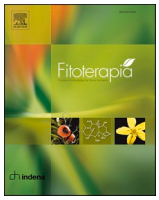
Fitoterapia 175 (2024) 105922



Contents lists available at ScienceDirect

Fitoterapia

journal homepage: www.elsevier.com/locate/fitote



Review

Bioactive alkaloidal and phenolic phytochemicals as promising epidrugs for diabetes mellitus 2: A review of recent development

Yusuf Oloruntoyin Ayipo [a,b,*], Chien Fung Chong [c], Hassan Taiye Abdulameed [d,e], Mohd Nizam Mordi [b]

[a] Department of Chemistry and Industrial Chemistry, Kwara State University, P. M. B., 1530, Malete, Ilorin, Nigeria
[b] Centre for Drug Research, Universiti Sains Malaysia, USM, 11800, Pulau Pinang, Malaysia
[c] Bioprocess Technology Division, School of Industrial Technology, Universiti Sains Malaysia, USM, 11800, Pulau Pinang, Malaysia
[d] Advanced Medical and Dental Institute, Universiti Sains Malaysia, USM, 11800, Pulau Pinang, Malaysia
[e] Department of Biochemistry, Kwara State University, P. M. B., 1530, Malete, Ilorin, Nigeria.

ARTICLE INFO

Keywords:
Metabolic disorders
Type 2 diabetes
Epigenetic regulatory mechanism
Phytotherapy
Antidiabetic epidrugs

ABSTRACT

Type 2 diabetes (T2D) remains a major chronic metabolic disorder affecting hundreds of millions of the global population, mostly among adults, engendering high rates of morbidity and mortality. It is characterized by complex aetiologies including insulin deficiency and resistance, and hyperglycemia, and these significantly constitute therapeutic challenges. Several pathways have been implicated in its pathophysiology and treatment including the epigenetic regulatory mechanism, notably, deoxyribonucleic acid (DNA) methylation/demethylation, histone modification, non-coding ribonucleic acid (ncRNA) modulation and other relevant pathways. Many studies have recently documented the implications of phytochemicals on the aforementioned biomarkers in the pathogenesis and treatment of T2D. In this review, the cellular and molecular mechanisms of the epigenetic effects of some bioactive alkaloidal and phenolic phytochemicals as potential therapeutic alternatives for T2D have been overviewed from the recent literature (2019–2024). From the survey, the natural product-based compounds, **C1-C32** were curated as potent epigenetic modulators for T2D. Their cellular and molecular mechanisms of anti-T2D activities with relevant epigenetic biomarkers were revealed. Although, more comprehensive experimental analyses are observably required for validating their activity and toxicological indices. Thus, perspectives and challenges were enumerated for such demanding future translational studies. The

Abbreviations: ADA, American Diabetes Association; adipor1, Adiponectin-adiponectin receptor 1; ADP, Adenosine diphosphate; AIDS, Acquired immunodeficiency syndrome; AMPK, Adenosine monophosphate-activated protein kinase; CAT, Catalase; CDC, Centre for Disease Control; CGM, Continuous glucose monitoring; circRNAs, Circular RNAs; CKD, Chronic kidney disease; CBP, CREB-binding protein; CD, Cluster of differentiation; COX-2, Cyclooxygenase 2; CpG, Cytosine-phosphate-guanine; DKD, Diabetic kidney disease; DM, Diabetes mellitus; DNA, Deoxyribonucleic acid; DNMT, DNA methyltransferase; DPP, Diabetes Prevention Programme; EASD, European Association for the Study of Diabetes; eNOS, endothelial nitric oxide synthase; EZH2, Zeste homolog 2; FAD, Flavin adenosine dinucleotide; FBG, Fasting blood glucose; FDA, Foods and Drugs Administration; GDM, Gestation diabetes mellitus; H3K4me2, Dimethylation of lysine 4 on histone H3; H3K4me3, Trimethylation of lysine 4 on histone H3; H3K9me2, Dimethylation of lysine 9 on histone H3; HAT, Histone-acetyltransferase; HbA1C, Haemoglobin A1C; HDAC, Histone deacetylase; HDMT, Histone demethylase; HFD, High-fat diet; HIPK3, Homeodomain interacting protein kinase 3; HIV, Human immunodeficiency virus; HMT, Histone methyltransferase; 11β-HSDs, 11β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenases; IDDM, Insulin-dependent diabetes mellitus; IGF1R, Insulin-like growth factor 1 receptor; IL, Interleukin; IR, Insulin receptor; IRS-1, Insulin receptor substrate 1; JAK2, Janus kinase 2; LSD, Lysine-specific demethylase; MALAT1, Metastasis-associated adenocarcinoma transcript 1; MAPK, Mitogen-activated protein kinase; MDA, Malondialdehyde; miRNA, Micro ribonucleic acid; MLL2, Lysine methyltransferase 2; MMP-14, Matrix metalloproteinase 14; mTOR, Mammalian target of rapamycin; NAD, Nicotinamide adenine dinucleotide; ncRNA, Non-coding ribonucleic acid; NFLD, Non-alcoholic fatty liver disease; NIDDM, Noninsulin-dependent diabetes mellitus; NOAEL, Non-observed-adverse-effect level; NOD, Nucleotide oligomerization domain; NF-κB, Nuclear factor kappa B; PARP, Poly (ADP-ribose) polymerase; PCK1, Phosphoenolpyruvate carboxykinase 1; PDN, Painful diabetic neuropathy; PDX-1, Pancreatic duodenal homeobox-1; PI3K, Phosphatidylinositol 3-kinase; PTP1B, Protein tyrosine phosphatase 1B; qRT-PCR, Real-time quantitative reverse transcription polymerase chain reaction; RNA, Ribonucleic acid; ROS, Reactive oxygen specie; SDR, Short-chain reductase; SETD7, SET domain-containing protein 7; Sirt, Sirtuin; SOD, Superoxide dismutase; STAT3, Signal transducer and activator of transcription 3; STZ, Streptozotocin; T2D, Type 2 diabetes; TLR4, Toll-like receptor 4; TXNIP, Thioredoxin interacting protein; UTR, 3′ untranslated region; LncRNA, Long non-coding RNA.

* Corresponding author at: Department of Chemistry and Industrial Chemistry, Kwara State University, P. M. B., 1530, Malete, Ilorin, Nigeria.
E-mail address: yusuf.ayipo@kwasu.edu.ng (Y.O. Ayipo).

https://doi.org/10.1016/j.fitote.2024.105922
Received 22 October 2023; Received in revised form 16 March 2024; Accepted 23 March 2024
Available online 27 March 2024
0367-326X/© 2024 Elsevier B.V. All rights reserved.

review reveals advances in scientific efforts towards reversing the global trend of T2D through epigenetic phytotherapeutics.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease inclusively characterized by insufficient pancreatic insulin production, resulting in hyperglycaemia (high blood sugar) [1]. It is termed a "silent killer" that usually displays a long-term effect and has been recognised as a major public health challenge globally [2]. In 2019, its global prevalence was alarming with an estimated 463 million carrier individuals among the world population. The number has been projected to increase to 578 million and 700 million by 2030 and 2045 respectively, indicating a serious threat to public health concern. The disease understandably affects more urban dwellers than rural settlers and similarly, is more popular in high-income countries than the low-income counterparts [3].

1.1. Types of diabetes

Based on the mechanisms of prognosis implicating insulin, DM is broadly classified as insulin-dependent DM (IDDM) and noninsulin-dependent DM (NIDDM) [2]. According to the American Diabetes Association (ADA) [4], DM is further categorised into:

1. Type 1 diabetes: reportedly caused by the destruction of the autoimmune β-cell which induces insulin deficiency.
2. Type 2 diabetes (T2D): usually results from a gradual and frequent loss of insulin secretion by β-cell, mostly induced by insulin resistance.
3. Gestation diabetes mellitus (GDM): oftentimes manifested during the second or third trimester of pregnancy without pre-pregnancy indications [3,4].
4. Specific types: specifically caused by other factors. These include:

- Monogenic diabetes syndromes e. g. neonatal and maturity-onset diabetes (usually affecting neonates and young people respectively.
- Exocrine pancreatic diseases e. g. pancreatitis and cystic fibrosis.
- Chemical- or drug-induced diabetes *e.g.* as aftereffects of treatments of organ transplantation and human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) [4].

Prominently, T2D exhibits a multifarious metabolic pathophysiology, implicating diverse genetic and epigenetic pathways, unusual biomarkers and irregular metabolism of some life-essential foods including carbohydrates, proteins and lipids. It remains the most complex DM type in clinical management with a low response to therapeutics and places the highest burden of diabetes on the global economic and healthcare systems [5–7]. Therefore, T2D is the main focus of this review.

1.2. Symptoms, pathogenesis and risk factors of T2D

According to some recent reports, factors that expose individuals to high risks of T2D include abysmal life style, non-regulated diet, physical inactivity, smoking, stress and depressive conditions, cardiometabolic factors [4,8,9], obesity [10], genetic changes and epigenetic aberrations such as DNA methylation/demethylation [1,11,12], posttranslational modifications of histone and transcription factors, lysine demethylation [13] constituting essential biomarkers. Some of the epigenetic changes including the methylation of DNA could be driven by environmental factors such as the prevalence of as chronic kidney disease (CKD) among a group of people [14].

Insulin resistance and reduced muscle quality are some major hallmarks of T2D. The effects of the T2D-inclined myopathy in forms of impaired muscle quality are reportedly caused by an irregular flux of the intracellular Ca^{2+} ion [$(Ca^{2+})i$], inducing a dysfunctional skeletal muscle contractile [15,16]. The risks of hip and proximal humeral fractures, as well as non-vertebral fractures are also associated with prediabetes and T2D [17,18], especially in carrier individuals above 50 years of age [19]. Other bone-related manifestations including decreased bone mass and increased bone fragility have also been reported [20]. DM critically constitutes a major risk factor for deadly clinical conditions such CKD [21] and its pathological renal fibrosis features. From a recent overview by Cheng and co-workers, almost half of all T2D patients and one-third of T1D carriers will experience CKD [22], indicating a significant connection. With other chronic manifestations, T2D engenders low quality of life and significantly contributes to disease-related mortality globally [12].

1.3. Diagnosis and screening of diabetes

The common diagnostic and screening methods of detecting diabetes and prediabetes include the haemoglobin A1C (HbA1C), fasting blood glucose (FBG), random blood glucose and 2-h blood glucose during 75-g oral glucose tolerance tests. The suitability and frequency of the tests vary across individuals with considerations for age, body size, family disease history, physical activity, race/ethnicity, cholesterol level, weight at birth and presence of other clinical conditions such as acanthosis nigricans, HIV, hypertension, obesity, pregnancy and polycystic ovary syndromes *etc.* [4].

1.4. Biomarkers and therapeutic targets

The dysfunction of the α- and β-cells significantly contributes to the progression of T2D through various mechanisms suggestively including a partial loss of identity. Although, its prevalence, cellular states, plasticity and functional outcome remain less precisely understood [23]. Therapeutic targets include insulin receptor (IR), α-amylase, and α-glucosidase [2]. Generally, a new class of small non-coding ribonucleic acids (RNAs), microRNAs (miRNAs) reportedly modify some prominent disease-associated genes and pathophysiological conditions [24], making them an interesting target in the scientific trends of disease management. Downregulation of the VPS39 gene could engender unpleasant alterations to the muscle stem cells (myoblasts) and myotubes, commonly observed in individuals with T2D. In addition, deficiency of the VPS39 gene has been linked to several T2D-associated pathophysiologies such as impaired autophagy, dysfunctional myogenic regulation, distorted differentiation, reduced glucose uptake, and irregular epigenetic programming [16]. These make the gene, VPS39 an important biomarker and therapeutic target for checkmating the prognosis and progression of T2D. Other biomarkers including the prominent targets for T2D-related pathophysiologies including inflammation and oxidative stress [25].

1.5. Comorbidities and complications of diabetes

Common comorbidities of T2D include cancer, dementia and impaired cognitive functions, non-alcoholic fatty liver disease (NFLD) [4] and diabetic kidney disease (DKD) [26]. Other complications commonly experienced by diabetes-burdened individuals include painful diabetic neuropathy (PDN) characterized by spinal microglia-inclined neuroinflammation [27], stroke, heart and renal failures, blindness, amputation [28] and kidney failure [12]. Being a metabolic disorder, DM shares some common pathways with cancer, including fatty acid oxidation [29]. Sometimes, DM manifests as a pre-existing

condition in pregnancy. A recent systematic review by Chivese and co-researchers indicates that even though there is a low prevalence of pre-existing diabetes in pregnancy overall, the number of such clinical cases has increased significantly between the years 1990 and 2020 [30].

1.6. Preventive and treatment interventions for T2D

Even though, prevention is understood to be cheaper than treatment of diabetes [9], still no preventive medication has been approved yet by the US Foods and Drugs Administration (FDA) for diabetes. However, from several experimental evaluations, metformin remains the most potent candidates. [4,8]. Its mechanisms of anti-T2D include the suppression of glucose-induced oxidative stress *via* several pathways [20]. Canagliflozin has also been overviewed as a promising therapeutic candidate for T2D–associated DKD [31]. Other recommendations for effective management of diabetes as provided by the American Diabetes Association include timely decisions with evidence-based guidelines and healthcare supports, the application of the Chronic Care Model and easy accessibility of diabetic patients to care systems [4]. Additionally, Diabetes Prevention Programme (DPP) also include weight monitoring, regular exercise and intensive life-style behavioural regulation [4,32].

The effectiveness and suitability of treatment options for individuals depend mostly on glycaemic and weight levels, underlying physiological conditions, drug side effects, control of medication regimen and accessibility to treatments [4]. For instance, an up-regulation of HbA1C to improve glycaemic control through the use of continuous glucose monitoring (CGM) approach has been proved beneficial [33]. Similarly, the enhancement of CGM and accessibility to endocrinology experts through social welfare approaches such as eConsult has been demonstrated to facilitate the delivery of adequate healthcare to T2D patients [34]. Various therapeutic advantages including lower costs, minimal side effects and patients' choices contribute to the rising interest in precision medicine application in the management of T2D according to the ADA and European Association for the Study of Diabetes (EASD) [35].

1.7. Phytotherapy for T2D

Among the emerging dietary phytomedicines amenable for effective prevention and treatment of T2D from shreds of clinical and pre-clinical experimental evidence include the flavonoids [36], polyphenols, non-flavonoid polyphenols and alkaloids. A recent systematic review by Delpino and Figueiredo projects the supplementation of resveratrol, a renowned natural polyphenol with strong antioxidant properties as an effective preventive candidate for T2D [9]. However, no details of cell-based analyses including the pharmacological targets and mechanisms of action of the compound have been reported. As such, further understanding of the therapeutic implications of such active phenolic compounds on epigenetic targets for T2D remains demanding.

Currently, around 12 different classes of drugs have been approved by the FDA for regulating blood sugar and modifying the course of DM. However, most of these medications are prescribed with little consideration for medical factors including side effects, comorbidities, cost and patient preference, and complicated biological mechanisms [35]. Progressively, the implications of epigenetic mechanisms in the initiation, progression and management of T2D and some comorbidities are unignorably essential as recently overviewed [12,22,24,37,38]. However, the modulatory contributions of therapeutic agents to such mechanisms remain sparse. In 2019, Huang and co-researchers surveyed some natural products as epigenetic modifiers for some chronic diseases generally [39] with less attention specifically to T2D. In addition, Menezes and *co*-workers reviewed the anti-T2D potential of some polyphenols in humans [40], however, the mechanisms of such activity remain underexplored. Similarly, the antidiabetic potential of some secondary metabolites was surveyed with less specificity on epigenetic alterations. In all, an in-depth focus on prominent epigenetic biomarkers of T2D such as DNA methylation/demethylation, histone modification and non-coding RNA (ncRNA)-associated gene silencing on the devastating disease remains underreported. Secondly, the modulatory contributions of vast polyphenolic and alkaloidal contents of the abundant, safer and economical natural products on such therapeutic epigenetic mechanisms are sparsely reported. Considering these shortfalls in these interestingly promising pathways for effective management of T2D, especially through the aforementioned critical biomarkers, further revelation of the state-of-the-art in this regard remains crucial for a timely suppression of the unpleasant trend of T2D globally.

In this overview, the mechanistic significance of various epigenetic biomarkers to the prognosis of diabetes was expanded. Furthermore, the antidiabetic effects of natural phenolic and alkaloidal compounds identified as promising epidrug potentials were analytically curated from 2019 to present-day literature, revealing detailed biochemical analysis and underlying epigenetic mechanisms.

2. Epigenetic mechanisms and pharmacology of diabetes

Diabetes is a metabolic disorder, due to a lack of insulin release from the β-cells and the abnormally high production of glucagon from the α -cells of the pancreas. However, epigenetic modification is a heritable alteration in phenotypic gene expression without any changes in the DNAsequence [41]. These modifications can be passed from one organism to its progeny. Epigenetic factor encompasses cytosine methylation, histone modification and non-coding miRNA. Several studies have found that epigenetic modification plays a significant role in the functioning of pancreatic islet cells [42]. The following transcriptional factors and genes are involved in the functioning of β-cells such as *INS*, *PDX-1*, *PPARGC1A,* and *GLP1R* which were hypermethylated in the case of diabetic patients [42]. Moreover, hypermethylation leads to transcriptional repression of specific genes in diabetic islets and which resulted in β-cell disruption in T2D. Notably, hyperglycaemia leads to increased DNA methylation at *PDX-1* and *INS* in β-cells [42]. The epigenetic mechanisms and diabetes are fully discussed below.

2.1. DNA methylation/demethylation

DNA methylation/demethylation is one of the epigenomic mechanisms that are associated with hallmark of T2D [37]. It is aided by S-adenosyl-methionine which acts as a methyl donor for methylation of cytosine residues (C-5 position) to yield 5-methylcytosine. This process is catalysed by DNA methyltransferases (DNMTs) and the regulation of these enzymes has a vital role in the progression of diabetes most especially in mitochondrial DNA [43]. In the mammalian genome (promoters, enhancers, gene bodies, and repetitive sequences), the majority of event takes part in CpG (cytosine-guanine) sites, but in some case, it also occurs in non-CpG sequences [44]. Depending on the region of genome, their actions can vary [42]. Typically, dense CpG methylation is responsible for maintaining long-lasting gene silencing by inhibition/avoiding transcription factor binding or by recruiting methylated-DNA binding proteins and their co-repressor protein partners [45]. Contrastingly, diminished CpG methylation promotes a permissive chromatin state to enhance gene transcription [46].

In recent years, a good number of studies have consistently reported a strong link between the CpG methylation and hyperglycaemia, making it convincing that DNA methylation profiles alterations are closely associated with the escalating T2D epidemic [47–49]. Accumulating evidence reveals that epigenetic changes caused by methylation may lead to the modifications in metabolic imprinted genes, resulting in the up- or down-regulation of pancreatic development, cell function, peripheral glucose uptake, and insulin resistance [47]. Importantly, these changes occur predominantly in T2D-related tissues, such as the pancreatic islets and insulin-target bodily parts (skeletal muscle, adipose tissue, and liver) [48].

Research findings have confirmed a negative correlation between the

expression of pancreatic duodenal homeobox-1 (PDX-1) mRNA and DNA methylation at the CpG site, alongside an inverse relationship between DNA methylation at CpG site within the enhancer region and gene expression levels. In the pancreatic islets of T2D patients, there is an observed increase in DNA methylation at multiple CpG sites of *PDX-1* gene promoter and its enhancer, causing reduced PDX-1 mRNA expression and subsequent interference with insulin secretion [47]. Similarly, this phenomenon extends to other genes relevant to pancreatic islet function, including *PPRGC1A*, *TCF7L2*, *FTO*, *KCNQ1*, *CDKN1A*, *PDE7B*, *SEPT9*, and *EXOC3L2* [50], all of which hold significant roles in regulating insulin and glucagon secretion/exocytosis [50]. In addition, hepatic genes such as *PRKCE*, *ABR*, *ARHGEF16*, *CTBP1*, *CCND1*, and *WNT11*, as well as skeletal or adipose tissue genes such as *PDK4* and *PPARGC1A*, have been found to correlated with insulin regulation, further supporting the effects of DNA methylation in the T2D pathophysiology [48].

2.2. Histone modification

Histone modification in eukaryotes cells involves four core histone proteins (H2A, H2B, H3 and H4), wherein lysine residues are susceptible to various modifications such as acetylation, methylation, phosphorylation, glycosylation and adenosine diphosphate (ADP) ribosylation. Increased acetylation of lysine residues on the amino-terminal by the histone-acetyltransferases (HATs) induces transcriptional activation, whereas decreased acetylation histone deacetylases (HDACs) leads to transcription repression [42]. When the acetyl groups are added, it would reduce the interaction between histones and DNA, giving more space for the transcriptional machinery to access, while removal of acetyl groups condense the histone and compress chromatin to inhibit gene transcription [42].

The methylation of histone mainly happens at the lysine or arginine residues, with the addition of one to three methyl groups. Methylation of histone protein can either activate or repress the transcription, depending on the gene region and the level of modification. Trimethylation of lysine 4 on histone H3 (H3K4me3) is associated with an active gene expression, but dimethylation (H3K4me2) can result in both inactive and active euchromatic genes, and dimethylation at lysine 9 (H3K9me2) generally leads to gene silencing [51]. In fact, histone methylation is much more stable and durable than histone acetylation.

Studies have broadly examined the epigenetic signature of aberrant histone modifications in patients with T2D compared to control subjects. Mainly, regulator of this event (*e.g.*, HDACs) were found to be significant in controlling of endocrine function, β-cell proliferation, function, and glucose homeostasis [47,52]. Under hyperglycaemia conditions, this profile becomes dysregulated, predisposing individuals to T2D features [53], not limited to the development of insulin resistance [54] and impairment of glucose-stimulated insulin secretion [55]. Besides, many genes have been identified with abnormal expression accompanied by aberrant epigenetic profiles. This is exemplified by histone modifications at the *PDX-1* promoter, reducing its expressions, thereby promote β-cell dysfunction [47]. However, these changes are reversible with the use of HDAC inhibitor, which decrease the recruitment level of H3K9me2 [47].

2.3. Non-coding RNA-associated gene silencing

Non-coding RNAs, which lack open reading frames for translation, represent a highly abundant and functional important class of RNAs. They include short ncRNAs with <200 nucleotides (such as miRNAs), as well as longer variants with >200 nucleotides such as long ncRNAs (LncRNAs) and circular RNAs (circRNAs) [51].

Micro RNAs, single-stranded RNA molecules measuring ~21–23 nucleotide in length, exert drastic influence over the output of many protein-coding genes by targeting 3′ untranslated region (UTR) of mRNAs, thereby regulating diverse biological processes vital to cellular function. Dysregulation of miRNAs has been implicated in multiple diseases, including cancer, diabetes, and Alzheimer's disease [51]. Plenty of literatures out there demonstrates that elevated blood glucose levels induce huge changes in miRNA expression profiles within diabetes-related bodily parts, correlating with the onset, severity, and complications of T2D [56,57]. Relevantly, they are among the crucial biomarkers [37]. For example, up-regulation of miRNAs (miRNA-195) can disrupt IR protein expression by binding complementary sequences within its 3'-UTR, consequently impeding insulin-receptor interactions and compromising liver insulin sensitivity [58]. Besides, miRNAs play important roles in metabolic controls overall [59].

LncRNAs, another subtype of ncRNAs exceeding 200 nucleotides in length, functionally regulate gene expression at the epigenetic level without encoding proteins. They play roles in the aetiology and pathophysiology of diabetes, as well as in response to hyperglycaemic conditions [60]. For instance, studies have elucidated that lncRNA metastasis-associated adenocarcinoma transcript 1 (MALAT1) induces the dysfunction of β-cells by reducing H3 histone acetylation at the *PDX-1* promoter, subsequently inhibiting the expression of PDX-1, and thereby suppressing insulin secretion [47]. CircRNAs, characterized by their closed circular and lack of protein-coding potential, exhibit structural stability and tissue specificity. Studies have highlighted their significant contributions to the occurrence and development of T2D. For example, circRNA homeodomain interacting protein kinase 3 (HIPK3) has been shown to cause hyperglycaemia and insulin resistance by sequestering miR-192-5p and up-regulating a transcription factor, FOXO expression. Next, among various identified circRNAs, circRNA Ankyrin repeat domain 3 (ANKRD36) was notably found to be significantly up-regulated in T2D patients in comparison to controls [47].

2.4. Other relevant biomarkers for the prognosis and treatment of diabetes

2.4.1. Protein tyrosine phosphatase 1B

Protein tyrosine phosphatase 1B (PTP1B) comes under the family of PTP enzyme family having 435 amino acids, encoded by PTpn1 genes with a molecular weight of 50 kDa [42]. PTP1B in unphosphorylated form has several functions such as cell differentiation, growth, and apoptosis. PTP1B has mainly two domains, the N-terminal domain, and the C-terminal domain. In the insulin pathway, PTP1B dephosphorylated the tyrosine residues 1162 and 1163 which resulted in the discontinuation of the tyrosine kinase receptor cascade. The attachment of insulin with IRs leads to IR phosphorylation which resulted in the activation of secondary messengers which helps in the regulation of glucose homeostasis [42]. PTB1B commands the interplay between endogenous insulin receptor substrate 1 (IRS-1) and IRS-2 that regulates the action of insulin in the liver and several tissues. Hence, PTB1B has an important role in insulin resistance, as it is a crucial drug target in the management of T2D.

2.4.2. 11β-hydroxysteroid dehydrogenase

11β-hydroxysteroid dehydrogenase (11β-HSDs) is a member of the short-chain reductases (SDR). It catalyzes the interconversion between the active glucocorticoids (corticosterone, cortisol) and the inert 11-keto forms (cortisone, 11-dehydrocorticosterone). 11β-HSD has several isoforms in humans, which are available in the liver, brain, adipocytes, lung, and other tissues. It is responsible for maintaining sufficient exposure of relatively low-affinity glucocorticoid receptors to their ligand [43]. Glucocorticoids increase glucose output in the liver, induce fat accumulation, and dampen glucose-dependent insulin sensitivity in the adipose tissue, thus increasing the risks of metabolic syndrome.

Cortisol plays a pivotal role in diabetes. Indeed, the abnormal regulation of glucocorticoid metabolism was linked to T2D. The antagonism of hepatic glucocorticoid receptor was found to reduce glucose levels in the serum of diabetic mice and to ameliorate insulin resistance. Thus, 11β-HSD is a potent therapeutic target whose inhibition might serve in the treatment of T2D [43].

2.4.3. Estradiol and 17β-hydroxysteroid dehydrogenase

17β-hydroxysteroid dehydrogenases (17β-HSDs) play key roles in the first step of the degradation of androgen and estrogen as well as the last step in their activation. The weaker estrone (E1) can be synthesized from the more potent estrogen, 17β-HSD2 catalyzes the production of E1 using nicotinamide adenine dinucleotide (NAD) as a cofactor. Conversely, E1 can be converted to E2 by reductive 17β-HSDs, including the highly active 17β-hydroxysteroid dehydrogenase 1 (17β-HSD1). The 17β-HSD1 isoform has a higher specific activity than the 17β-HSD2 enzyme. The 17β-HSD1 has a dual function, as it is also slightly involved in catalyzing the conversion of active androgens, such as 4-androstenedione, to inactive ones, *e.g.*, testosterone. Thus, accumulation of the circulating E2 in serum might be indicative of estrogen resistance. This indeed might be linked to metabolic deficiency and T2D. As a result, 17β-HSD1 might provide a good therapeutic target for inhibitory drugs for the treatment of diabetes. Nonetheless, most inhibitors of this steroid-converting enzyme are estrogen analogues, which poses an obstacle to the clearance of their estrogenic activities [43].

3. Epigenetic modulation of diabetes by alkaloids and phenolic compounds: prevention and therapy

The development of effective drugs for T2D remains a therapeutic challenge, primarily due to the complex nature of its pathology [61]. Chronic hyperglycaemia exerts deleterious effects on various organs involved in T2D, promoting epigenetic changes that persists and contribute to metabolic memory. This leads to irreversible microscopic to macroscopic alterations and increasing the likelihood of treatment failure [62]. However, recent advancements in molecular biology, particularly through epigenome-wide association studies, an array-based technique, have unravelled the critical role of epigenetic modifications in driving multiple metabolic abnormalities within the human epigenome [6,63].

Remarkably, these modifications demonstrate inherent reversibility, where their progression or regression is contingent upon genetic stressors and environmental factors [42]. This intriguing discovery paves the way for the potential utilization of specific small molecules with epigenetic activity, commonly referred to as epidrug candidates, to precisely manipulate these reversible modifications that contribute to the hyperglycaemic milieu associated with T2D [51,64]. Epidrugs can act in various mechanisms, such as epigenetic enzyme inhibition and therapy-induced epigenetic mechanisms alteration, among others [7]. Notably, the use of phytochemicals in the form of epidrugs has emerged as a highly acclaimed approach and has proven to be a resounding success, mainly due to the accessibility of relatively safe bioactive substances [6,65].

Polyphenols are natural products biosynthetically produced by plants as secondary metabolites with structural features including phenyl ring(s) and hydroxyl substituents. They are vast in dietary materials such as fruits, vegetables, seeds, nuts, flowers and other plant parts. They are also found in drinks are beverages including coffee, tea and wine, performing nutraceutical activities. As an essential class of natural phytochemicals, they have been explored for medicinal antagonistic effects on various categories of chronic diseases affecting humans with interesting outcomes [66–71]. Some of the potential antidiabetic phenolic and alkaloidal candidates are derived from renowned nutraceuticals and ethnopharmacological plants [72,73]. These include curcumin, epicatechin gallate, resveratrol [74–77], berberine [78] and baicalin [79].

Studies have also shown that a regular intake of their dietary sources interrupts the prognostic pathways and attenuates diabetes [68] inclusively through a mechanistic modulation of miRNAs [74]. Some polyphenols from Carob pod were also reported as promising suppressors of adipocyte differentiation through the regulations of the adipose tissues and adipocyte hypertrophy, renowned pathways of DM-associated obesity [80]. Similarly, a clinical study of the polyphenolic extract of pomegranate pod supported its beneficial suppressive effects on the inflammatory and oxidative stress markers of DM [25].

3.1. DNA methylation/demethylation

DNA methyltransferases are divided into two major types: maintenance methylase (DNMT1) and *de novo* methyltransferases (DNMT3a, and DNMT3b). Targeting them has the potential to reverse aberrant DNA methylation events, such as hypo- or hyper-methylation, which are known to influence gene function linked with T2D [11]. As reported by Yang et al., **epigallocatechin-3-gallate (C1)** derived from *Camellia sinensis* exhibits demethylation properties and holds promise as epigenetic modulation. An 8-week treatment with this flavanol (50 mg kg^{-1} day^{-1}) in diabetic *db/db* mice inhibits the methylation level of *Klotho* gene promoter *via* the reduction in DNMT3a (reduced by >2-fold), hence promoting an up-regulation in Klotho expression (increased by >2.5-fold). Similarly, treatment (at a concentration of 1 μM) of a high-glucose-stimulated HK-2 cell line not only improved cell viability but also showed a dose-dependent up-regulation of Klotho expression (approximately 3-fold). Additionally, two of the **C1**-treated models (*in vivo* and *in vitro*) demonstrated an up-regulation of DNMT3b expression, while DNMT1 expression displayed a moderate down-regulation. As such, the restoration of Klotho levels by **C1** exhibit a protective function through the inhibition of oxidative stress, fibrotic, and inflammatory pathways. Yet, in the absence of *Klotho* gene, **C1** intervention failed to decrease oxidative stress, fibrosis, and inflammatory markers. Interestingly, these epigenetic modulations can promote renal protective effects, suggesting their potential to alleviate one of the adverse T2D complications, DKD [64].

In their study, Chen and the team explored the efficacy of **curcumin (C2)** from *Curcuma longa* in targeting epigenetic cues. They investigated the effects of **C2** treatment (at a concentration of 10 μM) on the NCI-H929 cell line and found that it induced DNA hypermethylation at the *mTOR* gene promoter region. This hypermethylation decreased both mRNA and protein levels of the mammalian target of rapamycin (mTOR), with a respective reduction of 43.31 and 39.34%. Further investigation revealed that the alterations in DNA methylation were mediated by the regulation of DNMTs, specifically DNMT3a and DNMT3b, but not DNMT1 [81]. Collectively, mTOR down-regulation would possibly alleviate T2D by modulating multiple cell signalling, including insulin signalling, apoptosis, and autophagy.

Li and the team shed light on the epigenetic modulation effects of **genistein (C3)**, an isoflavone found in legumes like *Glycine* max and *Cicer arietinum*. In respect to their findings, pre-treatment with **C3** (10 mg kg^{-1} day^{-1}) for 1 week in unilateral ureteral occlusion-incurred mice resulted in the attenuation of hypermethylation in gene (*Klotho*) promoter. This observation was further confirmed *in vitro* using a TGFβ-treated HK-2 cell line, where **C3** treatment (15 μM) led to the demethylation of the pathological *Klotho* promoter. The researchers attributed this demethylation to the inhibitory action of **C3** on DNMT1 and DNMT3a enzymes, resulting in a reduction of their activity by around 200%. As a consequence, the restoration of Klotho expression exhibited renal-protective properties, thereby potentially hindering the progression of kidney fibrosis such as those T2D individuals with diabetic nephropathy [65].

Other than that, Zhang et al. highlighted the potential of **baicalin (C4)**, derived from *Scutellaria baicalensis*, as a promising epidrug. The researchers conducted experiments in streptozotocin (STZ)-induced mice, treating them with **C4** at a dosage of 40 mg kg^{-1} day^{-1} for 1 week. This treatment drastically alleviated FBG levels; however, hyperglycaemia persisted in comparison to the control group. They observed that **C4** influenced the expression of DNMT3a and DNMT3b, but not DNMT1, in the kidney tissue. This was evident from the significant reductions in mRNA and protein levels of DNMT3a (by 40% and 35%, respectively) and DNMT3b (by 275% and approximately 15%, respectively). Subsequently, this flavone restored Klotho expression by

reversing hypermethylation-induced silencing, although this methylation-repressing effect was observed only at specific CpG sites, such as CpG1 and CpG3 to CpG5. Similar findings were obtained in **C4**-treated high-glucose-stimulated HK-2 cell line experiments. After all, the normalization of Klotho expression through **C4** treatment promotes a better modulation of pathological features associated with diabetes, including damage to glomeruli and tubules [82].

Thus, as shown in Fig. 1, *de novo* DNMTs (DNMT3a and DNMT3b) predominantly contribute to DNA methylation/demethylation events through the addition of methyl groups to previously unmethylated DNA regions. The illustration highlights the role of DNMT1 in preserving existing methylation patterns, significantly contributing to the risk factor, development, and progression of T2D pathophysiology (Fig. 1a). The remission of such an unpleasant process is facilitated by active phytochemicals targeting the activity of DNMTs to prevent DNA methylation/demethylation events, indicating the potential to reduce the risk factor of T2D (Fig. 1b).

3.2. Histone modification

Histone modifications, which include acetylation, methylation, and phosphorylation, are crucial in controlling gene expression of glucose metabolism, insulin sensitivity, and pancreatic β-cell function. These modifications control the accessibility of DNA to the transcriptional machinery, determining whether genes are expressed or repressed. By targeting the key regulators of histone modifications, it is possible to modulate the "open" or "closed" state of DNA, thereby influencing gene expression patterns [83]. For instance, targeting well-known regulators like the class I HDACs, histone methyltransferases (HMTs), HATs, histone demethylases (HDMTs), and HDATs could lead to shifts in gene expression, bringing favourable outcomes in the context of T2D.

Ren et al. reported an intriguing finding that **C2** possesses the ability to alleviate conditions relevant to T2D by acting on the NAD-dependent HDAC, known as sirtuins (SIRTs). In their study, the administration of **C2** at a dosage of 100 mg kg^{-1} day^{-1} for 8 weeks in STZ-induced rats led to moderate improvements in hyperglycaemia and weight. The diabetic rats exhibited a greater degree of cardiomyocyte apoptosis and decreased levels of SIRT1. However, **C2** treatment effectively restored the expression to basal levels. A similar effect was observed in the H9c2 cell line stimulated with high fat and glucose, where treatment rescued SIRT1 expression and interfered with histone deacetylation. The authors emphasized that **C2** acts by rescuing SIRT1 expression, thereby modulating insulin secretion and attenuating α-cell hyperplasia. In addition, activation of the SIRT1-FOXO1 and phosphatidylinositol 3-kinase (PI3K)-Akt pathways functionally improved metabolic abnormalities and inhibit cardiomyocyte apoptosis, ultimately leading to a delayed onset of diabetic cardiomyopathy [84]. In addition to the effects of **C3** on DNA demethylation, the active compound also demonstrates anti-deacetylation properties. When applied to the HK-2 cell line at a concentration of 15 μM, it induced a dose-dependent up-regulation of histone 3 acetylation on the promoter of *Klothlo*. This up-regulation of histone acetylation, exceeding 100%, can be attributed to its ability to modulate HDAC levels. These findings suggest that **C3** effectively recover the Klotho-deficit condition, subsequently implicating its anti-renal fibrosis function [65].

Pitsillou and colleagues conducted an *in silico* docking study to evaluate the propensity of phenolic compounds derived from *Olea europaea* to interact with various epigenetic enzymes involved in T2D. Their findings revealed that three phenolic compounds, namely **scolymoside (C5)**, **acteoside (C6)**, and **quercetin-3-O-rutinoside (C7)**, exhibited strong binding affinities to important enzymes. They demonstrated significant inhibitory actions against lysine-specific demethylases 1/2 (LSD1/2), which have been implicated in the progression and development of T2D. The calculated binding scores for **C5**, **C6**, and **C7** with LSD1 were − 74.1, −73.9, and − 73.9 kcal mol^{-1}, respectively, whereas their binding scores with LSD2 were − 70.6, −73.0, and − 79.1 kcal mol^{-1}, respectively. Furthermore, inhibiting SET domain-containing protein 7 (SETD7) has shown the potential in improving vascular dysfunction in T2D patients. It also holds significant roles in controlling key β-cell function. The estimated inhibitory actions of **C5** (−82.8 kcal mol^{-1}), **C6** (−78.6 kcal mol^{-1}), and **C7** (−78.5 kcal mol^{-1}) against SETD7 indicate their potential for future clinical use against T2D, pending further validation through *in vitro* and *in vivo* experiments. The study suggests that these phenolic compounds interact with specific

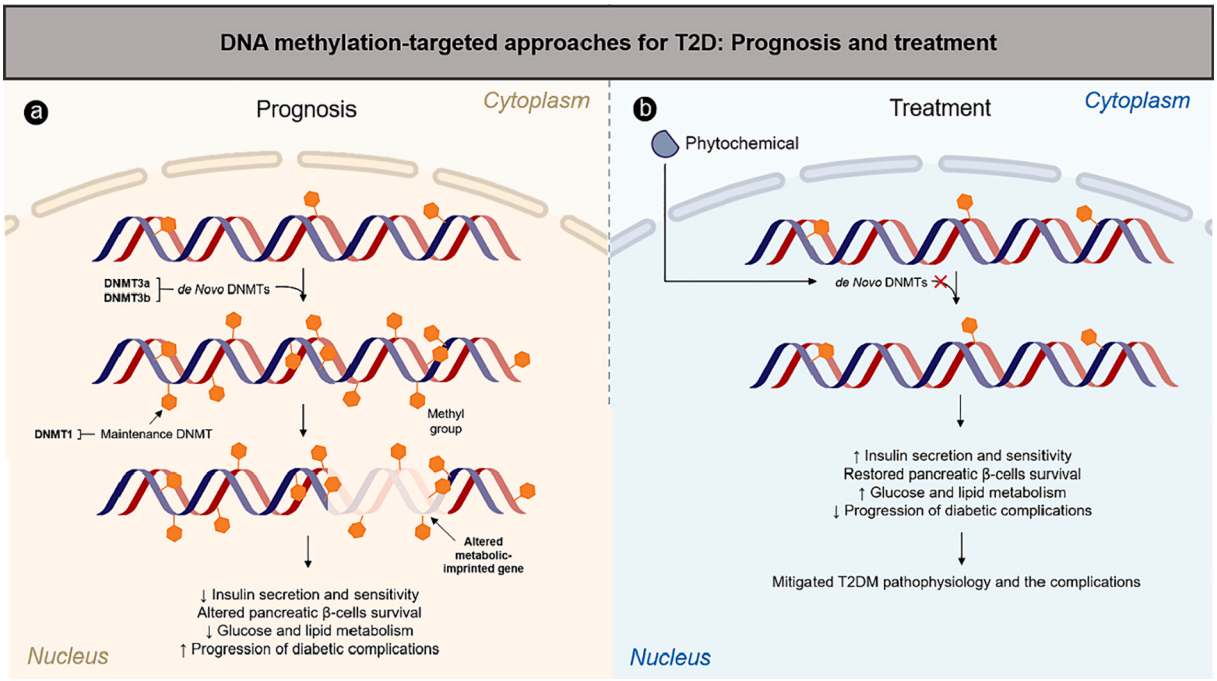


Fig. 1. DNA methylation in prognosis and treatment of T2D. (**a**) Pathophysiological contributions of DNMTs to the progression. (**b**) Interaction of phytochemicals on DNMTs to moderate DNA methylation patterns.

residues of LSD1 (such as negatively charged Asp555 and Asp556) and LSD2 (including Asn440 and Gln803), providing insight into their mechanism of action [85].

Wang and the team explored the potential use of **hesperetin (C8)** and **naringenin (C9)** abundantly found in fruits (like *Citrus paradisi* and *Citrus sinensis*) or herbs (*Petroselinum crispum*), as antidiabetic agents. The researchers administered these flavanones to diabetic *db/db* mice at the dose of 50 mg kg^{-1} day^{-1} for 6 weeks. Results indicated that both of them lowered biochemical indexes (FBG and insulin levels) in a dose-dependent manner. These effects were attributed to the multifaceted properties of **C8** (100 μM) and **C9** (100 μM), including the ability to suppress acetylation of histone H3 at lysine 18 (H3K18) and lysine 27 (H3K27), with a reduction of 1.5 to 2-fold, in the INS-1 cell line. This was achieved by regulating adenosine monophosphate-activated protein kinase (AMPK)-mediated inactivation of the protein p300. Consequently, thioredoxin interacting protein (TXNIP) showed a 4- to 6-fold reduction in the mRNA expression, leading to an improved glucose sensitivity in β-cells and inhibited hyperglycaemic-stimulated apoptotic events *in vitro* and *in vivo*. The research team concluded that although insulin produced by a single β-cell remains unchanged, the two compounds had the potential in managing advanced stages of T2D [86].

Puerarin (C10), an isoflavone derived from *Radix puerariae*, exhibit antidiabetic properties as evidenced by Guo and the collaborators. The team noticed that this compound gradually attenuate blood glucose and insulin levels following 18 weeks of treatment (at the dose of 50 mg kg^{-1} day^{-1}) in STZ-induced rats. Next, they found that it demonstrated the ability to inhibit HDAC1 and HDAC3 expression by approximately 2- to 3-fold. This inhibition was observed both *in vivo*, with **C10** treatment, and *in vitro*, with **C10** treatment (at a concentration of 20 μM) on a fructose-stimulated SaoS-2 cell line. The suppression of HDAC1/3 overexpression eventually prevent cellular inflammatory and apoptotic events, suggesting a potential mechanism for improving systemic insulin sensitivity. Supporting the potential of **C10** as promising epidrug is its supplementary benefit in mitigating diabetic osteoporosis. Importantly, the study also highlighted the high safety profile of **C10**, as the dosage of up to 50 mg kg^{-1} was found to represent the non-observed-adverse-effect level (NOAEL), emphasising its favourable tolerability and minimal undesirable effects [87].

Besides, Park and others discovered another potential epidrug with inhibitory effects on histone methylation: **kaempferol (C11)**, which is naturally found in *Malus domestica*, *Solanum lycopersicum*, and *Camellia sinensis*. They conducted treatments using different concentrations of the flavonol (50 μM and 100 μM, respectively) for 8 days on 3 T3-L1 and adipose-derived stem cells, where they revealed that the treatment can hamper the enrichment of active histone, H3K4me3, while enhancing deposition of repressive histone mark, H3K27me3. Consistently, the binding occupancy of lysine methyltransferase 2 (MLL2) was found to be decreased after treatment, validating the impaired accumulation of H3K4me3. More than that, the **C11**-mediated inhibition of histone methylation occurs specifically in the PPARγ target genes' promoter, leading to the suppression of its transcriptional activity, ultimately contributing to improvements in glucose homoeostasis, as well as insulin sensitivity [88].

Cuyàs and colleagues reported that *Olea europaea* contains the secoiridoid, **oleacein (C12)**, which has a potent inhibitory action against LSD1 (inhibitory concentration at 50%, IC_{50} value of around 2.5 μmol/L) in a dose-dependent manner, suppressing demethylase activity. Molecular dynamics and docking studies provided further insights into the mechanism of action, revealing that **C12** strongly binds to the flavin adenosine dinucleotide (FAD) cofactor cavity of LSD1 with a docking value of −155.861 kcal mol^{-1}. This binding interaction disrupted the anchorage of LSD1 to chromatin, particularly the interaction between LSD1 and histone H3, as well as the co-repressor RCOR1/CoREST. This interference with LSD1 activity was further supported by the suppression of LSD1-dependent endogenous transcription factor SOX2 mRNA and protein expressions by approximately 75% and 25%, respectively, following treatment with **C12** at a concentration of 10 μM in induced pluripotent stem cells. Based on the central role of LSD1 in multiple crucial events, the inhibition mediated by this compound holds promise for the epigenetic modulation of metabolism-related conditions, including T2D [89].

According to, Li et al., **juglanin (C13)**, a flavonol found in *Juglans spp.*, shows promise as a therapeutic agent for metabolic disorders. In the study where it (30 mg kg^{-1}) was co-administered with a high-fat diet (HFD) to mice for 16 weeks, it resulted in a drastic reduction in FBG and fasting insulin levels by 2.5-fold (from 15 to 6 mmol/L) and > 2.7-fold (from 20.5 to 7.5 mIU/L), respectively. The real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis revealed suppression of HDAC3 mRNA expression (5-fold difference) and protein expression (>2.5-fold difference) following treatment. Consistently, **C13** treatment (at the dose of 40 μM) on the HK-2 cell line displayed a dose-dependent restoration of HDAC3 levels back to the basal level. Mechanistic analysis inferred that this compound hindered the activation of HDAC3, particularly impacting the NF-κB/HDAC3 pathway. With this regulatory effect as an HDAC3 suppressor, it helps to ameliorate metabolic stresses and insulin resistance associated with dyslipidaemia. Moreover, its protective effect on renal cells is highly promising for treating renal diseases like diabetic nephropathy. Notably, in the HK-2 cell line, **C13** exhibited excellent tolerability even at high concentrations (100 μM), with cell viability exceeding 90% [90].

The primary alkaloid presents in *Piper nigrum*, **piperine (C14)**, expressed a dynamic regulation of histone modifications, as determined by Park et al. In response to the **C14** treatment (at a concentration of 50 μM) on the 3 T3-L1 cell line, there was a decline in active histone codes (like H3K4me4 and H3K9ac) accumulation. Conversely, the team showed enrichment of repressive histone markers (such as H3K27me3 and H3K9me2) at adipogenic-associated PPARγ target genes' promoters. A similar effect was observed when adipose-derived stem cells were treated with **C14** at a concentration of 100 μM. These changes in histone modifications were accompanied by alterations in the enrichment and binding patterns of histone-modifying enzymes. For example, CREB-binding protein (CBP), MLL2, and LSD1 were disassociated from the PPARγ-responsive element of the *Fabp4* gene, whilst simultaneously allowing Utx and enhancer of zeste homolog 2 (EZH2) to take their place. Eventually, the shift towards a repressive state of PPARγ target genes resulted in improved insulin sensitivity, as well as repression of adipocyte differentiation. It is worth mentioning that the doses of **C14** used in the study were within the NOAEL, signifying the potential safety and therapeutic significance [91].

Based on the LC-MS analysis, Luna-Vital and the team discovered that the water extract of purple maize (*Zea mays* L.) contains abundant amounts of hydroxycinnamic acids and anthocyanins, including the **ferulic acid** (**C15**; 40.89%), **cyanidin-3-O-glucoside** (**C16**; 22.05%), and **pelargonidin-3-O-glucoside** (**C17**; 18.15%). In a 12-week study on mice, the administration of this extract at a dose of 500 mg kg^{-1}, along with an HFD, resulted in the preservation of normal FBG and insulin levels, preventing their excessive elevation. The FBG levels decreased by 1.3-fold (from 330.7 to 257.5 mg/dL), while insulin levels decreased by 1.9-fold (from 2.1 to 1.1 ng/mL). This anti-diabetic property is owing to the compound's modulation of HDAC (*i.e.*, SIRT1), whereby the treated mice model had an up-regulation in the *SIRT1* gene in the liver. Therefore, activation of SIRT1 is known to initiate a series of downstream signalling events, resulting in the repression of white adipose tissue and the induction of brown adipose tissue. Lastly, this process counteracts insulin resistance and modulates metabolic dysfunction to improve metabolic health [92].

Nettore and co-authors highlighted the possible application of **quercetin (C18)**, a flavonol found abundantly in various sources such as *Vaccinium spp.*, *Rubus spp.*, and *Citrus sinensis*, as a therapeutic agent for metabolic disorders through its dual inhibitory action on HAT and HDAC, which can rescue epigenomic profiles. In their study, the researchers investigated the effects of **C18** treatment (at a concentration of

25 μM) on 3 T3-L1 cells on the fifth day of differentiation. They observed a downfall in the active histone mark (H3K4me2) and a marked increase in the repressive histone mark (H3K9me2) at the promoters of adipogenic-associated genes. Moreover, **C18** triggered a 2-fold drop in the binding capacity of LSD1 enzyme to the promoters of these genes, particularly in the 5′ region. As a result, the transcriptional activity of key adipogenic factors, such as *c/EBPα* and *PPARγ*, was maintained in a non-permissive state, leading to reduced expression and potentially mitigating insulin resistance. It is noteworthy that **C18** exhibited a modest cytotoxicity in the 3 T3-L1 cell line, with over 90% cell viability at a concentration of 25 μM. Its poor bioavailability *in vivo* necessitates higher concentrations to compensate. However, concentrations above 50 μM demonstrated significant cytotoxicity (<50% viable cells), amending the use of higher effective concentrations [93].

In a study led by Castrejón-Téllez, the epigenetic modulation effect of a mixture of **C18** (0.95 mg kg^{-1} day^{-1}) and **resveratrol, C19** (50 mg kg^{-1} day^{-1}) was investigated, where they found to strongly influence SIRTs. In their study, they treated both chronic and acute sucrose-stimulated rat models that showed metabolic syndrome and insulin resistance phenotypes. Following one-month combined treatment, a modest reduction in blood glucose level was observed, but, more significantly, the treatment effectively reversed the impaired insulin sensitivity, especially in the chronic stimulated model. Further investigation revealed that the mixture treatment in the chronic stimulated model led to a profound up-regulation of SIRT1 significantly by 30%. This up-regulation of SIRT1 was noted to direct the deacetylation and activation of endothelial nitric oxide synthase (eNOS), up-regulation by approximately 40%), which related to improved insulin sensitivity and alleviate hypertension through PI3K/Akt/eNOS pathway [94].

Similarly, a study conducted by Tshichase et al. observed the effect of **C19** (50 μM) on SIRT1. The researchers evaluated the efficacy of this compound treatment on a high-glucose stimulated HepG2 cell line over a period of 72 h, wherein they noted a restoration in the levels of SIRT1 (mRNA up-regulation of ~1.5-fold). Considering reduced SIRT1 expressions during high-glucose event can impair NF-κB subunit deacetylation, consequently enhancing transcription and intensify NF-κB-mediated inflammatory events. This cascade may lead to an increased expression of certain pro-inflammatory cytokines to exacerbate the condition of T2D. But the **C19**-treated cell line demonstrated a mitigation of these deleterious effects by inhibiting NF-κB activity and potentially reversing the enhanced levels of TNF-α, IL-6, IL-β, and cyclooxygenase 2 (COX-2) [95].

Therefore, the progression of T2D implicates alterations to the nucleosome and the constituent histone proteins (H2A, H2B, H3 and H4) with their flexible tails (Fig. 2). Various histone modification events including phosphorylation, methylation, ubiquitylation, ADP ribosylation, glycosylation, acetylation, and sumoylation contribute to the initiation and progression of T2D. The MLL2, EZH2, and SETD7 are examples of HMTs that mediate the methylation processes and, in turn, establish a repressive chromatin environment that limits transcription. Acetylation processes are facilitated by HAT such as CBP has been linked to transcriptional activation by promoting a permissive chromatin state. Such modifications impose regulatory control over chromatin structure and gene expression (Fig. 2a). These unpleasant events are mitigated by potentially active phytochemicals and reverse T2D complications as a promising therapeutic strategy (Fig. 2b).

3.3. Non-coding RNA-associated gene silencing

Non-coding RNAs, regardless of their inability of encoding the protein, play a significant role in cellular regulation through interactions with various small RNA molecules, such as miRNAs. These ncRNAs often bind to specific mRNA targets associated with T2D, leading to a reduction in functional mRNA availability and contributing to the progression of T2D and its concomitant complications. Interestingly, bioactive substances derived from plants have demonstrated the ability to manipulate the activity of these small RNA molecules.

In a notable investigation by Otton et al., the additional therapeutic

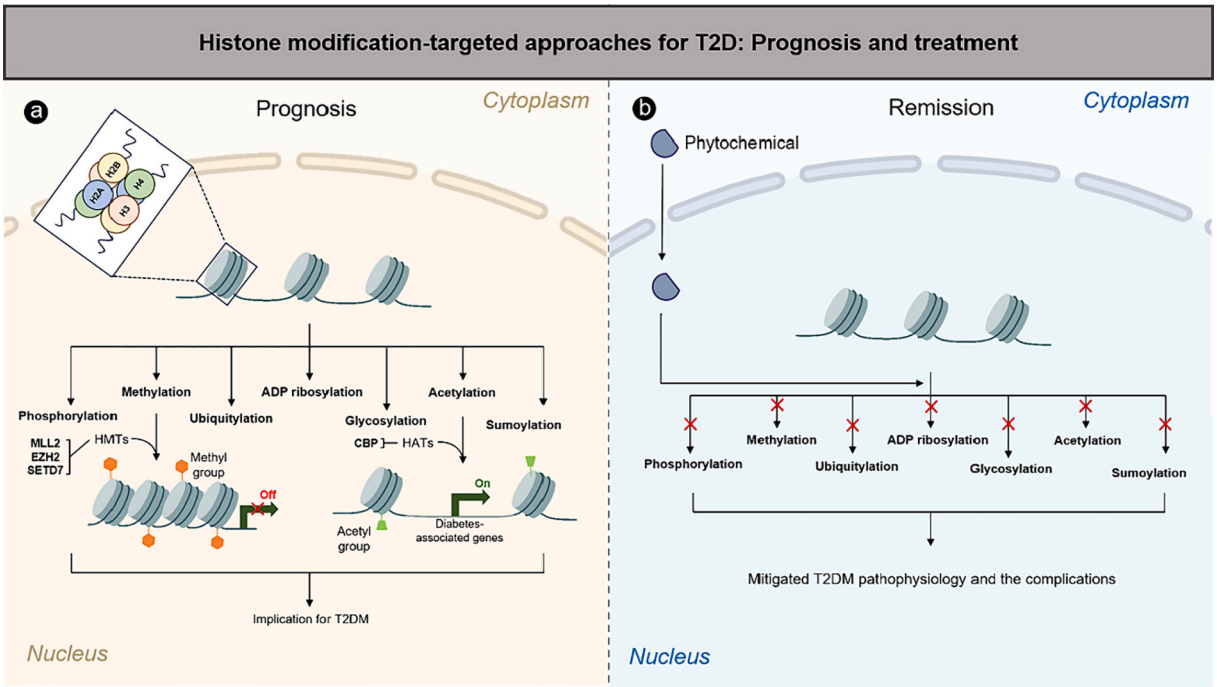


Fig. 2. Histone modification in prognosis and treatment of T2D. (**a**) A nucleosome showing the histone proteins (H2A, H2B, H3 and H4) and their flexible tails. Various histone modifications including phosphorylation, methylation, ubiquitylation, ADP ribosylation, glycosylation, acetylation, and sumoylation. MLL2, EZH2 and SETD7 are examples of HMTs that mediate the methylation processes and chromatin-inclined modulation of transcription, a pathway to T2D. Acetylation processes facilitated by HAT and CBP have been linked to transcriptional activation by promoting a permissive chromatin state. (**b**) The potential of active phytochemicals to arrest the undesired modification events and reverse T2D.

potential of **C1** in *Camellia sinensis* extract was explored. The administration of green tea extract (at the dose of 500 mg kg^{-1} day^{-1}) over 16-week period on HFD-fed obese mice yielded a reduction in insulin and FBG levels, indicating improved glycaemic control in the treated group. Additionally, the body weight and adiposity index significantly returned to basal levels. Mechanistically, the extract treatment successfully reversed the up-regulation levels of miRNA-155 (2.1-fold reduction) and miRNA-335 (7.6-fold reduction) in adipose tissue. By down-regulate these miRNAs, the extract precluded the effect of TNF-α, which is known to up-regulate insulin signalling- and lipid metabolism-associated genes. Consequently, TNF-α/miR-335 axis modulation improves insulin sensitivity, hampered inflammatory responses, and lowers adiposity. Lastly, the dosage administered in the study was determined to be NOAEL [96].

Again, the combination of **C1** (15 μM) and **C18** (15 μM) was described to display optimal synergistic anti-diabetic effect, as uncovered by Liu and the team. The detrimental effect caused by STZ is effectively minimised when the combined phenolic compounds are co-treated to the NIT-1 cell line for a day while STZ is induced. An in-depth analysis indicates that they elicit an inhibitory effect towards miRNA-16-5p, which happens to target B-cell lymphoma-2 (BCL-2). The authors confirmed that miRNA-16-5p modulation indeed influences the subsequent expression of BCL-2, with mRNA and protein expressions increased by 80% and 50%, respectively. Eventually, this combined treatment could protect β-cell against BCL-2/caspase-induced apoptotic event, as seen by a reduction in the apoptotic rate from 32.33 to 13.48% (>2-fold differences). Also, the targeted genes for T2D conditions (insulin resistance and β-cell development) may be affected by the down-regulation of miRNA-16-5p [97].

Furthermore, Gan and the teams investigated more antidiabetic mechanisms of **C3** in T2D *via* epigenetic modulation. They reported after giving mice **C3** (200 mg kg^{-1}) along with HFD for 8 weeks, the body weight indices and FBG levels (~2.3-fold reduction) are considerably lower than the control group, signifying the inhibition of HFD-induced obesity. Furthermore, it was shown that **C3** treatment (20 μM) in the NCTC1469 cell line caused miRNA-451, which has a binding interaction with gluconeogenesis-related genes (for instance, *G6pc* and *Gk*) to be up-regulated. The expression of a glucose-6-phosphatase catalytic subunit and glycerol kinase was then controlled, modulating gluconeogenesis to boost overall insulin sensitivity. In HFD mice evaluated with acute co-administration (dosage of 500 mg kg^{-1}) for 1 week, **C3** inhibited hepatic gluconeogenesis and alleviated insulin resistance while promoting miRNA-451 expression and hampering the expression of *G6pc* and *Gk* [98]. The teams found that **C3** (100 μmol/L) reduced miRNA-222 levels *in vivo* by roughly 7 times while decreasing their expression in the 3 T3-L1 cell line by around half. As such, miRNA-222's target genes, including *adipor1*, displayed rising expression, and this, in turn, enhances the adiponectin-adiponectin receptor 1 (adipor1) signalling pathway that modulates insulin resistance [99].

Zhang and collaborators stated that underexpression of miRNA-124 could be restored in STZ-induced diabetic mice shortly after an 8-week **C4** treatment (45 mg kg^{-1} day^{-1}). The results, where the mRNA level increased by almost 60%, were verified by qRT-PCR. The same outcomes were seen when **C4** (100 μmol/L) was applied to the high-glucose-stimulated HK-2 cell line. As a result, depletion of miRNA-124 that targets toll-like receptor 4 (TLR4) is likely to affect the pathophysiology of diabetes. It is interesting to note that by hindering the TLR4/NF-κB axis activation, type IV collagen and fibronectin expressions were reduced, which had a protective effect against degenerative events in diabetic nephropathy [100].

In a project conducted by Zhao and others, it was observed that the miRNA-targeting activity of **C9** is associated with endogenous IRS-1and insulin-like growth factor 1 receptor (IGF1R). The researchers presented that treatment with **C9** at a concentration of 50 nM mL^{-1} significantly down-regulated miRNA-140-3p in HTR-8/SVneo and HUVEC cell lines. As a consequence, more IR signalling occurred, leading to an improved cellular glucose uptake. Asides from its role in enhancing insulin signalling, **C9** is also partially involved in protecting the trophoblast and endothelial cells against a high-glucose milieu [101], indicating a promising epigenetic modifier for T2D treatment.

Another report on **C18** disclosed interesting amelioration effects of the active compound through the regulation of miRNA. After administration (50 mg kg^{-1}) for 6 weeks on STZ-induced diabetic rats, the FBG level dropped from approximately 340 to 130 mg/dL (>2.5-fold differences). Notably, it reversed the expression of miRNA-1306-5p (lowered by ~200%), a 17β-HSD targeting miRNA that was overexpressed in the diabetic rat. Likewise, **C18** (10 μM) on high-glucose-stimulated Leydig cells effectively inhibits the miRNA-1306-5p overexpression. Altogether, 17β-HSD mRNA and protein expressions grew *in vitro* (50%) and *in vivo* (35% and 50%, respectively). This is not only capable of tweaking T2D or metabolic parameters but they have also been shown to prevent endoplasmic reticulum stress to ameliorate testosterone secretion disorder connected with T2D. Still, the concentration of 20 μM exhibited mild cytotoxicity, triggering a drop in the cell viability to ~75% [102].

A double-blinded placebo-controlled randomised controlled trial (RCT) was accomplished by Mahjabeen et al. to access the amelioration effect of **C19** on T2D. The study involved selected T2D patients ($n = 55$) who were administered a daily dose of 200 mg of **C19** over 24 weeks. At the end of the experiment, there were significant improvements in key metabolic parameters (insulin, HbA1C, and FBG levels, but not lipid profiles) among the treated patients. Interestingly, the miRNA expression modulation by **C19** in the context of T2D was successfully demonstrated. The down-regulation of miRNA-21 (2.78-fold) suggests the beneficial effect of the compound in attenuating oxidative stress and decreasing glycolysis by pancreatic stellate cells, while miRNA-34a down-regulation (2.56-fold) augments the SIRT1 expression, which alleviates oxidative stress and inflammation conditions. In addition, the miRNA-375 down-regulation (2.27-fold) proposed to have an anti-apoptotic effect in β-cells, leading to sustained insulin secretion. The expression of miRNA-192, a key regulator of multiple effector proteins involved in DKD, was also found to be significantly decreased by 2.38-fold. The RCT findings signify the up-regulatory effect of **C19** for miRNA-126 (2.55-fold) and miRNA-132 (2.5-fold). The miRNA-126 modulatory effect would elevate PI3K/Akt signalling-stimulated insulin secretion, as well as amend β-cells damage and inflammation, whereas miRNA-132 level modulation was revealed to attenuate multiple inflammatory pathways: NF-kB, TNF-alpha, NOD-like receptor, and toll-like receptor signalling. Intriguingly, toxicological evaluation of the active phytochemical confirmed the good safety profile, with a NOAEL of 1 g kg^{-1} day^{-1} [103], demanding further assessment of the compound as a promising epigenetic-targeting anti-diabetic agent.

Like many other phenolic compounds, **isorhamnetin (C20)** from *Hippophaer hamnoides* L., *Oenanthe javanica*, and some other fruits, has emerged as a promising therapeutic agent for treating T2D, as reported by Matboli et al. After subjected STZ-HFD induced rats to a 3-week treatment regimen with **C20** (40 mg kg^{-1} day^{-1}), it showed striking results, with a significant decline in FBG (from 20 to 7 mol/L) and insulin levels (from 4.25 to 3 μL/L). The combinational approaches of *in silico* and *in vivo* analysis in the study provided insights into epigenetic modulation by **C20**, where this flavonol targets miRNA and lncRNA in a dose-dependent manner. Specifically, it up-regulates the expression of miRNA-1 and miRNA-1363 in both adipose tissue and skeletal muscle. Besides, the expression of lncRNA-RP11-773H22.4 was augmented or normalized to a basal level. These observations suggest that the modulation contributes to the therapeutic impact, exerting antioxidant effects and reversing insulin resistance [104].

A study done by Ni et al. on **dihydromyricetin (C21)** from *Ampelopsis grossedentata* evinced that this flavanonol can be used to treat diabetes with diabetic cardiomyopathy. The researchers utilised an STZ-induced diabetic mice model and examined the effects of **C21** treatment for two weeks at a dosage of 100 mg kg^{-1} day^{-1}. Despite it failed to

reduce the FBG level, it displayed the ability to down-regulate miRNA-34a expression *via* RT-PCR instead. Likewise, **C21** therapy (1 M) on high-glucose-stimulated mouse cardiomyocytes showed parallel results. Later, in cardiomyocytes, the autophagy event was enhanced and apoptotic cell death was decreased. By promoting these, **C21** may represent a good approach to preserving cardiac function in diabetic individuals and managing diabetic complications [105].

Salem et al. proved that **caffeic acid (C22)** in *Olea europaea* and *Coffea spp.*, at a dose of 40 mg kg^{-1} day^{-1} modulates epigenetic modification in STZ-induced rats after 2 months of therapy. Both the lipid profile and FBG levels have substantially reduced, from 428.75 to 257.50 (>1.5-fold), indicating the likelihood of ameliorating metabolic conditions. Using qRT-PCR, the team discovered that the treatment resulted in a down-regulation of miRNA-636 in the kidney (by about 2.5-fold). These findings imply that changes in miRNA-636 regulation not only mitigate hyperglycaemia associated with T2D but also offer protective action against the progression of diabetic nephropathy by potentially suppressing the miRNA-related MAPK signalling, which implicates in autophagy pathway [106].

Procyanidin B2 (**C23**; 20.25%), **epicatechin** (**C24**; 19.39%), and **chlorogenic acid** (**C25**; 15.17%) make up the majority of the extract of *Crataegus pinnatifida* Bge. According to Liu and the team's investigation, treatment with the extract (10 μg/mL) on the high-glucose-stimulated ARPE-19 cell line resulted in a 250% down-regulation of miRNA-34a, a crucial regulator of the *SIRT1* gene. The down-regulation of miRNA-34a expression was tested individually using the three main phenolic compounds, and it was still present, validating their ability epigenetic modulatory properties. The researchers noted that the expression of SIRT1 mRNA and protein is affected by >25% in their downstream examination. Hence, utilising the extract as therapy is proven to control downstream proteins' acetylation by SIRT1. This includes the silencing of the AMPK/SIRT1/NF-κB and miRNA-34a/SIRT1/p53 pathways, which govern apoptosis and inflammation, and ends up as a potential strategy for stopping the progression of T2D and diabetic retinopathy. However, the cell viability (70%) dramatically decreased in a dose-dependent manner at a concentration of 40 μg/mL [107].

In the study conducted by Ismail et al., the researchers delved into the antidiabetic effect of the polar ethanolic extract derived from golden chamomile (*Matricaria aurea*), aimed to access the impact on insulin resistance at the epigenetic level. This extract boasts a rich composition of potent active constituents, including a diverse array of phenolic compounds like **C15**, **C18, C25**, **apigenin (C26)**, **luteolin (C27)**, and ***p*-coumaric acid (C28)**. The teams observed after four weeks of consecutive treatment of extract (at the dose of 200 mg kg^{-1} day^{-1}) on STZ-HFD-induced diabetic rat model, the biochemical analysis like FBG level is normalized effectively, bringing them to a comparable range with the control group under treatment conditions. Using qRT-PCR, the extract was found with a robust capacity to down-regulate the expression of hepatic miRNA-29a by a 3.5-fold, compared to the diabetic control group. Notably, this modulation of miRNA-29a expression contributes to the epigenetic regulation of insulin resistance [5].

Undoubtedly, ncRNAs significantly interfere with the prognosis of T2D and represent a potential biomarker for the remission of the deleterious disease as illustrated in Fig. 3. The figure displays that the transcription of a mRNA from some diabetes-associated genes is affected by specific ncRNAs (Fig. 3**a**), while the interactions of some active phenolic and alkaloidal phytochemicals with such prominent biomarkers arrest the negative ncRNA-targeting events (Fig. 3**b**). The miRNAs such as miRNA-16-5p, miRNA-21, miRNA-34a, miRNA-124, and miRNA-155, as well as the lncRNA RP11-773H22.4 are strongly implicated in the interesting remission process. The ncRNAs operate as gene expression regulators, resulting in changed protein levels after translation and contributing to T2D risks.

3.4. Regulation of some other epigenetic biomarkers for T2D

3.4.1. 11β-Hydroxysteroid dehydrogenase inhibition

In terms of treating T2D, the 11β-HSD, which plays an essential role in regulating glucocorticoid action, has been identified as a strong candidate, with inhibition appeared to reduce insulin resistance and

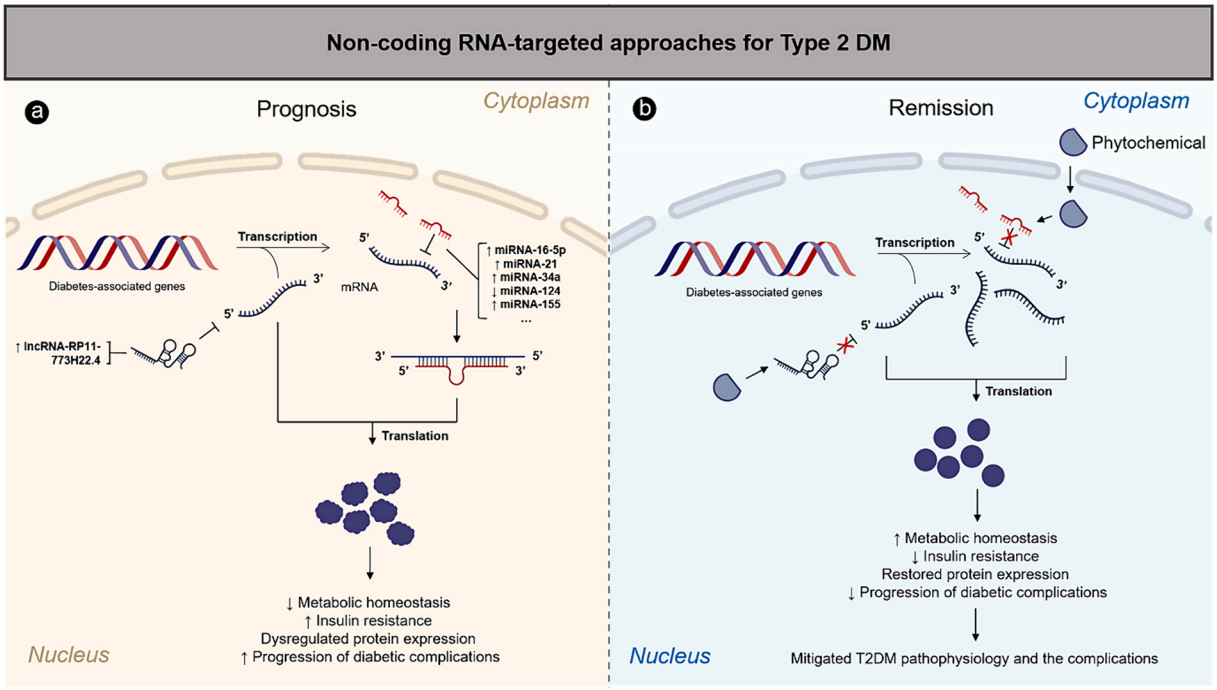


Fig. 3. Non-coding RNAs interference in prognosis and treatment of T2D. (**a**) Effects of relevant ncRNAs on the transcription of mRNAs from diabetes-associated genes. Interfering with mRNA are miRNAs such as miRNA-16-5p, miRNA-21, miRNA-34a, miRNA-124, and miRNA-155, as well as the lncRNA RP11-773H22.4. The ncRNAs operate as gene expression regulators, resulting in changed protein levels after translation thereby contributing to the risks of T2D. (**b**) Illustrates the active interactions of phytochemicals to ameliorate the negative prognostic miRNA-targeting events as a treatment approach.

improve metabolic parameters [6,43]. Ojo's docking and pharmacophore modelling studies anticipate that **C10** can inhibit 11β-HSD (−9.0 kcal mol^{-1}), besides interfering with the HDAC activity. Interestingly, the docking value is comparable to the control value, implying the potent binding action [108].

Using network pharmacology and docking analysis, Patil and Khatib proposed that *Barringtonia acutangular* (L.) Gaertn consists of vital phytochemicals with 11β-HSD targeting capacity, contributing to its known therapeutical role in T2D. The top compound is predicted to have the highest affinity, including **barringtogenol B** (**C29**; −11.3 kcal mol^{-1}). It could interact with active residues like Lys44, Ile46, Ile121, and Tyr183, among others. Uniquely, its capabilities to interact with 8 other protein targets involved in T2D-related pathways (*e.g.*, metabolic, insulin secretion, and PI3K-Akt signalling) were predicted [109].

The study conducted by Damián-Medina et al. presented a potential molecular mechanism of anthocyanins detected in *Phaseolus vulgaris* L. for managing T2D. Following ultra-performance liquid chromatography-electrospray ionization/quadrupole-time-of-flight high-definition mass spectrometry technique, they performed docking analysis, which determined potentially potent binding capability towards 11β-HSD by **delphinidin 3-glucoside (C30)** and **petunidin 3-O-glucoside (C31)**. The binding energies are −6.59 and − 6.87 kcal mol^{-1}, while inhibition constant (K_i) values are 44.82 and 9.19 μM, respectively. As a result, inhibiting 11β-HSD promotes insulin-mediated glucose uptake in the tissues [110].

3.4.2. Protein tyrosine phosphatase 1B inhibition

The inhibition of PTP1B in T2D is believed to be an ideal target for enhancing IR sensitivity due to its role in regulating insulin signalling pathways [6,111]. Kostrzewa and their colleagues illustrated that **C2** (IC_{50} value of 100 μM) possesses, better effectiveness for antidiabetic effect (10-fold differences) *via* PTP1B phosphatase inhibition, in contrast to **cinnamaldehyde (C32)** derived from the bark of *Cinnamomum* genus (IC_{50} value of 1 mM) [111]. From the docking study, **C10** was predicted to show binding affinity to PTP1B as well, with a docking score of −6.4 kcal mol^{-1}, surpassing that of the control [108].

Alternately, **C30** and **C31** may hold considerable potential for antidiabetic action through the PTP1B inhibiting mechanism, as proposed by Damián-Medina et al. The predicted binding energy and K_i value of the two anthocyanins are −6.22 kcal mol^{-1} and 27.59 μM, as well as −6.24 kcal mol^{-1} and 26.55 μM, respectively. After effective PTP1B inhibition, it is thought that the β-cell function will be enhanced, improving insulin secretion and preventing T2D with its complications [110].

3.4.3. Estradiol regulation via 17β-hydroxysteroid dehydrogenase

The inhibition of 17β-HSD has drawn interest when it comes to addressing T2D. This enzyme regulates oestradiol, that known to induce metabolic homeostasis, where the accumulation is strongly associated with T2D; however, the causality is still under investigation [6,43]. So, studies of inhibitory action on 17β-HSD suggest potential treatment aimed at restoring correct redox metabolic balance and a more favourable hormonal profile underlies T2D.

Wang's research found that **C18** increases the amount of 17β-HSD *in vitro* and *in vivo*. Following the up-regulation, cell apoptosis induced after high-glucose stimulation was diminished. Here, the findings suggest that **C18** treatment increases phosphorylated proteins (*i.e.*, JAK2 and STAT3), indicating the involvement of the JAK2/STAT3 pathway in controlling endoplasmic reticulum stress and apoptotic event, and that treatment effectively improves the T2D-linked testosterone secretion disorder [102].

Banerjee et al., provide new insights into the mechanism of **C19** treatment (50 mg^{-1} kg^{-1} day^{-1} for 9 weeks) in controlling protein and mRNA expressions of 17β-HSD *in vivo* (Wistar rat), going beyond its known regulatory effects on miRNA. Additionally, the dosage employed in the study had no adverse side effects [112].

3.4.4. Other non-epigenetic mechanisms

In addition to the aforementioned epigenetic activities of the bioactive phytochemicals, the compounds exhibit multi-targeted mechanisms implicating some non-epigenetic-directed biomarkers. For instance, the antidiabetic effect of *Matricaria aurea* extract with **C1** extends to specific T2D-related genes, resulting in their expressions being normalized compared to the diabetic control group. There was an up-regulation of phosphoinositide-3-kinase regulatory subunit 1, PIK3R1 (0.75-fold differences) and down-regulation of phosphoenolpyruvate carboxykinase 1, PCK1 (4.5-fold differences) and IL-1β (5-fold differences), all of which improve insulin signalling and hamper gluconeogenesis. Computational data, along with experimental studies, support the notion that the extract exerts its effects *via* multiple metabolic pathways: PI3K-Akt, FOXO, and AMPK signalling. Also, it possesses the ability to enhance antioxidant enzyme actions such as catalase (CAT) and superoxide dismutase (SOD), from 55.16 to 88.25 U/g of tissue (>1.5-fold) and from 2031 to 3885.40 U/g of tissue (~1.9-fold), respectively [5].

Liu et al. emphasized **C1**-**C18** combined treatment can influence *in vitro* antioxidant enzyme activities. This includes SOD (1.5-fold increased from 2.71 to 4.01 U/mg), glutathione peroxidase (GPx; 2.33-fold increased from 5.47 to 12.75 U/mg), as well as malondialdehyde level (MDA; 1.5-fold decreased from 0.61 to 0.42 nmol/mg). Ultimately, the ROS generation is attenuated in NIT-1 cells and hindered the β-cell dysfunction to restore insulin secretion capacity [97].

The inhibition of NF-κB signalling may also be a mechanism by which **C4** ameliorate T2D. Western blotting analysis validated that the treatment down-regulates the expression of inflammatory cells (*e.g.*, $CD3^+$ lymphocytes, $CD68^+$ macrophages) and p65 (mediator of NF-κB). Again, it lowered the MDA content while boosting SOC, GPx, and CAT actions. Overall, this is indicative of a general reduction in oxidative stress and inflammation [82].

The aforementioned **C8** and **C9** protective effects towards the β-cell under a high glucose environment can be partly due to their direct antioxidant activity *via* scavenging intracellular accumulation of reactive oxygen species (ROS) [86].

Meanwhile, **C11** showed some inhibitory activity towards the ligand-binding domain of PPARγ (dissociation constant, K_D of 44.54 μM). Notably, the **C11**-mediated antagonistic action happened in a dose-dependent manner and it was able to impair the interaction between PPARγ and its coactivator CBP [88].

C10, apart from inhibiting HDAC1/3, also targets the major inflammatory regulators such as TNF-α, IL-1β, COX-2 and matrix metalloproteinase 14 (MMP-14), as supported by *in vivo* and *in vitro* findings. Fructose-stimulated SaoS-2 cell line showed suppressed Caspase-3 and PARP activity, as well as nuclear factor kappa B (NF-κB). Together, this treatment can slow the course of diabetic osteoporosis, and relieve diabetic conditions, and other complications by hampering apoptotic and inflammation responses [87].

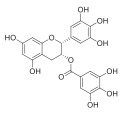
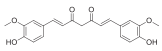
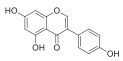
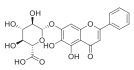
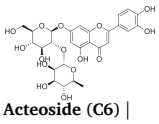
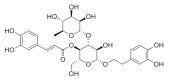
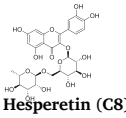
Significantly, **C18**'s ability to increase SOD activity in STZ-induced diabetic rats and high glucose-stimulated cells demonstrates its capacity to attenuate oxidative stress. Also, the MDA content and ROS are both lowered to control-like levels [102].

A continuation of the **C20** study, qRT-PCR shows that the compound affects IGF1R, mTOR, and Akt2. The authors proposed that down-regulation of IGF1R and mTOR, along with up-regulation of Akt2 holds benefits in managing T2D by modulating autophagy and insulin resistance signalling pathways [104]. The natural product source, molecular structure, epigenetic modulatory mechanisms, activity profile and safety indices of the selected bioactive compounds are summarily presented in Table 1.

4. Conclusion and outlook

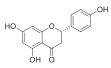
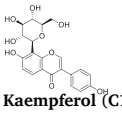
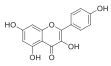
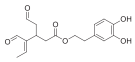
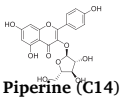
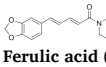
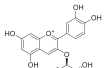
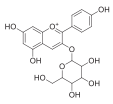
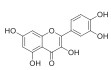
Diabetes mellitus in its various forms remains a global health challenge characterized by morbidity, mortality and low quality of life.

Table 1
Natural product source and mechanistic epigenetic activity profile of selected phenolic and alkaloidal phytochemicals.

Plant source	Compound, Class and Structure	Mechanism of Action	Activity Profile	Safety Assessment	Ref.
Camellia sinensis	**Epigallocatechin-3-gallate (C1)** | Flavanol 	• Up-regulation of epigenetic factor (*i.e.*, DNMT3b) • Down-regulation of epigenetic factor (*i.e.*, DNMT3a, DNMT1, miRNA-155, and miRNA-335) • Modulation *via* inflammatory, fibrotic, insulin signalling, and oxidative stress pathways	Potency: High Efficacy: High Concentration-dependent effects	Safety: High (NOAEL dosage of green tea extract at 500 mg kg^{-1} day^{-1} for 16 weeks in HFD-fed obese mice)	[64,96]
Curcuma longa	**Curcumin (C2)** | Curcuminoids 	• Interfere with DNA methyltransferase (*i.e.*, DNMT3a and DNMT3b) by promoting DNA hypermethylation at the *mTOR* gene's promoter • Interfere with histone deacetylation by activating SIRT1 associated with PI3K-Akt signalling • Modulation *via* insulin signalling, autophagy, and apoptosis pathways • IC_{50} value = 100 μM against PTPB1 phosphatase	Potency: Moderate Efficacy: Moderate Concentration-dependent effects	Safety: High (>95% viable H9c2 cell at 20 μM)	[81,84,111]
Cicer arietinum *Glycine* max	**Genistein (C3)** | Isoflavone 	• Interfere with DNA methyltransferase (*i.e.*, DNMT1 and DNMT3a) by inhibiting DNA hypermethylation at the *Klotho* gene's promoter • Interferes with histone acetyltransferase activity by inhibiting histone deacetylation at Klotho promoter • Up-regulation of epigenetic factor (*i.e.*, miRNA-451) • Down-regulation of epigenetic factor (*i.e.*, miRNA-222) • Modulation *via* insulin resistance and gluconeogenesis pathways	Potency: Moderate Efficacy: High	Safety: N/A	[65,98,99]
Scutellaria baicalensis	**Baicalin (C4)** | Flavone 	• Interfere with DNA methyltransferase (*i.e.*, DNMT3a and DNMT3b) by inhibiting DNA hypermethylation at the *Klotho* gene • Up-regulation of epigenetic factor (*i.e.*, miRNA-124) • Modulation *via* oxidative stress and inflammatory pathways • Increase antioxidant enzymes' activity (SOD, GPx, and CAT)	Potency: Moderate Efficacy: Moderate	Safety: N/A	[82,100]
Olea europaea	**Scolymoside (C5)** | Flavone glycoside  **Acteoside (C6)** | Phenylethanoid glycoside  **Quercetin-3-O-rutinoside (C7)** | Flavonol glycoside	• Theoretical inhibitory effects on histone demethylases (LSD1, LSD2) and histone methyltransferase (SETD7)	Potency: N/A Efficacy: N/A	Safety: N/A	[85]
Citrus paradisi *Citrus sinensis* *Petroselinum crispum*	**Hesperetin (C8)** | Flavanone  **Naringenin (C9)** | Flavanone	• Down-regulation of epigenetic factor (*i.e.*, miRNA-140-3p) • Interferes with histone acetylation • Modulation *via* apoptotic pathway	Potency: High Efficacy: Moderate Concentration-dependent effects	Safety: N/A	[86,101]

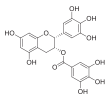
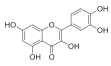
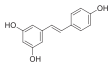
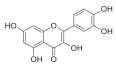
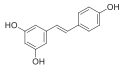
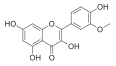
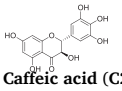
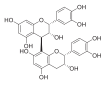
(*continued on next page*)

Table 1 (*continued*)

Plant source	Compound, Class and Structure	Mechanism of Action	Activity Profile	Safety Assessment	Ref.
Radix puerariae	 **Puerarin (C10)** | Isoflavone	• Interferes with histone deacetylase activity by inhibiting HDAC1 and HDAC3 • Theoretical inhibitory effects on 11β-HSD and PTP1B • Modulation *via* apoptotic and inflammatory pathways	Potency: High Efficacy: Moderate	Safety: High (NOAEL dosage at 50 mg kg^{-1} day^{-1} for 18 weeks in STZ-induced rat)	[87]
Camellia sinensis *Malus domestica* *Solanum lycopersicum*	 **Kaempferol (C11)** | Flavonol	• Interfere with histone methyltransferase by inhibiting histone modification at *PPARγ* target genes' promoter • K_D value = 44.45 μM against the ligand-binding domain of PPARγ	Potency: Moderate Efficacy: High	Safety: N/A	[88]
Olea europaea	 **Oleacein (C12)** | Secoiridoid	• IC_{50} value = ~2.5 μmol/L against LSD1 • Interfere with chromatin binding activity of LSD1/RCOR1/CoREST complex	Potency: High Efficacy: High Concentration-dependent effects	Safety: N/A	[89]
Juglans spp.	 **Juglanin (C13)** | Flavonol	• Interferes with histone deacetylase activities • Modulation *via* inflammatory and lipid metabolism pathways	Potency: Moderate Efficacy: High Concentration-dependent effects	Safety: High (>90% viable HK-2 cell at 100 μM)	[90]
Piper nigrum	 **Piperine (C14)** | Amides	• Interfere with histone methyltransferases (MLL2 and EZH2), acetyltransferase (CBP), and demethylases (LSD1 and Utx) by inhibiting histone modification at *PPARγ* target genes' promoter	Potency: Moderate Efficacy: High	Safety: High (NOAEL dosage of 50 μM for 3 T3-L1; 100 μM for adipose-derived stem cells)	[91]
Zea mays L.	 **Ferulic acid (C15)** | Hydroxycinnamic acid  **Cyanidin-3-O-glucoside (C16)** | Anthocyanin	• Up-regulation of epigenetic factor (*i.e.*, SIRT1) • Modulation *via* insulin resistance and metabolic dysfunction pathways	Potency: Low Efficacy: Moderate	Safety: N/A	[92]
Citrus sinensis *Rubus spp.* *Vaccinium spp.*	 **Pelargonidin-3-O-glucoside (C17)** | Anthocyanin  **Quercetin (C18)** | Flavonol 	• Interferes with histone acetyltransferase and deacetylase activities by inhibiting histone modification at adipogenic-associated genes' promoter • Down-regulation of epigenetic factor (*i.e.*, miRNA-1306-5p) • Up-regulate mRNA and protein expressions of 17β-HSD • Modulation *via* apoptotic and oxidative stress pathways	Potency: Moderate Efficacy: High	Safety: Moderate (<50% viable 3 T3-L1 cell at 50 μM; ~75% viable Leydig cell at 20 μM) Low bioavailability *in vivo*	[93,102]
Combination therapy	**Epigallocatechin-3-gallate (C1)** | Flavanol	• Down-regulation of epigenetic factor (*i.e.*, miRNA-16-5p)	Potency: High Efficacy: High Synergistic effect	Safety: N/A	[97]

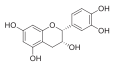
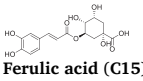
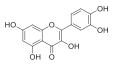
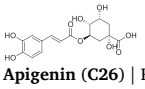
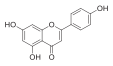
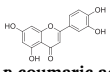
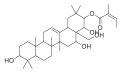
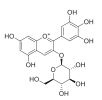
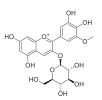
(*continued on next page*)

Table 1 (*continued*)

Plant source	Compound, Class and Structure	Mechanism of Action	Activity Profile	Safety Assessment	Ref.
		• Modulation *via* oxidative stress, insulin signalling, and apoptotic pathways • Increase antioxidant enzymes' activity (SOD and GPx)			
Arachis hypogaea *Prunus domestica* *Vaccinium spp.* *Vitis vinifera*	**Quercetin** (**C18**) | Flavonol 	**Resveratrol** (**C19**) | Stilbene 	• Down-regulation of epigenetic factor (*i.e.*, miRNA-21, miRNA-34a, miRNA-375, miRNA-192) • Up-regulation of epigenetic factors (miRNA-126, miRNA-132) • Regulate mRNA and protein expressions of 17β-HSD • Up-regulation of epigenetic factor (*i.e.*, SIRT1) • Modulation *via* NF-κB-mediated inflammatory pathway	Potency: Moderate Efficacy: High	Safety: High (NOAEL dosage at 1 g kg^{-1} day^{-1} in T2D patients; 50 mg^{-1} kg^{-1} day^{-1} for 9 weeks in rat)
[103,112]					
Combination therapy	**Quercetin** (**C18**) | Flavonol  **Resveratrol** (**C19**) | Stilbene	• Interfere with histone deacetylation by activating SIRT1 associated with eNOS • Modulation *via* insulin pathway	Potency: High Efficacy: Moderate	Safety: N/A	[94]
Hippophaer hamnoides L. *Oenanthe javanica*	 **Isorhamnetin** (**C20**) | Flavonol  **Dihydromyricetin** (**C21**) | Flavanonol	• Up-regulation of epigenetic factors (*i.e.*, miRNA-1 and miRNA-1363) • Down-regulation of epigenetic factor (*i.e.*, lncRNA-RP11-773H22.4) • Modulation *via* insulin resistance and autophagy pathways	Potency: High Efficacy: High Concentration-dependent effects	Safety: N/A	[104]
Ampelopsis grossedentata		• Down-regulation of epigenetic factor (*i.e.*, miRNA-34a) • Modulation *via* autophagy pathway	Potency: Moderate Efficacy: Low	Safety: N/A	[105]
Coffea spp. *Olea europaea*	 **Caffeic acid** (**C22**) | Hydroxycinnamic acid 	• Down-regulation of epigenetic factor (*i.e.*, miRNA-636) • Modulation *via* autophagy pathway	Potency: Low Efficacy: Moderate	Safety: N/A	[106]
Crataegus pinnatifida Bge.	**Procyanidin B2** (**C23**) | Procyanidin 	• Down-regulation of epigenetic factor (*i.e.*, miRNA-34a) • Modulation *via* inflammatory and apoptosis pathways	Potency: High Efficacy: Moderate	Safety: Moderate (~70% viable ARPE-19 cell at 40 μg/mL)	[107]

(*continued on next page*)

Table 1 (*continued*)

Plant source	Compound, Class and Structure	Mechanism of Action	Activity Profile	Safety Assessment	Ref.
	Epicatechin (C24) | Flavanol				
	 **Chlorogenic acid (C25)** | Hydroxycinnamic acid				
	 **Ferulic acid (C15)** | Hydroxycinnamic acid				
	 **Quercetin (C18)** | Flavanol				
	 **Chlorogenic acid (C25)** | Hydroxycinnamic acid				
Matricaria aurea	 **Apigenin (C26)** | Flavone	• Down-regulation of IL-1β, PCK1, and epigenetic factor (*i.e.*, miR29a) • Up-regulation of PIK3R1 • Modulation *via* inflammatory, energy-sensing/ endocrine/metabolic, and oxidative stress pathways • Increase antioxidant enzymes' activity (CAT and SOD)	Potency: Moderate Efficacy: Moderate Concentration-dependent effects	Safety: N/A	[5]
	 **Luteolin (C27)** | Flavone				
	 ***p*-coumaric acid (C28)** | Hydroxycinnamic acid				
	 **Barringtogenol B (C29)** | Flavonol				
Barringtonia acutangular (L.) Gaertn	 **Delphinidin 3-glucoside (C30)** | Anthocyanin	• Theoretical inhibitory effects on 11β-HSD • Modulation *via* metabolic, insulin secretion, and PI3K-Akt pathways	Potency: N/A Efficacy: N/A	Safety: N/A	[109]
Phaseolus vulgaris L.	 **Petunidin 3-O-glucoside (C31)** | Anthocyanin	• Theoretical inhibitory effects on 11β-HSD and PTP1B	Potency: N/A Efficacy: N/A	Safety: N/A	[110]
					

(*continued on next page*)

Table 1 (*continued*)

Plant source	Compound, Class and Structure	Mechanism of Action	Activity Profile	Safety Assessment	Ref.
Cinnamomum spp.	**Cinnamaldehyde (C32)** | Phenylpropanoid 	• IC_{50} value = 1 mM against PTPB1 phosphatase	Potency: Low Efficacy: Low Concentration-dependent effects	Safety: N/A	[111]

Notes: N/A = not available in the report, NOAEL = no-observed-adverse-effect level.

Specifically, T2D is mostly implicated in clinical environments, demanding concerted scientific efforts for curbing its current scary trends and alarming epidemiological forecasts. Being a complex metabolic disease, several metabolism-associated biomarkers and pathways have been implicated in its prognosis and progression, constituting therapeutic complications. Among the prominent pathways, epigenetic regulatory mechanisms significantly contribute to the remission bottlenecks due to their overlap with several essential programming for cellular functions. The crucial roles of epigenetic factors and their aberrations in the on-set development and progression of T2D pose them as promising biomarkers for monitoring and ameliorating the devastating disorder.

In this overview, prominent epigenetic modifications for both prognostic and treatment pathways have been surveyed. These include DNA methylation/demethylation, histone modification, ncRNA modulation and other relevant genetic and epigenetic regulatory mechanisms. For instance, *de novo* DNMTs significantly contribute to DNA methylation processes through the addition of methyl groups to the unmethylated DNA regions. As such, the process remains a pathophysiological risk factor for the development and progression of T2D. The reversal of such an unpleasant process is facilitated by active phytochemicals targeting the activity of DNMTs to prevent DNA methylation events, indicating the potential to reduce the risk factor of T2D. Among the active phenolic and alkaloidal phytochemicals reported between 2019 and the present, the natural product-based compounds, **C1-C3** were reported with interesting modulatory effects on the DNMTs as potential epigenetic anti-T2D candidates for further assessment.

Similarly, various histone modification events including phosphorylation, methylation, ubiquitylation, ADP ribosylation, glycosylation, acetylation, and sumoylation were revealed. Such modifications impose regulatory control over chromatin structure and gene expression thereby contributing to the initiation and progression of T2D. The unpleasant histone-targeted nuclear events are mitigated by potentially active phytochemicals as a promising therapeutic strategy for reversing T2D complications. The bioactive compounds analysed with such interesting profiles include **C10-C18** for future translational studies. Their reported epigenetic mechanisms of action include the inhibition of HDAC, LSDs and SETD7, and modifications of HMTs at target T2D promoter genes.

Furthermore, ncRNAs significantly constitute epigenetic factors and interfere with potent biomarkers for the prognosis and remission of T2D. The transcription of mRNAs from some diabetes-associated genes is affected by specific ncRNAs while the interactions of some active phenolic and alkaloidal phytochemicals with such prominent biomarkers arrest the negative ncRNA-targeting T2D events. The miRNAs such as miRNA-16-5p, miRNA-21, miRNA-34a, miRNA-124, and miRNA-155, as well as the lncRNA RP11-773H22.4 are strongly implicated in the interesting remission process. They act as regulators of gene expression and protein levels after translation. Among the surveyed bioactive compounds targeting the ncRNAs, **C1** and **C19-C25** were selected with interesting modulatory effects on the targets. They represent potent phytochemicals for the epigenetic-targeted arrest of T2D signalling.

In addition to the focused targets, some compounds such as **C15-C32** showed mechanistic anti-T2D regulatory potential on other relevant biomarkers including estradiol, IL-1β, PCK-1, PIK3R1, PI3K-Akt, 1Lβ-HSD and PTPB1 phosphatase.

Despite the interesting activities reported for the highlighted compounds, the experimental assessments were limited in most of the studies. Thus, a complemental dual-faceted approach incorporating both cell-based *in vitro* and animal-based *in vivo* experimental validation would enrich the conclusion on the epigenetic activities of the compounds. Again, the criteria for acceptability of a candidate for therapeutic application necessary involve a good safety profile. However, in most of the overviewed studies, the assessment of such important factors remains generally underexplored. On a few occasions, brief analyses were demonstrated for a mere prediction of safety properties while others were largely left out in this regard. Thus, a comprehensive analysis of safety and toxicity for each of the selected compounds would be worthy of research. Similarly, the pharmacokinetic and pharmacodynamic properties that define the druggability were less evaluated for the selected compounds. As such, future studies on these parameters remain demanding to lower the chance of metabolic complications, especially considering the proposed therapeutic application sites. For medicinal chemists, pharmacists and other relevant drug design scientists, the availability of chemical structures for the selected phytochemicals could support structure-activity relationship studies amenable to the derivatization of better scaffolds. Again, the involvement of some of the implicated epigenetic alterations in various beneficial systemic processes necessitates a target-directed therapeutic approach for mitigating T2D progression. Thus, a nano design of the selected compounds through nanotechnology could facilitate their acute delivery to the proposed targets and minimize the chance for undesired actions.

In summary, the survey provides an intriguing insight into the development of T2D, focusing on prominent epigenetic aberrations. More interestingly, it critically channels therapeutic advances for retarding the global trend of T2D menace for future pharmacological research.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

This work was financially supported by the Tertiary Education Fund Nigeria (grant no. TETF/ES/ASTD/UNIV/MALETE/2019), Fundamental Research Grant Scheme, Ministry of Higher Education of Malaysia (grant no. 203.CDADAH.6711955).

CRediT authorship contribution statement

Yusuf Oloruntoyin Ayipo: Writing – original draft, Resources, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chien Fung Chong:** Writing – original draft, Formal analysis, Data

curation. **Hassan Taiye Abdulameed:** Writing – original draft, Formal analysis, Data curation. **Mohd Nizam Mordi:** Writing – review & editing, Visualization, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgement

Authors profoundly appreciate the Tertiary Education Fund Nigeria, Ministry of Higher Education Malaysia and Universiti Sains Malaysia for supports.

References

[1] R.A. Alhazzaa, T. Heinbockel, A.B. Csoka, Diabetes and epigenetics, in: Epigenetics to Optogenetics - A New Paradig. Study Biol, Intech Open, 2021, pp. 1–15. https://www.intechopen.com/books/advanced-biometric-technologies/liveness-detection-in-biometrics.

[2] M. Balbaa, M. El-Zeftawy, S.A. Abdulmalek, Therapeutic screening of herbal remedies for the management of diabetes, Molecules 26 (2021) 1–18, https://doi.org/10.3390/molecules26226836.

[3] P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A.A. Motala, K. Ogurtsova, J.E. Shaw, D. Bright, R. Williams, Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9th edition, Diabetes Res. Clin. Pract. 157 (2019) 107843, https://doi.org/10.1016/j.diabres.2019.107843.

[4] American Diabetes Association, Standards of Care in Diabetes—2023 abridged for primary care providers, Clin. Diabetes 41 (2023) 4–31, https://doi.org/10.2337/cd23-as01.

[5] Y. Ismail, D.M. Fahmy, M.H. Ghattas, M.M. Ahmed, W. Zehry, S.M. Saleh, D. M. Abo-elmatty, Integrating experimental model, LC-MS/MS chemical analysis, and systems biology approach to investigate the possible antidiabetic effect and mechanisms of Matricaria aurea (Golden chamomile) in type 2 diabetes mellitus, Front. Pharmacol. 13 (2022) 1–28, https://doi.org/10.3389/fphar.2022.924478.

[6] K. Kochar Kaur, G. Allahbadia, M. Singh, Therapeutic potential and epigenetic alterations of plant phytochemicals (as epi-drugs) for the treatment of type 2 diabetes mellitus: a systematic review, Adv. Obesity, Weight Manag. Control. 11 (2021) 195–206, https://doi.org/10.15406/aowmc.2021.11.00355.

[7] C. Ling, Pharmacoepigenetics in type 2 diabetes: is it clinically relevant? Diabetologia 65 (2022) 1849–1853, https://doi.org/10.1007/s00125-022-05681-x.

[8] CDC, National Diabetes Prevention Program: working together to prevent type 2 diabetes, centers dis, Control Prev. (2022). https://www.cdc.gov/diabetes/prevention/index.html (accessed June 7, 2023).

[9] F.M. Delpino, L.M. Figueiredo, Resveratrol supplementation and type 2 diabetes: a systematic review and meta-analysis, Crit. Rev. Food Sci. Nutr. 62 (2022) 4465–4480, https://doi.org/10.1080/10408398.2021.1875980.

[10] J. Bhattacharjee, V.J. Borra, E.S.B. Salem, C. Zhang, K. Murakami, R.K. Gill, A. Kim, J.K. Kim, R.M. Salazar-Gonzalez, M. Warren, R. Kohli, T. Nakamura, Hepatic Ago2 regulates PPARα for oxidative metabolism linked to glycemic control in obesity and post bariatric surgery, Endocrinol. (United States). 162 (2021) 1–16, https://doi.org/10.1210/endocr/bqab007.

[11] G. Chen, H. Chen, S. Ren, M. Xia, J. Zhu, Y. Liu, L. Zhang, L. Tang, L. Sun, H. Liu, Z. Dong, Aberrant DNA methylation of mTOR pathway genes promotes inflammatory activation of immune cells in diabetic kidney disease, Kidney Int. 96 (2019) 409–420, https://doi.org/10.1016/j.kint.2019.02.020.

[12] J.B. Cole, J.C. Florez, Genetics of diabetes mellitus and diabetes complications, Nat. Rev. Nephrol. 16 (2020) 377–390, https://doi.org/10.1038/s41581-020-0278-5.

[13] M.B. Backe, C. Jin, L. Andreone, A. Sankar, K. Agger, K. Helin, A.N. Madsen, S. S. Poulsen, M. Bysani, K. Bacos, C. Ling, M.J. Perone, B. Holst, T. Mandrup-Poulsen, The lysine demethylase KDM5B regulates islet function and glucose homeostasis, J. Diabetes Res. 2019 (5451038) (2019) 1–16, https://doi.org/10.1155/2019/5451038.

[14] K. Bomsztyk, O. Denisenko, Y. Wang, DNA methylation yields epigenetic clues into the diabetic nephropathy of Pima Indians, Kidney Int. 93 (2018) 1272–1275, https://doi.org/10.1016/j.kint.2018.02.015.

[15] R. Correa-De-Araujo, A.P. Rossi, M. Zamboni, O. Addison, I. Miljkovic, B. Goodpaster, Editorial: muscle quality in skeletal muscle function deficit: recent advances and potential clinical and therapeutic implications, Front. Mater. 13 (2022) 1–3, https://doi.org/10.3389/fphys.2022.847883.

[16] C. Davegårdh, J. Säll, A. Benrick, C. Broholm, P. Volkov, A. Perfilyev, T. I. Henriksen, Y. Wu, L. Hjort, C. Brøns, O. Hansson, M. Pedersen, J.U. Würthner, K. Pfeffer, E. Nilsson, A. Vaag, E. Stener-Victorin, K. Pircs, C. Scheele, C. Ling, VPS39-deficiency observed in type 2 diabetes impairs muscle stem cell differentiation via altered autophagy and epigenetics, Nat. Commun. 12 (2021) 1–20, https://doi.org/10.1038/s41467-021-22068-5.

[17] T. Vilaca, M. Schini, S. Harnan, A. Sutton, E. Poku, I.E. Allen, S.R. Cummings, R. Eastell, The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: a systematic review and meta-analysis update, Bone 137 (2020) 115457, https://doi.org/10.1016/j.bone.2020.115457.

[18] J.T. Schousboe, S.N. Morin, G.A. Kline, L.M. Lix, W.D. Leslie, Differential risk of fracture attributable to type 2 diabetes mellitus according to skeletal site, Bone 154 (2022) 116220, https://doi.org/10.1016/j.bone.2021.116220.

[19] Y.J. Sur, The risk of hip fractures in individuals over 50 years old with prediabetes and type 2 diabetes – a longitudinal nationwide population-based study, Bone 154 (2022) 116224, https://doi.org/10.1016/j.bone.2021.116224.

[20] B. Chen, Q. He, J. Yang, Z. Pan, J. Xiao, W. Chen, W. Chi, M. Li, S. Li, J. Zeng, C. Chen, F.C. Wang, X. Pang, Y. Yi, H. Tu, H. Wang, P. Chen, Metformin suppresses oxidative stress induced by high glucose via activation of the Nrf2/HO-1 signaling pathway in type 2 diabetic osteoporosis, Life Sci. 312 (2023) 121092, https://doi.org/10.1016/j.lfs.2022.121092.

[21] B. Bikbov, C.A. Purcell, A.S. Levey, M. Smith, A. Abdoli, M. Abebe, O.M. Adebayo, M. Afarideh, S.K. Agarwal, M. Agudelo-Botero, E. Ahmadian, Z. Al-Aly, V. Alipour, A. Almasi-Hashiani, R.M. Al-Raddadi, N. Alvis-Guzman, S. Amini, T. Andrei, C.L. Andrei, Z. Andualem, M. Anjomshoa, J. Arabloo, A.F. Ashagre, D. Asmelash, Z. Ataro, M.M.D.W. Atout, M.A. Ayanore, A. Badawi, A. Bakhtiari, S. H. Ballew, A. Balouchi, M. Banach, S. Barquera, S. Basu, M.T. Bayih, N. Bedi, A. K. Bello, I.M. Bensenor, A. Bijani, A. Boloor, A.M. Borzì, L.A. Cámera, J.J. Carrero, F. Carvalho, F. Castro, F. Catalá-López, A.R. Chang, K.L. Chin, S.C. Chung, M. Cirillo, E. Cousin, L. Dandona, R. Dandona, A. Daryani, R. Das Gupta, F. M. Demeke, G.T. Demoz, D.M. Desta, H.P. Do, B.B. Duncan, A. Eftekhari, A. Esteghamati, S.S. Fatima, J.C. Fernandes, E. Fernandes, F. Fischer, M. Freitas, M.M. Gad, G.G. Gebremeskel, B.M. Gebresillassie, B. Geta, M. Ghafourifard, A. Ghajar, N. Ghith, P.S. Gill, I.A. Ginawi, R. Gupta, N. Hafezi-Nejad, A. Haj-Mirzaian, A. Haj-Mirzaian, N. Hariyani, M. Hasan, M. Hasankhani, A. Hasanzadeh, H.Y. Hassen, S.I. Hay, B. Heidari, C. Herteliu, C.L. Hoang, M. Hosseini, M. Hostiuc, S.S.N. Irvani, S.M.S. Islam, N. Jafari Balalami, S. L. James, S.K. Jassal, V. Jha, J.B. Jonas, F. Joukar, J.J. Jozwiak, A. Kabir, A. Kahsay, A. Kasaeian, T.D. Kassa, H.G. Kassaye, Y.S. Khader, R. Khalilov, E. A. Khan, M.S. Khan, Y.H. Khang, A. Kisa, C.P. Kovesdy, B. Kuate Defo, G. A. Kumar, A.O. Larsson, L.L. Lim, A.D. Lopez, P.A. Lotufo, A. Majeed, R. Malekzadeh, W. März, A. Masaka, H.A.A. Meheretu, T. Miazgowski, A. Mirica, E.M. Mirrakhimov, P. Mithra, B. Moazen, D.K. Mohammad, R. Mohammadpourhodki, S. Mohammed, A.H. Mokdad, L. Morales, I. Moreno Velasquez, S.M. Mousavi, S. Mukhopadhyay, J.B. Nachega, G. N. Nadkarni, J.R. Nansseu, G. Natarajan, J. Nazari, B. Neal, R.I. Negoi, C. T. Nguyen, R. Nikbakhsh, J.J. Noubiap, C. Nowak, A.T. Olagunju, A. Ortiz, M. O. Owolabi, R. Palladino, M. Pathak, H. Poustchi, S. Prakash, N. Prasad, A. Rafiei, S.B. Raju, K. Ramezanzadeh, S. Rawaf, D.L. Rawaf, L. Rawal, R.C. Reiner, A. Rezapour, D.C. Ribeiro, L. Roever, D. Rothenbacher, G.M. Rwegerera, S. Saadatagah, S. Safari, B.W. Sahle, H. Salem, J. Sanabria, I.S. Santos, A. Sarveazad, M. Sawhney, E. Schaeffner, M.I. Schmidt, A.E. Schutte, S. G. Sepanlou, M.A. Shaikh, Z. Sharafi, M. Sharif, A. Sharifi, D.A.S. Silva, J. A. Singh, N.P. Singh, M.M.M. Sisay, A. Soheili, I. Sutradhar, B.F. Teklehaimanot, B. Etsay Tesfay, G.F. Teshome, J.S. Thakur, M. Tonelli, K.B. Tran, B.X. Tran, C. Tran Ngoc, I. Ullah, P.R. Valdez, S. Varughese, T. Vos, L.G. Vu, Y. Waheed, A. Werdecker, H.F. Wolde, A.B. Wondmieneh, S. Wulf Hanson, T. Yamada, Y. Yeshaw, N. Yonemoto, H. Yusefzadeh, Z. Zaidi, L. Zaki, S. Bin Zaman, N. Zamora, A. Zarghi, K.A. Zewdie, J. Ärnlöv, J. Coresh, N. Perico, G. Remuzzi, C. J.L. Murray, Global, Regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017, Lancet 395 (2020) 709–733, https://doi.org/10.1016/S0140-6736(20)30045-3.

[22] Y. Cheng, Y. Chen, G. Wang, P. Liu, G. Xie, H. Jing, H. Chen, Y. Fan, M. Wang, J. Zhou, Protein methylation in diabetic kidney disease, Front. Med. 9 (2022) 1–9, https://doi.org/10.3389/fmed.2022.736006.

[23] D. Avrahami, K.H. Kaestner, The dynamic methylome of islets in health and disease, Mol. Metab. 27 (2019) S25–S32, https://doi.org/10.1016/j.molmet.2019.06.007.

[24] M. Eini, J. Kiani, E.S. Hosseini, M.A. Zarei, S. Parsi, M. Barati, G. Bahramali, A. Hosseini, An overview on the pathophysiological roles of microRNA-802: a literature review, Biointerface Res. Appl. Chem. 13 (2023) 1–13, https://doi.org/10.33263/BRIAC132.172.

[25] M. Grabež, R. Škrbić, M.P. Stojiljković, V. Vučić, V.R. Grujić, V. Jakovljević, D. M. Djuric, R. Suručić, K. Šavikin, D. Bigović, N. Vasiljević, A prospective, randomized, double-blind, placebo-controlled trial of polyphenols on the outcomes of inflammatory factors and oxidative stress in patients with type 2 diabetes mellitus, Rev. Cardiovasc. Med. 23 (2022) 1–11, https://doi.org/10.31083/j.rcm2302057.

[26] J. Barrera-Chimal, F. Jaisser, Pathophysiologic mechanisms in diabetic kidney disease: a focus on current and future therapeutic targets, diabetes, Obes. Metab. 22 (2020) 16–31, https://doi.org/10.1111/dom.13969.

[27] X. Chen, Y. Le, S.Q. Tang, W.Y. He, J. He, Y.H. Wang, H.B. Wang, Painful diabetic neuropathy is associated with compromised microglial IGF-1 signaling which can

be rescued by green tea polyphenol EGCG in mice, Oxidative Med. Cell. Longev. 2022 (6773662) (2022) 1–21, https://doi.org/10.1155/2022/6773662.
[28] F. Becker, H.A. Dakin, S.D. Reed, Y. Li, J. Leal, S.M. Gustavson, E. Wittbrodt, A. F. Hernandez, A.M. Gray, R.R. Holman, Lifetime cost-effectiveness simulation of once-weekly exenatide in type 2 diabetes: a cost-utility analysis based on the EXSCEL trial, Diabetes Res. Clin. Pract. 183 (2022) 1–8, https://doi.org/10.1016/j.diabres.2021.109152.
[29] C. Frezza, Metabolism and cancer: the future is now, Br. J. Cancer 122 (2020) 133–135, https://doi.org/10.1038/s41416-019-0667-3.
[30] T. Chivese, C.A. Hoegfeldt, M. Werfalli, L. Yuen, H. Sun, S. Karuranga, N. Li, A. Gupta, J. Immanuel, H. Divakar, C.E. Powe, N.S. Levitt, X. Yang, D. Simmons, IDF diabetes atlas: the prevalence of pre-existing diabetes in pregnancy – a systematic review and meta-analysis of studies published during 2010–2020, Diabetes Res. Clin. Pract. 183 (2022) 109049, https://doi.org/10.1016/j.diabres.2021.109049.
[31] B. Fernandez-Fernandez, R. Fernandez-Prado, J.L. Górriz, A. Martinez-Castelao, J. F. Navarro-González, E. Porrini, M.J. Soler, A. Ortiz, Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation and study of diabetic nephropathy with Atrasentan: what was learned about the treatment of diabetic kidney disease with canagliflozin and atrasentan? Clin. Kidney J. 12 (2019) 313–321, https://doi.org/10.1093/ckj/sfz070.
[32] N. Yumi Noronha, G. da Silva Rodrigues, I. Harumi Yonehara Noma, C. Fernanda Cunha Brandao, K. Pereira Rodrigues, A. Colello Bruno, C. Sae-Lee, L. Moriguchi Watanabe, M. Augusta de Souza Pinhel, I. Mello Schineider, M. Luciano de Almeida, F. Barbosa Júnior, D. Araújo Morais, W. Tavares de Sousa Júnior, T. Plösch, C. Roberto Bueno Junior, C. Barbosa Nonino, 14-weeks combined exercise epigenetically modulated 118 genes of menopausal women with prediabetes, Front. Endocrinol. (Lausanne). 13 (2022) 1–15, https://doi.org/10.3389/fendo.2022.895489.
[33] E. Bosi, G. Gregori, C. Cruciani, C. Irace, P. Pozzilli, R. Buzzetti, The use of flash glucose monitoring significantly improves glycemic control in type 2 diabetes managed with basal bolus insulin therapy compared to self-monitoring of blood glucose: a prospective observational cohort study, Diabetes Res. Clin. Pract. 183 (2022) 109172, https://doi.org/10.1016/j.diabres.2021.109172.
[34] K.L. Fantasia, M.C. Stockman, Z. Ju, P. Ortega, E.L. Crable, M.L. Drainoni, A. J. Walkey, M. Bergstrom, K. O'Brien, D. Steenkamp, Professional continuous glucose monitoring and endocrinology eConsult for adults with type 2 diabetes in primary care: results of a clinical pilot program, J. Clin. Transl. Endocrinol. 24 (2021) 100254, https://doi.org/10.1016/j.jcte.2021.100254.
[35] W.K. Chung, K. Erion, J.C. Florez, A.T. Hattersley, M.F. Hivert, C.G. Lee, M. I. McCarthy, J.J. Nolan, J.M. Norris, E.R. Pearson, L. Philipson, A.T. McElvaine, W.T. Cefalu, S.S. Rich, P.W. Franks, Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD), Diabetes Care 43 (2020) 1617–1635, https://doi.org/10.2337/dci20-0022.
[36] H. Alkhalidy, Y. Wang, D. Liu, Dietary flavonoids in the prevention of T2D: An overview, Nutrients 10 (2018) 1–33, https://doi.org/10.3390/nu10040438.
[37] A.G. Izquierdo, A.B. Crujeiras, Role of epigenomic mechanisms in the onset and management of insulin resistance, Rev. Endocr. Metab. Disord. 20 (2019) 89–102, https://doi.org/10.1007/s11154-019-09485-0.
[38] M. Kato, R. Natarajan, Epigenetics and epigenomics in diabetic kidney disease and metabolic memory, Nat. Rev. Nephrol. 15 (2019) 327–345, https://doi.org/10.1038/s41581-019-0135-6.
[39] D. Huang, L.Q. Cui, S. Ahmed, F. Zainab, Q. Wu, X. Wang, Z. Yuan, An overview of epigenetic agents and natural nutrition products targeting DNA methyltransferase, histone deacetylases and microRNAs, Food Chem. Toxicol. 123 (2019) 574–594, https://doi.org/10.1016/j.fct.2018.10.052.
[40] R. Menezes, P. Matafome, M. Freitas, M.T. García-Conesa, Updated information of the effects of (poly)phenols against Type-2 diabetes mellitus in humans: reinforcing the recommendations for future research, Nutrients 14 (2022) 3563, https://doi.org/10.3390/nu14173563.
[41] Y.O. Ayipo, A.T. Ajiboye, W.A. Osunniran, A.A. Jimoh, M.N. Mordi, Epigenetic oncogenesis, biomarkers and emerging chemotherapeutics for breast cancer, Biochim. Biophys. Acta - Gene Regul. Mech. 1865 (2022) 194873, https://doi.org/10.1016/j.bbagrm.2022.194873.
[42] R. Singh, S. Chandel, D. Dey, A. Ghosh, S. Roy, V. Ravichandiran, D. Ghosh, Epigenetic modification and therapeutic targets of diabetes mellitus, Biosci. Rep. 40 (2020) 1–22, https://doi.org/10.1042/BSR20202160.
[43] S. Shanak, B. Saad, H. Zaid, J.C.T. Carvalho, Metabolic and epigenetic action mechanisms of antidiabetic medicinal plants, evidence-based complement, Altern. Med. 2019 (3583067) (2019) 1–19, https://doi.org/10.1155/2019/3583067.
[44] H.S. Jang, W.J. Shin, J.E. Lee, J.T. Do, CpG and non-CpG methylation in epigenetic gene regulation and brain function, Genes (Basel) 8 (2017) 2–20, https://doi.org/10.3390/GENES8060148.
[45] N. Roshanzamir, V. Hassan-Zadeh, Methylation of specific CpG sites in IL-1β and IL1R1 genes is affected by Hyperglycaemia in type 2 diabetic patients, Immunol. Investig. 49 (2020) 287–298, https://doi.org/10.1080/08820139.2019.1656227.
[46] M. Curradi, A. Izzo, G. Badaracco, N. Landsberger, Molecular mechanisms of gene silencing mediated by DNA methylation, Mol. Cell. Biol. 22 (2002) 3157, https://doi.org/10.1128/MCB.22.9.3157-3173.2002.
[47] J. Liu, G. Lang, J. Shi, Epigenetic regulation of pdx-1 in type 2 diabetes mellitus, diabetes, Metab. Syndr. Obes. 14 (2021) 431–442, https://doi.org/10.2147/DMSO.S291932.
[48] G.A. Raciti, A. Desiderio, M. Longo, A. Leone, F. Zatterale, I. Prevenzano, C. Miele, R. Napoli, F. Beguinot, DNA Methylation and Type 2 Diabetes: Novel Biomarkers for Risk Assessment? Int. J. Mol. Sci. 22 (2021) 11652, https://doi.org/10.3390/IJMS222111652.
[49] A.C.H. Chen, W. Huang, S.W. Fong, C. Chan, K.C. Lee, W.S.B. Yeung, Y.L. Lee, Hyperglycemia altered DNA methylation status and impaired pancreatic differentiation from embryonic stem cells, Int. J. Mol. Sci. 22 (2021) 10729, https://doi.org/10.3390/IJMS221910729/S1.
[50] T. Dayeh, P. Volkov, S. Salö, E. Hall, E. Nilsson, A.H. Olsson, C.L. Kirkpatrick, C. B. Wollheim, L. Eliasson, T. Rönn, K. Bacos, C. Ling, Genome-wide DNA methylation analysis of human pancreatic islets from type 2 diabetic and non-diabetic donors identifies candidate genes that influence insulin secretion, PLoS Genet. 10 (2014) 1004160, https://doi.org/10.1371/JOURNAL.PGEN.1004160.
[51] R.A. Kowluru, G. Mohammad, Epigenetic modifications in diabetes, Metabolism 126 (2022) 154920, https://doi.org/10.1016/j.metabol.2021.154920.
[52] S. Kaimala, C.A. Kumar, M.Z. Allouh, S.A. Ansari, B.S. Emerald, Epigenetic modifications in pancreas development, diabetes, and therapeutics, Med. Res. Rev. 42 (2022) 1343, https://doi.org/10.1002/MED.21878.
[53] Y. Yang, Y. Luan, Q. Feng, X. Chen, B. Qin, K. Di Ren, Y. Luan, Epigenetics and beyond: targeting histone methylation to treat type 2 diabetes mellitus, Front. Pharmacol. 12 (807413) (2021) 1–15, https://doi.org/10.3389/FPHAR.2021.807413.
[54] H. Maude, C. Sanchez-Cabanillas, I. Cebola, Epigenetics of hepatic insulin resistance, Front. Endocrinol. (Lausanne). 12 (2021) 681356, https://doi.org/10.3389/FENDO.2021.681356/BIBTEX.
[55] M. Daneshpajooh, K. Bacos, M. Bysani, A. Bagge, E. Ottosson Laakso, P. Vikman, L. Eliasson, H. Mulder, C. Ling, HDAC7 is overexpressed in human diabetic islets and impairs insulin secretion in rat islets and clonal beta cells, Diabetologia 60 (2017) 116–125, https://doi.org/10.1007/S00125-016-4113-2.
[56] X. Tang, G. Tang, S. Özcan, Role of MicroRNAs in diabetes, Biochim. Biophys. Acta 1779 (2008) 697, https://doi.org/10.1016/J.BBAGRM.2008.06.010.
[57] P.T. Dzung, N.T. Trung, L. Van Khanh, D.D. Chinh, D. Van De, H. Van Tong, N. L. Toan, Clinical association and diagnostic significance of miRNA-29a and miRNA-147b in type 2 diabetes mellitus, Int. J. Med. Sci. 20 (2023) 1316, https://doi.org/10.7150/IJMS.84899.
[58] W.M. Yang, H.J. Jeong, S.Y. Park, W. Lee, Saturated fatty acid-induced miR-195 impairs insulin signaling and glycogen metabolism in HepG2 cells, FEBS Lett. 588 (2014) 3939–3946, https://doi.org/10.1016/J.FEBSLET.2014.09.006.
[59] E. Ji, C. Kim, W. Kim, E.K. Lee, Role of long non-coding RNAs in metabolic control, Biochim. Biophys. Acta - Gene Regul. Mech. 1863 (2020) 194348, https://doi.org/10.1016/j.bbagrm.2018.12.006.
[60] A. Leung, R. Natarajan, Long noncoding RNAs in diabetes and diabetic complications, Antioxid. Redox Signal. 29 (2018) 1064, https://doi.org/10.1089/ARS.2017.7315.
[61] F. Pivari, A. Mingione, C. Brasacchio, L. Soldati, Curcumin and type 2 diabetes mellitus: prevention and treatment, Nutrients 11 (2019) 1837, https://doi.org/10.3390/nu11081837.
[62] S. Copur, P. Rossing, B. Afsar, A.A. Sag, D. Siriopol, M. Kuwabara, A. Ortiz, M. Kanbay, A primer on metabolic memory: why existing diabesity treatments fail, Clin. Kidney J. 14 (2021) 756, https://doi.org/10.1093/CKJ/SFAA143.
[63] R.A. Alhazzaa, T. Heinbockel, A.B. Csoka, Diabetes and Epigenetics, 2016, https://doi.org/10.5772/intechopen.104653.
[64] X.H. Yang, B.L. Zhang, X.M. Zhang, J.D. Tong, Y.H. Gu, L.L. Guo, H.M. Jin, EGCG attenuates renal damage via reversing klotho Hypermethylation in diabetic db/db mice and HK-2 cells, Oxidative Med. Cell. Longev. 2020 (2020) 6092715, https://doi.org/10.1155/2020/6092715.
[65] Y. Li, F. Chen, A. Wei, F. Bi, X. Zhu, S. Yin, W. Lin, W. Cao, Klotho recovery by genistein via promoter histone acetylation and DNA demethylation mitigates renal fibrosis in mice, J. Mol. Med. 97 (2019) 541–552, https://doi.org/10.1007/s00109-019-01759-z.
[66] A. Bertelli, M. Biagi, M. Corsini, G. Baini, G. Cappellucci, E. Miraldi, Polyphenols: from theory to practice, Foods 10 (2021) 2595.
[67] L. Chen, Y. Pu, Y. Xu, X. He, J. Cao, Y. Ma, W. Jiang, Anti-diabetic and anti-obesity: efficacy evaluation and exploitation of polyphenols in fruits and vegetables, Food Res. Int. 157 (2022) 111202, https://doi.org/10.1016/j.foodres.2022.111202.
[68] L.M. da Fonseca Cardoso, J.A. de Souza Monnerat, I.W.S. de Medeiros Silva, R. da Silva Ferreira, N. da Fiochi, Matta Alvarez Pimenta, B.F. Mota, M. Dolisnky, F. L. do Carmo, S.G. Barroso, C.A.S. da Costa, M.B. Stockler-Pinto, G. de Souza Rocha, Beverages Rich in resveratrol and physical activity attenuate metabolic changes induced by high-fat diet, J. Am. Coll. Nutr. 40 (2021) 485–495, https://doi.org/10.1080/07315724.2020.1805374.
[69] I. Fernandes, J. Oliveira, A. Pinho, E. Carvalho, The role of nutraceutical containing polyphenols in diabetes prevention, Metabolites 12 (2022) 184, https://doi.org/10.3390/metabo12020184.
[70] D. Pandita, A. Pandita, Omics Technology for the Promotion of nutraceuticals and functional foods, Front. Physiol. 13 (2022) 1–12, https://doi.org/10.3389/fphys.2022.817247.
[71] S. Sukhikh, O. Babich, A. Prosekov, O. Kalashnikova, S. Noskova, A. Bakhtiyarova, O. Krol, E. Tsvetkova, S. Ivanova, Antidiabetic properties of plant secondary metabolites, Metabolites 13 (2023) 513, https://doi.org/10.3390/metabo13040513.
[72] B. Debnath, K. Manna, Formulating anti-diabetic nutraceutical tablets based on edible plants from Tripura, India, Foods Raw Mater. 10 (2022) 227–234, https://doi.org/10.21603/2308-4057-2022-2-532.
[73] J.H. He, L.X. Chen, H. Li, Progress in the discovery of naturally occurring anti-diabetic drugs and in the identification of their molecular targets, Fitoterapia 134 (2019) 270–289, https://doi.org/10.1016/j.fitote.2019.02.033.

[74] E. Cione, C. La Torre, R. Cannataro, M.C. Caroleo, P. Plastina, L. Gallelli, Quercetin, epigallocatechin gallate, curcumin, and resveratrol: from dietary sources to human MicroRNA modulation, Molecules 25 (2020) 63, https://doi.org/10.3390/molecules25010063.
[75] W. Gu, J. Geng, H. Zhao, X. Li, G. Song, Effects of resveratrol on metabolic indicators in patients with type 2 diabetes: a systematic review and Meta-analysis, Int. J. Clin. Pract. 2022 (2022) 9734738, https://doi.org/10.1155/2022/9734738.
[76] F.U. Hassan, M.S.U. Rehman, M.S. Khan, M.A. Ali, A. Javed, A. Nawaz, C. Yang, Curcumin as an alternative epigenetic modulator: mechanism of action and potential effects, Front. Genet. 10 (2019) 1–16, https://doi.org/10.3389/fgene.2019.00514.
[77] M.M. Jeyaraman, N.S.H. Al-Yousif, A. Singh Mann, V.W. Dolinsky, R. Rabbani, R. Zarychanski, A.M. Abou-Setta, Resveratrol for adults with type 2 diabetes mellitus, Cochrane Database Syst. Rev. 17 (2020) (2020) CD011919, https://doi.org/10.1002/14651858.CD011919.pub2.
[78] S. Habtemariam, The quest to enhance the efficacy of berberine for type-2 diabetes and associated diseases: physicochemical modification approaches, Biomedicines 8 (2020) 1–19, https://doi.org/10.3390/biomedicines8040090.
[79] H. Jiang, Q. Yao, Y. An, L. Fan, J. Wang, H. Li, Baicalin suppresses the progression of type 2 diabetes-induced liver tumor through regulating METTL3/m6A/HKDC1 axis and downstream p-JAK2/STAT1/clevaged Capase3 pathway, Phytomedicine 94 (2022) 153823, https://doi.org/10.1016/j.phymed.2021.153823.
[80] K. Fujita, T. Norikura, I. Matsui-Yuasa, S. Kumazawa, S. Honda, T. Sonoda, A. Kojima-Yuasa, Carob pod polyphenols suppress the differentiation of adipocytes through posttranscriptional regulation of C/EBPβ, PLoS One 16 (2021) 1–23, https://doi.org/10.1371/journal.pone.0248073.
[81] J. Chen, Y. Ying, H. Zhu, T. Zhu, C. Qu, J. Jiang, B. Fang, Curcumin-induced promoter hypermethylation of the mammalian target of rapamycin gene in multiple myeloma cells, Oncol. Lett. 17 (2019) 1108–1114, https://doi.org/10.3892/ol.2018.9662.
[82] X.T. Zhang, G. Wang, L.F. Ye, Y. Pu, R.T. Li, J. Liang, L. Wang, K.K.H. Lee, X. Yang, Baicalin reversal of DNA hypermethylation-associated klotho suppression ameliorates renal injury in type 1 diabetic mouse model, Cell Cycle 19 (2020) 3329–3347, https://doi.org/10.1080/15384101.2020.1843815.
[83] S.J. Lee, S.E. Choi, H.B. Lee, M.W. Song, Y.H. Kim, J.Y. Jeong, Y. Kang, H.J. Kim, T.H. Kim, J.Y. Jeon, K.W. Lee, A class I histone deacetylase inhibitor attenuates insulin resistance and inflammation in palmitate-treated C2C12 Myotubes and muscle of HF/HFr diet mice, Front. Pharmacol. 11 (2020) 1–13, https://doi.org/10.3389/fphar.2020.601448.
[84] B. Cheng Ren, Y. Fei Zhang, S. Shan Liu, X. Jing Cheng, X. Yang, X. Guang Cui, X. Rui Zhao, H. Zhao, M. Feng Hao, M. Dan Li, Y. Yuan Tie, L. Qu, X. Yi Li, Curcumin alleviates oxidative stress and inhibits apoptosis in diabetic cardiomyopathy via Sirt1-Foxo1 and PI3K-Akt signalling pathways, J. Cell. Mol. Med. 24 (2020) 12355–12367, https://doi.org/10.1111/jcmm.15725.
[85] E. Pitsillou, J. Liang, A. Hung, T.C. Karagiannis, Chromatin modification by olive phenolics: in silico molecular docking studies utilising the phenolic groups categorised in the OliveNetTM database against lysine specific demethylase enzymes: chromatin modification by olive phenolics, J. Mol. Graph. Model. 97 (2020) 107575, https://doi.org/10.1016/j.jmgm.2020.107575.
[86] S. Wei Wang, H. Sheng, Y. Feng Bai, Y. Yuan Weng, X. Yu Fan, F. Zheng, J. Qi Fu, F. Zhang, Inhibition of histone acetyltransferase by naringenin and hesperetin suppresses Txnip expression and protects pancreatic β cells in diabetic mice: Naringenin and hesperetin protect pancreatic β cells, Phytomedicine 88 (2021) 153454, https://doi.org/10.1016/j.phymed.2020.153454.
[87] C.J. Guo, J.J. Xie, R.H. Hong, H.S. Pan, F.G. Zhang, Y.M. Liang, Puerarin alleviates streptozotocin (STZ)-induced osteoporosis in rats through suppressing inflammation and apoptosis via HDAC1/HDAC3 signaling, Biomed. Pharmacother. 115 (2019) 108570, https://doi.org/10.1016/j.biopha.2019.01.031.
[88] U.H. Park, J.T. Hwang, H.S. Youn, E.J. Kim, S.J. Um, Kaempferol antagonizes adipogenesis by repressing histone H3K4 methylation at PPARγ target genes, Biochem. Biophys. Res. Commun. 617 (2022) 48–54, https://doi.org/10.1016/j.bbrc.2022.05.098.
[89] E. Cuyàs, J. Gumuzio, J. Lozano-Sánchez, D. Carreras, S. Verdura, L. Llorach-Pares, M. Sanchez-martinez, E. Selga, J.P. Guillermo, F.S. Scornik, R. Brugada, Extra virgin olive oil contains a phenolic inhibitor of the histone demethylase LSD1/KDM1A, Nutrients 11 (2019) 1656.
[90] Q. Li, C. Ge, J. Tan, Y. Sun, Q. Kuang, X. Dai, S. Zhong, C. Yi, L.F. Hu, D.S. Lou, M. Xu, Juglanin protects against high fat diet-induced renal injury by suppressing inflammation and dyslipidemia via regulating NF-κB/HDAC3 signaling, Int. Immunopharmacol. 95 (2021) 107340, https://doi.org/10.1016/j.intimp.2020.107340.
[91] U.H. Park, J.T. Hwang, H.S. Youn, E.J. Kim, S.J. Um, Piperine inhibits adipocyte differentiation via dynamic regulation of histone modifications, Phyther. Res. 33 (2019) 2429–2439, https://doi.org/10.1002/ptr.6434.
[92] D. Luna-Vital, I. Luzardo-Ocampo, M.L. Cuellar-Nuñez, G. Loarca-Piña, E. Gonzalez de Mejia, Maize extract rich in ferulic acid and anthocyanins prevents high-fat-induced obesity in mice by modulating SIRT1, AMPK and IL-6 associated metabolic and inflammatory pathways, J. Nutr. Biochem. 79 (2020) 108343, https://doi.org/10.1016/j.jnutbio.2020.108343.
[93] I.C. Nettore, C. Rocca, G. Mancino, L. Albano, D. Amelio, F. Grande, F. Puoci, T. Pasqua, S. Desiderio, R. Mazza, D. Terracciano, A. Colao, F. Bèguinot, G. L. Russo, M. Dentice, P.E. Macchia, M.S. Sinicropi, T. Angelone, P. Ungaro, Quercetin and its derivative Q2 modulate chromatin dynamics in adipogenesis and Q2 prevents obesity and metabolic disorders in rats, J. Nutr. Biochem. 69 (2019) 151–162, https://doi.org/10.1016/j.jnutbio.2019.03.019.
[94] V. Castrejón-Téllez, M. Villegas-romero, M.E. Rubio-Ruiz, I. Pérez-Torres, E. Carreón-Torres, E. Díaz-Díaz, V. Guarner-Lans, Effect of a resveratrol / quercetin mixture on the reversion of hypertension induced by a short-term exposure to high sucrose levels near weaning and a long-term exposure that leads to metabolic syndrome in rats, Int. J. Mol. Sci. 2231 (2020).
[95] A.M. Tshivhase, T. Matsha, S. Raghubeer, Resveratrol attenuates high glucose-induced inflammation and improves glucose metabolism in HepG2 cells, Sci. Report. 141 (14) (2024) 1–13, https://doi.org/10.1038/s41598-023-50084-6.
[96] R. Otton, A.P. Bolin, L.T. Ferreira, M.P. Marinovic, A.L.S. Rocha, M.A. Mori, Polyphenol-rich green tea extract improves adipose tissue metabolism by down-regulating miR-335 expression and mitigating insulin resistance and inflammation, J. Nutr. Biochem. 57 (2018) 170–179, https://doi.org/10.1016/j.jnutbio.2018.03.024.
[97] H. Liu, L. Wang, F. Li, Y. Jiang, H. Guan, D. Wang, D. Sun-Waterhouse, M. Wu, D. Li, The synergistic protection of EGCG and quercetin against streptozotocin (STZ)-induced NIT-1 pancreatic β cell damage via upregulation of BCL-2 expression by miR-16-5p, J. Nutr. Biochem. 96 (2021) 108748, https://doi.org/10.1016/j.jnutbio.2021.108748.
[98] M. Gan, X. Chen, Z. Chen, L. Chen, S. Zhang, Y. Zhao, L. Niu, X. Li, L. Shen, L. Zhu, Genistein alleviates high-fat diet-induced obesity by inhibiting the process of gluconeogenesis in mice, Nutrients 14 (2022) 1551, https://doi.org/10.3390/nu14081551.
[99] M. Gan, L. Shen, S. Wang, Z. Guo, T.I. Zheng, Y. Tan, Y. Fan, L. Liu, L. Chen, A. Jiang, X. Li, S. Zhang, L. Zhu, Genistein inhibits high fat diet-induced obesity through miR-222 by targeting BTG2 and adipor1, Food Funct. 11 (2020) 2418–2426, https://doi.org/10.1039/C9FO00861F.
[100] S. Zhang, L. Xu, R. Liang, C. Yang, P. Wang, Baicalin suppresses renal fibrosis through microRNA-124/TLR4/NF-κB axis in streptozotocin-induced diabetic nephropathy mice and high glucose-treated human proximal tubule epithelial cells, J. Physiol. Biochem. 76 (2020) 407–416, https://doi.org/10.1007/s13105-020-00747-z.
[101] C. Zhao, C. Zhao, H. Zhao, Defective insulin receptor signaling in patients with gestational diabetes is related to dysregulated miR-140 which can be improved by naringenin, Int. J. Biochem. Cell Biol. 128 (2020) 105824, https://doi.org/10.1016/j.biocel.2020.105824.
[102] D. Wang, Y. Li, Q.Q. Zhai, Y.F. Zhu, B.Y. Liu, Y. Xu, Quercetin ameliorates testosterone secretion disorder by inhibiting endoplasmic reticulum stress through the miR-1306-5p/HSD17B7 axis in diabetic rats, Bosn. J. Basic Med. Sci. 22 (2022) 191–204, https://doi.org/10.17305/bjbms.2021.6299.
[103] W. Mahjabeen, D.A. Khan, S.A. Mirza, Role of resveratrol supplementation in regulation of glucose hemostasis, inflammation and oxidative stress in patients with diabetes mellitus type 2: a randomized, placebo-controlled trial, Complement. Ther. Med. 66 (2022) 102819, https://doi.org/10.1016/j.ctim.2022.102819.
[104] M. Matboli, M. Saad, A.H. Hasanin, L.A. Saleh, W. Baher, M.M. Bekhet, S. Eissa, New insight into the role of isorhamnetin as a regulator of insulin signaling pathway in type 2 diabetes mellitus rat model: molecular and computational approach, Biomed. Pharmacother. 135 (2021) 111176, https://doi.org/10.1016/j.biopha.2020.111176.
[105] T. Ni, N. Lin, W. Lu, Z. Sun, H. Lin, J. Chi, H. Guo, Dihydromyricetin prevents diabetic cardiomyopathy via miR-34a suppression by activating autophagy, Cardiovasc. Drugs Ther. 34 (2020) 291–301, https://doi.org/10.1007/s10557-020-06968-0.
[106] A.M. Salem, A.S. Ragheb, M.G.A. Hegazy, M. Matboli, S. Eissa, Caffeic acid modulates miR-636 expression in diabetic nephropathy rats, Indian, J. Clin. Biochem. 34 (2019) 296–303, https://doi.org/10.1007/s12291-018-0743-0.
[107] S. Liu, Y. Fang, J. Yu, X. Chang, Hawthorn polyphenols reduce high glucose-induced inflammation and apoptosis in ARPE-19 cells by regulating miR-34a/SIRT1 to reduce acetylation, J. Food Biochem. 45 (2021) 1–12, https://doi.org/10.1111/jfbc.13623.
[108] O.A. Ojo, Puerarin as a potential drug candidate for the management of type-2 diabetes: molecular docking and pharmacophore modeling studies, Biointerface Res. Appl. Chem. 11 (2021) 8751–8759, https://doi.org/10.33263/BRIAC112.87518759.
[109] V.S. Patil, N.A. Khatib, Triterpene saponins from Barringtonia acutangula (L.) Gaertn as a potent inhibitor of 11β-HSD1 for type 2 diabetes mellitus, obesity, and metabolic syndrome, Clin. Phytoscience 6 (2020) 1–5, https://doi.org/10.1186/s40816-020-00210-y.
[110] K. Damián-Medina, Y. Salinas-Moreno, D. Milenkovic, L. Figueroa-Yáñez, E. Marino-Marmolejo, I. Higuera-Ciapara, A. Vallejo-Cardona, E. Lugo-Cervantes, In silico analysis of antidiabetic potential of phenolic compounds from blue corn (Zea mays L.) and black bean (Phaseolus vulgaris L.), Heliyon 6 (2020) 3632, https://doi.org/10.1016/j.heliyon.2020.e03632.
[111] T. Kostrzewa, P. Przychodzen, M. Gorska-Ponikowska, A. Kuban-Jankowska, Curcumin and cinnamaldehyde as PTP1B inhibitors with antidiabetic and anticancer potential, Anticancer Res. 39 (2019) 745–749, https://doi.org/10.21873/anticanres.13171.
[112] B. Banerjee, S. Chakraborty, P. Chakraborty, D. Ghosh, K. Jana, Protective effect of resveratrol on benzo(a)pyrene induced dysfunctions of steroidogenesis and steroidogenic acute regulatory gene expression in Leydig cells, Front. Endocrinol. (Lausanne). 10 (2019) 1–14, https://doi.org/10.3389/fendo.2019.00272.