inflammation (Rönn et al. 2023). Elevated production of reactive oxygen species and inflammatory mediators alters the activity of epigenetic enzymes such as DNA methyltransferases, histone acetyltransferases, and histone deacetylases (Kong et al. 2019). These changes can further lead to prolonged modifications or changes in the expression of certain genes associated with glucose metabolism, insulin signaling, lipid homeostasis, and vascular function (Ye et al. 2025). Moreover, targeting epigenetic pathways has gained significant consideration as it can modulate disease progression beyond systematic glucose control (Rönn et al. 2023).

Plant-derived compounds have significantly gained attention in recent times as they have emerged as a bioactive compound that has the potential to alter or influence epigenetic regulation in metabolic disorders. Some of the most discussed polyphenols, like curcumin, rutin and quercetin, are widely distributed in dietary sources and are very much known for their antioxidant and anti-inflammatory properties (Kaabi, 2022). Even though individual polyphenols have been studied extensively for their different properties, which include antidiabetic properties, a comprehensive understanding of their epigenetic modes of action remains poorly understood. Research has mainly focused on the glycemic control or general effects related to antioxidants, with limited emphasis on epigenetic regulation as a mechanism.

This review mainly aims to understand the role of plant-derived polyphenols, specifically curcumin, rutin and quercetin, in the epigenetic modulation of diabetes mellitus. From integrating the already existing experimental or proven studies from in vitro, in vivo, and other mechanistic studies, this review highlights how these compounds can influence the key epigenetic pathways involved in insulin signaling, inflammation, and oxidative stress. Furthermore, the therapeutic prospects, limitations and further research related to polyphenol-based epigenetic studies in diabetes management are discussed.

2. Epigenetic Mechanisms Involved in Pathogenesis of Diabetes Mellitus

2.1. DNA Methylation and Diabetes Mellitus

DNA Methylation is key regulator in epigenetic modulation. DNA methylation is the mechanism by which a methyl group is added onto the 5' cytosine residues in the CpG islands (Ahmed et al. 2020). This entire mechanism is catalysed by the enzyme DNA methyltransferases (DNMTs) (Nadiger et al. 2024). The two main activities that take place here are hypermethylation, which happens when the promoter region is methylated, resulting in repression of the genes, called as gene silencing. On the other hand, hypomethylation is when the promoters are not methylated, which would stay transcriptionally active and result in gene activation (Pinzón-Cortés et al. 2017). The two main DNMTs, which have a central role, are DNMT1, which maintains the methylation during cell division, while DNMT3a/3b establishes new methylation patterns in response to developmental or environmental cues (Castillo-Aguilera et al. 2017).

Pancreatic β -cells are the only specialised cells that can synthesise and secrete insulin. It is well established that insulin is essential for the glucose uptake by tissues such as the liver, muscle and adipose tissue (Rutter et al. 2015). Therefore, when the β -cells fail to do their function, it results in insulin dysregulation, which would further develop chronic hyperglycaemia; therefore, β -cell dysfunction is the core of diabetes pathogenesis (Frank & Tadros 2014). These β -cells express a highly specific set of genes, and therefore, they must maintain a stable identity while remaining metabolically flexible (Swisa et al. 2017). β -cells mainly rely on glucose-sensing pathways, suppression of cells other than β -cells, and they depend on epigenetic mechanisms, mainly DNA methylation, which enables the β -cell-specific genes to be active and to silence the genes that are not needed or harmful to insulin secretion (Sun et al., 2021). β -cells generally have low antioxidant capacity; they are always exposed to constant glucose fluctuations, which makes the β -cells

vulnerable (Sun et al., 2021). These fluctuations or alterations can alter the activity of the DNMTs and can induce abnormal methylation patterns. Hence, the epigenetic disruptions in β -cells can transform the transient metabolic stress into persistent defects in insulin secretion, which can contribute to the progression to diabetes mellitus (Del Prato et al., 2016).

While β -cells are the key to secrete insulin, other tissues are equally important in regulating glucose. Insulin signals the tissues to absorb the glucose or to suppress the glucose production (Lizcano & Alessi 2002). If these tissues become resistant to insulin, the normal insulin secretion cannot maintain the balance of glucose, and this condition is called as insulin resistance, which is the main reason for type 2 diabetes (Petersen & Shulman 2018). Genes like Insulin Receptor Substrate-1 (IRS-1) and glucose transporter in muscle and fat (GLUT4) are the essential genes for insulin to work efficiently (Li et al. 2015). Hypermethylation of the promoters of these genes can result in weakening the insulin signalling, which would result in the glucose staying in the blood instead of entering the cells (Zou et al. 2013). Each tissue, precisely each cell, has its own epigenetic modulation, which would either enhance or suppress the gene expression. When the DNA methylation pattern is abnormal, it would contribute widely to insulin resistance, and when it connects with β -cell dysfunction would together drive hyperglycaemia and type 2 diabetes (Frank & Tadros 2014).

When the blood glucose level is higher than usual, not only it affect the β -cells, liver or muscle but also affects the immune cells. The methylation can alter the genes to become either hypermethylated or hypomethylated (Frank & Tadros 2014). The hypomethylation of the promoters can over activate or the hypermethylation can under activate inflammatory genes like TNF- α , IL-6 (Ali et al. 2022). These epigenic changes can cause the immune cells to produce more inflammatory molecules that can damage tissues. This emphasises that methylation is a molecular mechanism which connects oxidative stress, inflammation and metabolic dysfunction in diabetes mellitus (Yara et al. 2015).

Even though the DNA methylation represents a stable epigenetic modification contributing to diabetes, it acts closely with other mechanisms like histone modifications, which regulate chromatin structure and gene accessibility in metabolic tissues.

2.2. Histone Modifications and Diabetes Mellitus

Histones are a family of proteins that are rich in lysine and arginine and are found in the nucleus of eukaryotic cells. DNA is wrapped around these proteins, which helps the DNA to achieve a compact shape by forming a structure known as a nucleosome, which is the basic unit of chromatin (An, 2007). The N-terminal of this protein can undergo modifications, which makes it dynamic and reversible. There are mainly two types of modifications: one is histone acetylation, which is controlled by histone acetyltransferases (HATs), that add acetyl groups and histone deacetylases (HDACs), that remove the acetyl groups (Martin et al., 2021).

Histones usually carry a positive charge because of the presence of lysine and arginine. Acetylation of histones can neutralise these positive charges on them, which would loosen up the DNA-histone interaction, resulting in gene activation. The second major type is the histone methylation, which refers to the addition of methyl groups to the specific amino acids on the histone terminal region, mostly to the histone H3 (Fallah et al., 2021).

2.2.1. Histone Acetylation

Histone acetylation is also one of the central epigenetic modulations that plays a significant role in regulating gene expression (Kukkala Kumar et al., 2024). This mechanism is mainly controlled by two enzymes: one, the histone acetyltransferases (HATs), which add acetyl groups to the lysine residues on histone and open up the chromatin structure, and second, the histone deacetylases (HDACs), which remove these acetyl groups and lead to condensation of the chromatin, which leads to gene repression. In diabetes mellitus, the changes being developed by the histone acetylation have created a strong impact on the β -cell dysfunction and insulin resistance. In pancreatic β -cells, the reduced acetylation on the promoter region of the Pdx1 gene, which is a transcription factor that is a

major component required for insulin production and β -cell identity, can cause abnormalities in the secretion and synthesis of insulin (Inoue et al., 2021). In the same way, changes in the patterns of histone acetylation in the liver and skeletal muscle can disrupt the expression of genes involved in glucose metabolism and insulin signalling, including the ones that are involved in regulating gluconeogenesis and GLUT4-mediated glucose uptake. Persistent and chronic hyperglycaemia and oxidative stress can also interfere with the balance between HAT and HDAC activity, leading to long-term and persistent epigenetic modulations. Overall, this contributes to insulin resistance, gene repression and β -cell failure, highlighting the significance in the development and progression of type 2 diabetes mellitus (Filgueiras et al., 2017).

2.2.2. Histone Methylation

Here, methylation does not alter the charge or loosen the interaction between the DNA and the histone; instead, it acts as a molecular tag that marks or signals the cells to turn on or turn off a particular gene. This process is regulated by the enzyme histone methyltransferases (HMTs), whose primary function is to add methyl groups. While the histone demethylases (KDMs), which remove them, ensure control of gene expression (Małodobra-Mazur et al., 2021). The outcome of histone methylation depends on the degree of methylation and the modified lysine residue. For example, histone H3 lysine 4 (H3K4) is associated with transcriptionally active chromatin and is most found at promoter regions of genes that are involved in glucose metabolism, insulin synthesis and β -cell function. Therefore methylation in H3K9 or H3K27 can result in chromatin condensation, which can cause gene repression, which plays an essential role in gene silencing. In diabetic conditions, abnormal methylation patterns can disrupt normal gene expression and can contribute to impaired insulin secretion and β -cell dysfunction. In addition, unwanted histone methylation in immune cells can also influence the expression of inflammatory genes, thereby linking epigenetic alterations to chronic inflammation in diabetes (Ma et al., 2025).

3. Therapeutic Epigenetic Modulation by Plant-Derived Polyphenols.

3.1. Curcumin

3.1.1. Source and Chemical Nature

Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a naturally occurring phenolic compound that is derived from the rhizome of *Curcuma longa* L. (turmeric), a plant that belongs to the Zingiberaceae family. Turmeric has been used for more than a thousand years as a flavouring spice, food colouring agent, traditional medicine, and insect repellent or pesticide. The yellow colour of turmeric is mainly due to curcumin, also known as diferuloylmethane (Sharifi-Rad et al., 2020).

Turmeric contains approximately 2-5% curcumin by its dry weight. Marketed curcumin formulations, collectively known as curcuminoids, mainly consist of three major components: curcumin I (diferuloylmethane, ~77%), desmethoxycurcumin (curcumin II, ~17%), and bisdemethoxycurcumin (curcumin III, ~3%). Among these, curcumin I is considered the most bioactive compound.

Curcumin is a crystalline yellow colour compound and demonstrates keto-enol tautomerism, with the keto form being stable in neutral and acidic environmental conditions, while the enol form is much more stable in alkaline conditions in the solid state. In addition to the natural curcuminoids, several other curcumin analogues, such as tetrahydrocurcumin, desmethoxycurcumin, bisdemethoxycurcumin, and synthetic derivatives, have also been developed to enhance biological efficacy and stability (Sharifi-Rad et al., 2020).

3.1.2. Epigenetic Modulation by Curcumin

As mentioned earlier, epigenetic modifications, specifically DNA methylation and histone modifications, play a major role in regulating gene expression in response to metabolic and environmental changes. In diabetes, the elevated levels of glucose levels can disrupt these mechanisms, which can lead to abnormalities in gene expression. It can further result in metabolic dysregulation, inflammation and other complications. One of the important modulators identified to modulate these epigenetic mechanisms is Curcumin, which exhibits protective effects through redox-dependent and enzyme-specific pathways (Paneni et al., 2021).

There is an increase in the reactive oxygen species (ROS) under diabetic conditions. This ROS can cause a significant change in the DNA methyltransferases (DNMTs), which play a significant role in transcription, and this alteration of modification can lead to altered methylation patterns that can contribute to pathological or abnormal gene expression. An experimental study was conducted where retinal pigment epithelial (RPE) cells were used as a model of diabetic retinopathy. These cells were exposed to a high glucose level, which showed an increase in oxidative stress and a disruption in DNA methyltransferases was observed. Curcumin was used to treat these cells. 25 μ M of curcumin was induced, which resulted in a significant reduction in the intracellular ROS levels and restored the DNMTs activity. Most importantly, curcumin specifically normalised the DNMT1's expression, which is majorly responsible for maintaining the DNA methylation during cell division. Therefore, these results explain that curcumin affects or supports the maintenance of existing methylation patterns rather than inducing newer ones. Another study that analysed LIN-1 methylation, which is basically a marker of global DNA methylation, showed no significant changes with curcumin, indicating that its effects are in a controlled and selective manner rather than causing unwanted widespread epigenetic modulation (Maugeri et al., 2018; Tang et al., 2022).

Curcumin not just influences DNA methylation but also influences histone modification, particularly histone acetylation. Histone acetylation is associated with gene activation, while histone deacetylation is linked to gene repression. Curcumin has been shown to inhibit histone acetyltransferases (HAT) activity, specifically targeting GCN5, leading to reduced acetylation of histone H3 at lysine residues K9 and K14. These modifications are associated with transcriptionally active chromatin. Therefore, their reduction may result in decreased expression of pro-inflammatory genes. While the excessive histone acetylation can contribute to the persistent activation of inflammatory pathways (Yun et al., 2011).

Overall, curcumin plays a significant role in epigenetic effects by reducing or controlling oxidative stress, restoring the enzyme activity of DNMTs, and by modulating histone acetylation. Curcumin, therefore, doesn't affect or cause changes in the whole genome; it focuses on only specific important pathways. The dual action of curcumin shows it as a potential epigenetic-based therapeutic agent in diabetes (Yun et al., 2011; Marcu et al., 2006).

3.1.3. Antidiabetic Mechanisms

Curcumin exhibits significant antidiabetic potential by improving glucose homeostasis, enhancing insulin sensitivity, and preserving pancreatic β -cell function. Several clinical studies have been conducted to study different conditions on patients with type 2 diabetes mellitus (T2DM). Studies have shown that curcumin supplementation significantly reduces fasting plasma glucose, glycated haemoglobin (HbA1c), and insulin resistance, which was indicated by lower HOMA-IR values (Chuengsamarn et al., 2012; Dehzad et al., 2023).

Curcumin has also been documented to improve β -cell function, which is evidenced by increased HOMA- β scores. Improvements in glycaemic control are often the results of reducing the body weight and body mass index (BMI), particularly in obese people with T2DM. Beyond this, curcumin supplementation has been actively associated with increased adiponectin levels and reduced leptin concentrations, which indicated the improved adipose tissue function and reduced systemic inflammation (Dehzad et al., 2023).

Preclinical studies using pancreatic β -cell lines and animal models have provided strong evidence for the cytoprotective effects of curcumin. In streptozotocin-induced diabetic models,

curcumin has been shown to reduce oxidative stress, reduce inflammation, and prevent β -cell apoptosis. Nano-formulated curcumin preparations have shown enhanced intracellular uptake and persistent release, resulting in effective protection against oxidative damage compared to the unformulated curcumin (Metawea et al., 2023).

Clinical trials that involve randomised, double-blind, placebo-controlled studies have experimentally demonstrated that ethanol-extracted curcumin efficiently improved glycaemic parameters, insulin resistance, and β -cell function in patients with T2DM, with minimal toxic effects. These findings contributed to understand the potential of curcumin as a safe and effective adjunctive treatment in diabetes management (Dehzad et al., 2023).

3.1.4. Limitations

Despite its persistent potential, the application of curcumin is quite limited because of its poor bioavailability, rapid metabolism, and limited systemic uptake. Moreover, most of the evidence on the epigenetic modulations is from cell-based assays or on animal-based studies; human clinical trials are rare, which contributes to the ambiguity in the dosage. To address these concerns, various strategies have been employed, such as nano formulations, encapsulation, and structural analogue development, which are being explored and used. Future research focuses mainly on optimising delivery systems, establishing standardised dosing regimens, and conducting large-scale clinical trials to fully elucidate the role of curcumin in diabetes prevention and management (Anand et al., 2007; Tabanelli et al., 2021).

3.2. Rutin

3.2.1. Source and Chemical Nature

Rutin, quercetin-3-O-rutinoside, is a naturally occurring compound (flavanol glycoside) that is widely present in the plant kingdom. The chemical structure of rutin comprises aglycone quercetin, which is linked at the C-3 position to a disaccharide compound composed of one glucose molecule and one rhamnose, the molecular formula $C_{27}H_{30}O_{16}$. Due to their extensive role in maintaining the capillary fragility, it was widely part of a flavonoids were widely referred to as 'vitamin P'. It was first isolated from *Ruta graveolens*, and it has been identified in several different plant categories, which includes plants like buckwheat, citrus fruits, tobacco, hydrangea etc. Rutin has culturally been used in order to manage vascular disorders like venous insufficiency, haemorrhoids, retinal haemorrhages, and diabetic microvascular complications by reducing the capillary fragility and permeability. Rutin has also been shown to exhibit impressive pharmacological properties, including antioxidant, anti-inflammatory, antidiabetic, cardioprotective, hepatoprotective, and neuroprotective activities (Tobar-Delgado et al., 2023).

3.2.2. Epigenetic Modulation by Rutin

In comparison to curcumin, rutin is not a strong direct inhibitor of epigenetic enzymes. It has an indirect activity which is mediated through oxidative stress reduction, by suppressing chronic inflammation and by improving metabolic homeostasis (Ghorbani, 2017; Pan et al., 2023). These mechanisms efficiently regulate the activity of DNMTs, HDACs, and histone methyltransferases in diabetic tissues. Therefore, rutin acts as a metabolic epigenetic stabiliser rather than an epigenetic drug like curcumin. Rutin helps in reducing the intracellular ROS, which prevents the oxidative damage to DNA and maintains normal DNMTs activity. By stabilising the DNMTs, it prevents the hypermethylation of insulin signalling genes like IRS-1, GLUT4, and reduces abnormal methylation of genes involved in glucose metabolism. In histone modifications, rutin's efficient lowering of the ROS plays a notable role, when there is an elevated glucose level in the circulatory system the concentration of ROS also significantly increases and this leads to the activation of histone deacetylases (HDACs) which would remove the acetyl group which would result in tightening of the DNA around histones making the genes less accessible leading to reduced gene repression. The rutin,

which lowers the oxidative stress, balances the cellular redox reactions that control or manage the gene activation and repression (Paneni et al., 2015; Wang et al., 2024).

Rutin also suppresses inflammatory mediators such as TNF- α and IL-6. By reducing the mediators, it prevents long-term epigenetic locking of inflammatory gene expression and limits immune cell-driven epigenetic damage in diabetic tissues. Rutin's antioxidant activity protects β -cell chromatin structure and prevents stress-induced epigenetic drift. This activity contributes to preserving the β -cell identity and persistent insulin secretion (Demirb ker et al., 2025).

3.2.3. Antidiabetic Mechanisms

Rutin exhibits its antidiabetic effects through several mechanisms that are interconnected with each other, involving regulating oxidative stress, inflammation, glucose metabolism, and insulin signalling (Guo et al., 2020). Oxidative stress plays a central role in the development of diabetes and its problems. Multiple other studies have demonstrated that rutin significantly increases endogenous antioxidant defence mechanisms by elevating the activity of certain enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, while decreasing lipid peroxidation markers such as malondialdehyde (Iqbal et al., 2024). Furthermore, rutin has also been shown to suppress the activation of nuclear factor- κ B (NF- κ B), which limits the synthesis of inflammatory mediators that effectively contribute to insulin resistance and tissue damage (Ragheb et al., 2023).

Experimental studies using diet-induced and streptozotocin-induced diabetic models have provided strong evidence for the antihyperglycemic activity of rutin. Rutin administration has been reported to significantly reduce fasting blood glucose and glycated haemoglobin levels, while also inhibiting non-enzymatic protein glycation and the formation of advanced glycation end-products. These effects are particularly relevant for preventing chronic diabetic complications. The antioxidant and anti-inflammatory actions of rutin further contribute to improved metabolic homeostasis by downregulating pro-inflammatory cytokines such as interleukin-6, interleukin-8, and tumour necrosis factor- α , which are known to impair insulin signalling (Iqbal et al., 2024).

At the molecular level, rutin has been shown to improve insulin sensitivity by enhancing insulin receptor activity and activating downstream signalling pathways, including IRS-1/IRS-2, phosphoinositide-3 kinase, and protein kinase B (AKT). Activation of this pathway promotes glucose uptake through increased translocation of GLUT4 to the cell membrane in insulin-responsive tissues, while simultaneously suppressing hepatic gluconeogenesis and promoting glycogen synthesis. Furthermore, rutin protects pancreatic β -cells from oxidative damage, thereby supporting insulin secretion and preserving β -cell function in diabetic conditions. In addition to its systemic metabolic effects, rutin has demonstrated protective effects against diabetes-associated organ damage, including attenuation of cardiac remodelling in diabetic cardiomyopathy and reduction of intestinal inflammation (Zou et al., 2025), highlighting its potential role in mitigating both metabolic dysregulation and diabetic complications (Guimar es et al., 2015).

Limitations

Despite its effective therapeutic capabilities, it has several limitations, one of such limitations or challenge associated with rutin is its poor bioavailability. Rutin has significantly lower solubility in an aqueous environment, which limits its absorption efficiency. Rutin often needs to get hydrolysed to quercetin by the gut microbes before absorption, which creates a higher variability with respect to each individual. In addition to this, rutin undergoes extensive metabolic transformation once it enters the human circulatory system. It might conjugate itself into many other compounds like glucuronide, sulphate or methylated metabolites, which may differ in the biological activity of rutin. Therefore, this creates confusion in confirming if the anti-diabetic activity is from the rutin or its conjugates.

Most of the studies with rutin are done on cell culture-based assays or by using rodent models, while human clinical trials, which include epigenetic endpoints and long-term glycaemic studies, are rare or absent; therefore, the translational evidence remains uncertain. In addition to this, the dosage of rutin varies across studies, hence there is no standardised therapeutic dose which exists for diabetes, which raises concerns about safety and long-term use. The sensitivity of rutin to light, heat and pH and poor stability limits its use in conventional formulation (Ou-yang et al., 2013).

4. Conclusions and Future Perspectives

Although diabetes mellitus has been extensively studied, most of the study focuses on metabolic outcomes such as hyperglycaemia, insulin resistance and oxidative stress mechanisms, which are considered as the primary effects, while epigenetic modulations are often pushed or treated as secondary effects (Paneni et al., 2021; Yang et al., 2022). Considerable evidence indicates that modulations in DNA methylation and Histone modifications occur early in disease progression and contribute to long-term metabolic dysregulation, highlighting further investigation is needed to delineate the underlying molecular mechanism(s) (Zhang et al., 2025).

Phytochemicals like curcumin and rutin exhibit strong antidiabetic and antioxidant properties, exploring their epigenetic mechanistic offers a fascinating area for future research. Most of the studies investigate individual compounds or single tissues, which limits the integrated functionality of these phytochemicals on diabetes. Furthermore, most of the evidence in the ongoing research is mostly from in vitro and animal studies, with limited clinical evidence supporting epigenetic modulations in humans (Paneni et al., 2021; Liang et al., 2013).

Future research should therefore focus more on epigenetic modulations than the abovementioned primary research. Targeting enzymes like DNA methyltransferases and histone-modifying proteins may lead to reverse persistent metabolic defects and can provide an excessive advantage over the existing antidiabetic therapies (Zhang et al., 2025; Odimegwu et al., 2024).

The comparative analysis associated with phytochemical(s) is much needed to determine when their overlapping redox reactions and epigenetic effects can act synergistically. Additionally, creating epigenetic markers associated with diabetes would enable early detection, diagnosis, and the employment of various therapeutic strategies (Ling & Rönn, 2016).

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