EURASIAN EXPERIMENT JOURNAL OF MEDICINE AND MEDICAL SCIENCES (EEJMMS)
ISSN: 2992-4103
©EEJMMS Publications Volume 6 Issue 3 2025

The Role of Natural Products in Epigenetic Regulation of Genes Involved in Obesity and Diabetes

Kamanzi Ntakirutimana G.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

Obesity and diabetes are complex metabolic disorders influenced by genetic, environmental, and epigenetic factors. Emerging evidence suggests that epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, play critical roles in the regulation of genes implicated in the pathogenesis of these diseases. Natural products such as bioactive compounds derived from plants, fungi, and marine organisms have garnered significant interest due to their potential to modulate epigenetic mechanisms. This review summarizes current knowledge on how natural products influence epigenetic regulation of genes involved in obesity and diabetes. We highlight key classes of natural compounds, such as polyphenols, flavonoids, alkaloids, and terpenoids, and their mechanistic roles in modifying epigenetic marks that affect metabolic pathways, insulin sensitivity, adipogenesis, and inflammation. Understanding the epigenetic impact of these natural agents could pave the way for novel preventive and therapeutic strategies targeting obesity and diabetes.

Keywords: Epigenetics, Natural products, Obesity, Diabetes, DNA methylation

INTRODUCTION

Obesity and diabetes represent two of the most pressing global health challenges of the 21st century[1–3]. Both conditions are characterized by disruptions in metabolic homeostasis and are often accompanied by a state of chronic, low-grade inflammation that contributes to the progression of metabolic dysfunction[4–6]. Obesity, defined by excessive accumulation of adipose tissue, increases the risk of developing insulin resistance, which can ultimately lead to type 2 diabetes mellitus (T2DM)[7–9]. The coexistence of obesity and diabetes exacerbates the risk for a wide array of complications, including cardiovascular disease, kidney failure, and neuropathy, making their effective management a critical priority worldwide[10–13].

The development of obesity and diabetes is influenced by a complex interplay of genetic, environmental, and lifestyle factors. While inherited genetic variants do contribute to an individual's susceptibility to these metabolic diseases, it has become increasingly clear that genetics alone cannot fully explain the rising incidence rates globally[14, 15]. Epigenetic mechanisms have emerged as key players in bridging the gap between genetic predisposition and environmental exposures. These mechanisms dynamically regulate gene expression without altering the underlying DNA sequence, allowing cells to respond and adapt to environmental stimuli such as diet, physical activity, stress, and exposure to toxins[7, 16].

Epigenetics encompasses a variety of molecular processes that influence gene expression patterns, including DNA methylation, histone modifications, and the action of non-coding RNAs such as microRNAs and long non-coding RNAs. DNA methylation typically involves the addition of methyl groups to cytosine bases in the genome, leading to gene silencing or activation depending on the context[17]. Histone modifications, such as acetylation and methylation, alter chromatin structure and accessibility, thereby influencing transcriptional activity. Non-coding RNAs regulate gene expression post-transcriptionally by modulating mRNA stability and translation[18, 19]. Collectively, these epigenetic modifications play crucial roles in regulating metabolic pathways, inflammatory responses, and cellular differentiation all of which are dysregulated in obesity and diabetes.

Importantly, epigenetic changes are not static; they are reversible and responsive to environmental and lifestyle interventions, making them attractive targets for therapeutic strategies[20]. This understanding has spurred significant interest in identifying compounds that can modulate epigenetic marks and restore healthy gene

expression profiles in metabolic tissues. Natural products, derived from plants, fungi, and other organisms, have a long history of use in traditional medicine for managing metabolic disorders. Many bioactive compounds found in natural products possess potent antioxidant, anti-inflammatory, and metabolic regulatory properties[21]. More recently, research has begun to reveal that several natural products can also influence epigenetic mechanisms directly. These compounds have the potential to modify DNA methylation patterns, alter histone acetylation or methylation status, and regulate the expression of non-coding RNAs involved in metabolic regulation[22]. For example, polyphenols such as resveratrol, curcumin, and epigallocatechin gallate (EGCG) have demonstrated the ability to influence epigenetic marks associated with metabolic disease genes[23, 24]. Resveratrol, found in grapes and berries, is known to activate sirtuins histone deacetylases that play a role in energy metabolism and inflammation[25–27]. Curcumin, the active component of turmeric, has been shown to inhibit DNA methyltransferases and histone acetyltransferases, thereby affecting gene expression related to insulin sensitivity and lipid metabolism[28–30]. EGCG, abundant in green tea, modulates DNA methylation and histone modifications linked to adipogenesis and glucose homeostasis[31, 32].

The therapeutic potential of these natural products lies not only in their ability to target individual epigenetic enzymes but also in their multifaceted effects on multiple epigenetic pathways and metabolic processes. This broad-spectrum activity may provide synergistic benefits for the prevention and treatment of obesity and diabetes. Additionally, natural products often exhibit fewer side effects compared to synthetic drugs, which enhances their appeal for long-term use. This review aims to provide a comprehensive overview of current research on the role of natural products in modulating epigenetic modifications relevant to obesity and diabetes. By exploring the molecular mechanisms through which these compounds exert their effects, the review seeks to highlight novel avenues for developing epigenetic-based therapies. Understanding how natural products interact with epigenetic regulators will not only deepen our knowledge of metabolic disease pathogenesis but also pave the way for more personalized and effective treatment strategies. In sum, obesity and diabetes are multifactorial diseases influenced by genetic and environmental factors, with epigenetic mechanisms playing a crucial mediating role. Natural products offer promising opportunities to modulate these epigenetic marks, thereby improving metabolic health and offering novel therapeutic approaches for these widespread disorders. Further research and clinical studies are needed to translate these findings into safe and effective interventions for patients worldwide.

Epigenetic Mechanisms in Obesity and Diabetes

DNA Methylation

DNA methylation is a crucial epigenetic mechanism involving the addition of a methyl group to the 5-carbon position of cytosine residues, predominantly occurring within CpG dinucleotides[33]. These CpG sites often cluster in regions called CpG islands, which are frequently located near gene promoters. Methylation at these promoter CpG islands generally leads to transcriptional repression by impeding the binding of transcription factors or recruiting methyl-CpG-binding domain proteins that facilitate chromatin condensation[33]. However, methylation within gene bodies or other genomic contexts can sometimes be associated with gene activation, highlighting the complex regulatory roles of DNA methylation.

In the context of metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM), aberrant DNA methylation patterns have been widely documented[34]. Key metabolic genes involved in insulin signaling pathways, glucose homeostasis, lipid metabolism, and adipogenesis are subject to altered methylation states[35]. For instance, hypermethylation of the promoter region of the insulin receptor substrate 1 (IRS1) gene can reduce its expression, impairing insulin signaling and contributing to insulin resistance. Similarly, genes regulating adipocyte differentiation, such as peroxisome proliferator-activated receptor gamma (PPARγ), can exhibit dysregulated methylation patterns that affect fat storage and distribution[36].

Environmental factors, including diet, physical activity, and exposure to toxins, can influence DNA methylation landscapes, thereby modulating gene expression relevant to metabolic health. Importantly, these methylation changes may be reversible, providing a potential avenue for therapeutic interventions[37]. Studies using peripheral blood or adipose tissue from obese and diabetic patients have consistently reported differential methylation profiles, which could serve as biomarkers for disease risk, progression, or response to treatment[38]. In summary, DNA methylation acts as a dynamic epigenetic regulator whose dysregulation plays a critical role in the pathophysiology of obesity and diabetes.

Histone Modifications

Histone modifications are a diverse group of post-translational chemical alterations occurring mainly on the amino-terminal tails of histone proteins, including histones H3 and H4, which are components of the nucleosome core[39]. These modifications include acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and others. Each modification influences chromatin structure and accessibility, thereby modulating gene expression by either facilitating or hindering transcription factor binding and recruitment of chromatin remodelers[39].

Histone acetylation, typically catalyzed by histone acetyltransferases (HATs), neutralizes the positive charge on lysine residues, loosening chromatin and promoting gene transcription. Conversely, histone deacetylases

(HDACs) remove acetyl groups, leading to chromatin compaction and transcriptional repression[40]. Histone methylation can either activate or repress gene expression depending on the specific lysine or arginine residues modified. For example, trimethylation of histone H3 lysine 4 (H3K4me3) is associated with active promoters, whereas trimethylation of H3 lysine 27 (H3K27me3) correlates with gene silencing[40].
In metabolic disorders such as obesity and diabetes, dysregulation of histone modifications contributes to altered gene expression profiles involved in energy metabolism, insulin sensitivity, and inflammatory responses[41]. For instance, aberrant histone acetylation and methylation patterns have been identified at the promoters of genes regulating glucose uptake and adipocyte function. Chronic low-grade inflammation, a hallmark of obesity, is also epigenetically influenced by histone modifications that regulate pro-inflammatory cytokine gene expression in adipose tissue and immune cells[42].

Emerging evidence suggests that environmental cues such as nutrient availability, oxidative stress, and hormonal changes can influence histone-modifying enzymes, thereby altering chromatin landscapes in metabolic tissues[43]. Therapeutic targeting of histone modification enzymes, such as HDAC inhibitors, has shown promise in preclinical models to improve insulin sensitivity and reduce inflammation. Overall, histone modifications serve as pivotal regulators of chromatin dynamics, and their perturbation significantly impacts the gene networks underlying metabolic disease[43].

Non-Coding RNAs

Non-coding RNAs (ncRNAs) are a broad class of RNA molecules that do not encode proteins but play essential regulatory roles in gene expression at multiple levels, including transcriptional and post-transcriptional control[44]. Among these, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have emerged as critical modulators of metabolic processes related to obesity and diabetes[44]. MiRNAs are short (~22 nucleotides) single-stranded RNAs that primarily function by binding complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression[45]. Numerous miRNAs have been identified that regulate genes involved in insulin signaling, adipocyte differentiation, lipid metabolism, and inflammation[45]. For example, miR-103 and miR-107 have been implicated in insulin resistance by targeting caveolin-1, a protein essential for insulin receptor function. Similarly, miR-34a modulates adipogenesis and inflammation in adipose tissue, influencing metabolic homeostasis[46].
LncRNAs are a more diverse group of transcripts longer than 200 nucleotides that can regulate gene expression via various mechanisms, including chromatin remodeling, transcriptional interference, and acting as molecular sponges for miRNAs. Specific lncRNAs have been associated with pancreatic β-cell function, insulin secretion, and adipocyte metabolism[47]. For instance, lncRNA H19 has been shown to regulate insulin sensitivity and glucose metabolism, while lncRNA MEG3 influences β-cell apoptosis and inflammatory pathways[47].
The expression of these ncRNAs is often altered in metabolic disease states, contributing to pathogenesis by disrupting normal gene regulatory networks. Moreover, ncRNAs can serve as circulating biomarkers for early detection and prognosis of diabetes and obesity. Advances in RNA-based therapeutics, such as miRNA mimics or inhibitors and lncRNA modulation, are being explored to correct metabolic dysfunctions[48]. Thus, non-coding RNAs represent a vital layer of epigenetic regulation impacting the development and progression of obesity and diabetes.

Natural Products as Epigenetic Modulators

Natural products exert epigenetic effects by targeting enzymes such as DNA methyltransferases (DNMTs), histone deacetylases (HDACs), and histone methyltransferases. Below are major classes of natural products studied for their epigenetic roles in obesity and diabetes:

Polyphenols

Polyphenols are a diverse group of naturally occurring compounds found in plants, known for their potent antioxidant and anti-inflammatory properties[23, 24]. Among them, resveratrol, curcumin, and epigallocatechin-3-gallate (EGCG) have garnered attention for their epigenetic regulatory effects[24]. These compounds modulate gene expression by influencing DNA methylation and histone modifications—key mechanisms in epigenetic regulation. For instance, resveratrol activates Sirtuin 1 (SIRT1), a class III histone deacetylase involved in cellular metabolic regulation. SIRT1 activation leads to the deacetylation of histones and non-histone proteins, improving insulin sensitivity, enhancing mitochondrial function, and modulating lipid metabolism[49]. Curcumin, derived from turmeric, has been reported to inhibit histone acetyltransferases (HATs) and DNA methyltransferases (DNMTs), thereby altering the expression of genes involved in adipogenesis and glucose homeostasis. Similarly, EGCG, a major catechin found in green tea, regulates the methylation status of tumor suppressor genes and metabolic regulators, contributing to improved metabolic profiles[28, 50]. Collectively, these polyphenols influence pathways critical to energy homeostasis, inflammation, and insulin signaling[23, 51, 52]. Their epigenetic actions offer promising avenues for the prevention and management of metabolic disorders such as obesity, type 2 diabetes, and cardiovascular diseases, thereby highlighting the therapeutic potential of dietary polyphenols as epigenetic modulators in human health.

Flavonoids

Flavonoids are a subgroup of polyphenolic compounds widely distributed in fruits, vegetables, and legumes, known for their antioxidant, anti-inflammatory, and cardioprotective properties[51, 53]. Emerging evidence suggests that flavonoids such as quercetin and genistein exert significant epigenetic effects, particularly in the regulation of metabolic processes. Quercetin, commonly found in apples, onions, and berries, has been shown to inhibit histone deacetylases (HDACs), resulting in increased histone acetylation and modulation of gene expression linked to adipocyte differentiation and lipid metabolism[54, 55]. On the other hand, genistein, a soy isoflavone, can demethylate DNA at the promoter regions of genes implicated in insulin secretion, such as *INS* and *Pdx1*, thereby restoring their expression in diabetic models. Both flavonoids also regulate non-coding RNAs, including microRNAs (miRNAs), that are involved in glucose homeostasis, insulin signaling, and fat storage[56, 57]. These compounds influence peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT/enhancer-binding proteins (C/EBPs), and other transcription factors critical for adipogenesis and energy balance. The ability of flavonoids to modulate epigenetic marks makes them attractive therapeutic candidates for combating obesity, insulin resistance, and other metabolic disorders. Through dietary intake or supplementation, flavonoids may provide a non-pharmacological means to influence metabolic health via epigenetic pathways.

Alkaloids

Alkaloids are nitrogen-containing secondary metabolites found in a wide variety of plants and known for their diverse biological activities, including antimicrobial, anti-inflammatory, and antidiabetic properties[58, 59]. One prominent example is berberine, an isoquinoline alkaloid derived from plants like *Berberis vulgaris*. Berberine exhibits potent antidiabetic effects, partly through its epigenetic modulation of gene expression. It regulates both histone modifications and non-coding RNAs, particularly microRNAs (miRNAs), which are essential for post-transcriptional gene regulation[60, 61]. Berberine has been reported to upregulate miR-122 and miR-21 while downregulating miR-34a, thereby affecting genes involved in insulin signaling, glucose metabolism, and lipid homeostasis. Additionally, berberine modulates histone acetylation by influencing histone deacetylase (HDAC) activity, contributing to improved insulin sensitivity and reduced inflammatory gene expression in adipose tissues[62, 63]. Its capacity to inhibit nuclear factor-kappa B (NF-κB) further enhances its anti-inflammatory action, which is crucial for mitigating insulin resistance in metabolic disorders. Berberine also impacts the AMP-activated protein kinase (AMPK) pathway, a central regulator of cellular energy balance, which is epigenetically modulated to improve glucose uptake and fatty acid oxidation[63]. These multifaceted epigenetic effects position berberine as a promising natural therapeutic for the treatment of type 2 diabetes, obesity, and metabolic syndrome.

Terpenoids

Terpenoids, also known as isoprenoids, are a large and structurally diverse class of natural compounds derived from five-carbon isoprene units[64, 65]. They are found in a wide range of plants and exhibit various biological activities, including antioxidant, anti-inflammatory, and metabolic regulatory effects[65]. Notable terpenoids such as ginsenosides from *Panax ginseng* and ursolic acid from apple peels and rosemary have been shown to influence epigenetic mechanisms that control metabolic homeostasis[66]. Ginsenosides modulate DNA methylation patterns and histone acetylation, which affect the transcriptional activity of genes involved in glucose metabolism, energy expenditure, and adipocyte differentiation. Ursolic acid, a pentacyclic triterpenoid, has been shown to enhance histone acetylation and activate AMPK and PGC-1α pathways, thereby improving mitochondrial biogenesis and fatty acid oxidation[66]. Furthermore, terpenoids can modulate the activity of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), reshaping the chromatin structure and reactivating silenced genes important for insulin sensitivity and anti-inflammatory responses[65, 67]. Their effects also extend to the regulation of microRNAs that govern lipid metabolism and adipogenesis. Through these epigenetic mechanisms, terpenoids offer promising therapeutic potential for the prevention and management of obesity, diabetes, and related metabolic disorders by targeting gene expression pathways critical to energy balance and cellular function.

Mechanisms of Action

Natural products exert their therapeutic effects through various epigenetic mechanisms, contributing to the modulation of obesity and diabetes-related gene expression. One major pathway is the inhibition of DNA methyltransferases (DNMTs)[68]. DNMTs are enzymes responsible for adding methyl groups to DNA, often leading to the silencing of critical genes. In obesity and type 2 diabetes, hypermethylation of genes involved in insulin signaling, such as *PPARγ* or *IRS1*, contributes to impaired glucose uptake and insulin resistance. Certain phytochemicals, such as epigallocatechin gallate (EGCG) from green tea, can inhibit DNMTs, thereby reversing this hypermethylation and restoring gene function[68].

Natural compounds also modulate histone modifications, another key component of epigenetic regulation. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulate the acetylation status of histones, which in turn affects chromatin structure and gene accessibility[69]. For instance, curcumin and sulforaphane have been shown to inhibit HDACs, leading to a relaxed chromatin state and the activation of genes that enhance

insulin sensitivity and lipid metabolism[70]. In addition, natural products can influence microRNAs (miRNAs)—small non-coding RNAs that regulate gene expression post-transcriptionally[70]. By upregulating or downregulating specific miRNAs, compounds like quercetin and berberine modulate key metabolic pathways. For example, altering miRNAs that target *SIRT1* or *AMPK* mRNAs can enhance energy balance and glucose homeostasis.

Finally, many natural products possess antioxidant and anti-inflammatory properties, indirectly influencing the epigenome[21, 30, 71]. Chronic oxidative stress and inflammation, common in metabolic disorders, can lead to detrimental epigenetic modifications. By reducing these stressors, natural compounds may help maintain a healthier epigenetic landscape, further promoting metabolic health and preventing disease progression.

5. Evidence from Preclinical and Clinical Studies

A growing body of preclinical evidence supports the epigenetic effects of natural products in obesity and diabetes. In vitro studies using adipocytes, hepatocytes, and pancreatic β-cells have shown that phytochemicals such as resveratrol, curcumin, and genistein can significantly alter epigenetic markers[72]. These include reductions in DNA methylation at metabolic gene promoters and increases in histone acetylation that favor gene expression associated with glucose regulation and lipid metabolism. For example, curcumin has been found to enhance the expression of genes involved in insulin signaling by modulating DNMT activity in diabetic mouse models, leading to improved glucose tolerance and reduced insulin resistance[72].

Animal studies have further corroborated these findings. In high-fat diet-induced obese mice, supplementation with EGCG not only mitigated weight gain but also modulated histone modifications and miRNA expression patterns linked to inflammation and lipid metabolism[73]. Similarly, berberine was shown to upregulate miR-122 and downregulate lipogenic genes, reducing hepatic fat accumulation and improving insulin sensitivity[73].

Clinical evidence, though still emerging, is promising. In a randomized controlled trial, resveratrol administration in obese individuals led to improved insulin sensitivity and favorable changes in DNA methylation patterns related to metabolic pathways[74, 75]. Other small-scale trials have reported that quercetin and omega-3 fatty acid supplementation can influence histone acetylation and DNA methylation profiles in human blood cells, suggesting systemic epigenetic modulation.

Despite these advances, clinical studies remain limited by small sample sizes, short durations, and variability in natural product formulations. Nonetheless, these findings highlight the translational potential of natural compounds as modulators of epigenetic changes in metabolic diseases, warranting more extensive and standardized human trials to confirm efficacy and mechanism.

6. Challenges and Future Perspectives

Despite encouraging data on the epigenetic effects of natural products in metabolic disorders, several challenges must be addressed before these agents can be reliably integrated into clinical practice. One major limitation is bioavailability. Many phytochemicals, including curcumin and resveratrol, exhibit poor absorption, rapid metabolism, and limited systemic availability, which can reduce their therapeutic effectiveness. Strategies such as nanoformulations, liposomal delivery, or conjugation with bioenhancers are being explored to overcome these issues.

Another challenge is the dose- and context-dependent nature of epigenetic modulation. The same compound may exhibit different effects depending on concentration, cell type, or disease stage. This complexity complicates the identification of standardized doses and target populations. Moreover, the long-term safety and off-target effects of sustained epigenetic modulation by natural products are not fully understood.

Additionally, human studies on epigenetic outcomes remain sparse. Many existing clinical trials focus on metabolic endpoints without evaluating changes in DNA methylation, histone marks, or miRNA profiles. Integrating epigenomic profiling into clinical research could provide deeper insights into the mechanisms of action and help identify biomarkers predictive of response to treatment.

Looking ahead, future research should emphasize combinatorial approaches that explore synergistic effects of multiple natural products or their use alongside conventional therapies. Advances in systems biology, epigenomics, and personalized medicine can guide the development of tailored interventions. Furthermore, the creation of targeted delivery systems, such as epigenetic drug-loaded nanoparticles, could enhance precision and efficacy.

In summary, while natural products hold great promise as epigenetic modulators in obesity and diabetes management, multidisciplinary efforts are needed to optimize their therapeutic potential and translate laboratory findings into safe, effective clinical applications.

CONCLUSION

Natural products hold significant potential in modulating epigenetic mechanisms implicated in obesity and diabetes. Their ability to regulate gene expression through DNA methylation, histone modification, and non-coding RNAs provides a promising avenue for novel therapeutic interventions. Further research and clinical validation could lead to effective epigenetic therapies harnessing natural compounds to combat the growing burden of metabolic diseases.

REFERENCES

1. Abdali, D., Samson, S.E., Grover, A.K.: How effective are antioxidant supplements in obesity and diabetes? Med Princ Pract. 24, 201–215 (2015). https://doi.org/10.1159/000375305
2. Anand, S., Patel, T.N.: Integrating the metabolic and molecular circuits in diabetes, obesity and cancer: a comprehensive review. Discov Onc. 15, 779 (2024). https://doi.org/10.1007/s12672-024-01662-1
3. Alum, E.U.: Metabolic memory in obesity: Can early-life interventions reverse lifelong risks? Obesity Medicine. 55, 100610 (2025). https://doi.org/10.1016/j.obmed.2025.100610
4. Chadt, A., Scherneck, S., Joost, H.-G., Al-Hasani, H.: Molecular links between Obesity and Diabetes: "Diabesity." In: Feingold, K.R., Ahmed, S.F., Anawalt, B., Blackman, M.R., Boyce, A., Chrousos, G., Corpas, E., de Herder, W.W., Dhatariya, K., Dungan, K., Hofland, J., Kalra, S., Kaltsas, G., Kapoor, N., Koch, C., Kopp, P., Korbonits, M., Kovacs, C.S., Kuohung, W., Laferrère, B., Levy, M., McGee, E.A., McLachlan, R., Muzumdar, R., Purnell, J., Rey, R., Sahay, R., Shah, A.S., Singer, F., Sperling, M.A., Stratakis, C.A., Trence, D.L., and Wilson, D.P. (eds.) Endotext. MDText.com, Inc., South Dartmouth (MA) (2000)
5. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
6. Chellappan, D.K., Chellian, J., Rahmah, N.S.N., Gan, W.J., Banerjee, P., Sanyal, S., Banerjee, P., Ghosh, N., Guith, T., Das, A., Gupta, G., Singh, S.K., Dua, K., Kunnath, A.P., Norhashim, N.A., Ong, K.H., Palaniveloo, K.: Hypoglycaemic Molecules for the Management of Diabetes Mellitus from Marine Sources. DMSO. 16, 2187–2223 (2023). https://doi.org/10.2147/DMSO.S390741
7. Huang, X., Liu, G., Guo, J., Su, Z.: The PI3K/AKT pathway in obesity and type 2 diabetes. Int J Biol Sci. 14, 1483–1496 (2018). https://doi.org/10.7150/ijbs.27173
8. Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.Ak.: Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obesity Medicine. 100622 (2025). https://doi.org/10.1016/j.obmed.2025.100622
9. Min, S.H.: Mechanisms of Glucagon Receptor Agonism and GLP-1/Glucagon/GIP Receptor Triple Agonism for Treatment of Diabetes and Obesity. J Korean Diabetes. 25, 82–88 (2024). https://doi.org/10.4093/jkd.2024.25.2.82
10. Queiroz, M., Sena, C.M.: Perivascular adipose tissue: a central player in the triad of diabetes, obesity, and cardiovascular health. Cardiovascular Diabetology. 23, 455 (2024). https://doi.org/10.1186/s12933-024-02549-9
11. Agwupuye, E.I., Obeten, U.N., Maitra, S., Subramaniyan, V., Wong, L.S., Aljarba, N.H., Kumarasamy, V.: Tetracarpidium conophorum nuts (African walnuts) up-regulated adiponectin and PPAR-γ expressions with reciprocal suppression of TNF-α gene in obesity. J Cell Mol Med. 28, e70086 (2024). https://doi.org/10.1111/jcmm.70086
12. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., De Campos, O.C., Udeozor, P.A., Nfona, S.O., Lawal, B., Alum, E.U.: Modulation of Lipogenesis by Tetracarpidium conophorum Nuts via SREBP-1/ACCA-1/FASN Inhibition in Monosodium-Glutamate-Induced Obesity in Rats. Natural Product Communications. 20, 1934578X251344035 (2025). https://doi.org/10.1177/1934578X251344035
13. Orji, O.U., Awoke, N.J., Uti, D.E., Obasi, O.D., Aja, P.M., Nwamaka, E.N., et al.: The Therapeutic Role of Gastrodin in Combating Insulin Resistance, Inflammation, and Oxidative Stress Induced by Bisphenol-A. Natural Product Communications. 19, 1934578X241310096 (2024). https://doi.org/10.1177/1934578X241310096
14. Uti, D.E., Atangwho, I.J., Eyong, E.U., Umoru, G.U., Egbung, G.E., Rotimi, S.O., Nna, V.U.: African walnuts (Tetracarpidium conophorum) modulate hepatic lipid accumulation in obesity via reciprocal actions on HMG-CoA reductase and paraoxonase. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 20, 365–379 (2020)
15. Uti, D.E., Atangwho, I.J., Eyong, E.U., Umoru, G.U., Egbung, G.E., Nna, V.U., Udeozor, P.A.: African walnuts attenuate ectopic fat accumulation and associated peroxidation and oxidative stress in monosodium glutamate-obese Wistar rats. Biomed Pharmacother. 124, 109879 (2020). https://doi.org/10.1016/j.biopha.2020.109879
16. Suren Garg, S., Kushwaha, K., Dubey, R., Gupta, J.: Association between obesity, inflammation and insulin resistance: Insights into signaling pathways and therapeutic interventions. Diabetes Research and Clinical Practice. 200, 110691 (2023). https://doi.org/10.1016/j.diabres.2023.110691
17. Lee, H.-T., Oh, S., Ro, D.H., Yoo, H., Kwon, Y.-W.: The Key Role of DNA Methylation and Histone Acetylation in Epigenetics of Atherosclerosis. J Lipid Atheroscler. 9, 419–434 (2020). https://doi.org/10.12997/jla.2020.9.3.419

18. Bure, I.V., Nemtsova, M.V., Kuznetsova, E.B.: Histone Modifications and Non-Coding RNAs: Mutual Epigenetic Regulation and Role in Pathogenesis. Int J Mol Sci. 23, 5801 (2022). https://doi.org/10.3390/ijms23105801
19. Ikpozu, E.N., Offor, C.E., Igwenyi, I.O., Obaroh, I.O., Ibiam, U.A., Ukaidi, C.U.A.: RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diabetes & Vascular Disease Research. 22, 14791641251334726 (2025). https://doi.org/10.1177/14791641251334726
20. Mahmoud, A.M.: An Overview of Epigenetics in Obesity: The Role of Lifestyle and Therapeutic Interventions. Int J Mol Sci. 23, 1341 (2022). https://doi.org/10.3390/ijms23031341
21. Uti, D.E., Atangwho, I.J., Alum, E.U., Egba, S.I., Ugwu, O.P.-C., Ikechukwu, G.C.: Natural Antidiabetic Agents: Current Evidence and Development Pathways from Medicinal Plants to Clinical use. Natural Product Communications. 20, 1934578X251323393 (2025). https://doi.org/10.1177/1934578X251323393
22. Dai, W., Qiao, X., Fang, Y., Guo, R., Bai, P., Liu, S., Li, T., Jiang, Y., Wei, S., Na, Z., Xiao, X., Li, D.: Epigenetics-targeted drugs: current paradigms and future challenges. Sig Transduct Target Ther. 9, 332 (2024). https://doi.org/10.1038/s41392-024-02039-0
23. Aatif, M.: Current Understanding of Polyphenols to Enhance Bioavailability for Better Therapies. Biomedicines. 11, 2078 (2023). https://doi.org/10.3390/biomedicines11072078
24. Bešlo, D., Golubić, N., Rastija, V., Agić, D., Karnaš, M., Šubarić, D., Lučić, B.: Antioxidant Activity, Metabolism, and Bioavailability of Polyphenols in the Diet of Animals. Antioxidants (Basel). 12, 1141 (2023). https://doi.org/10.3390/antiox12061141
25. Bitterman, J.L., Chung, J.H.: Metabolic effects of resveratrol: addressing the controversies. Cell Mol Life Sci. 72, 1473–1488 (2014). https://doi.org/10.1007/s00018-014-1808-8
26. Salla, M., Karaki, N., El Kaderi, B., Ayoub, A.J., Younes, S., Abou Chahla, M.N., Baksh, S., El Khatib, S.: Enhancing the Bioavailability of Resveratrol: Combine It, Derivatize It, or Encapsulate It? Pharmaceutics. 16, 569 (2024). https://doi.org/10.3390/pharmaceutics16040569
27. Alum, E.U.: Role of phytochemicals in cardiovascular disease management: Insights into mechanisms, efficacy, and clinical application. Phytomedicine Plus. 5, 100695 (2025). https://doi.org/10.1016/j.phyplu.2024.100695
28. Bertoncini-Silva, C., Vlad, A., Ricciarelli, R., Giacomo Fassini, P., Suen, V.M.M., Zingg, J.-M.: Enhancing the Bioavailability and Bioactivity of Curcumin for Disease Prevention and Treatment. Antioxidants. 13, 331 (2024). https://doi.org/10.3390/antiox13030331
29. Dai, C., Lin, J., Li, H., Shen, Z., Wang, Y., Velkov, T., Shen, J.: The Natural Product Curcumin as an Antibacterial Agent: Current Achievements and Problems. Antioxidants (Basel). 11, 459 (2022). https://doi.org/10.3390/antiox11030459
30. Ntaobeten, E., Obeten, U.N., Bawa, I., Agada, S.A., Ukam, C.I.-O., Egbung, G.E.: Antioxidants in cancer therapy mitigating lipid peroxidation without compromising treatment through nanotechnology. Discover Nano. 20, 70 (2025). https://doi.org/10.1186/s11671-025-04248-0
31. Mokra, D., Joskova, M., Mokry, J.: Therapeutic Effects of Green Tea Polyphenol (–)-Epigallocatechin-3-Gallate (EGCG) in Relation to Molecular Pathways Controlling Inflammation, Oxidative Stress, and Apoptosis. Int J Mol Sci. 24, 340 (2022). https://doi.org/10.3390/ijms24010340
32. Wu, G., Cheng, H., Guo, H., Li, Z., Li, D., Xie, Z.: Tea polyphenol EGCG ameliorates obesity-related complications by regulating lipidomic pathway in leptin receptor knockout rats. The Journal of Nutritional Biochemistry. 118, 109349 (2023). https://doi.org/10.1016/j.jnutbio.2023.109349
33. Morales-Nebreda, L., McLafferty, F.S., Singer, B.D.: DNA methylation as a transcriptional regulator of the immune system. Transl Res. 204, 1–18 (2019). https://doi.org/10.1016/j.trsl.2018.08.001
34. Aja, P.M., Agu, P.C., Ogbu, C., Fasogbon, I.V., Musyoka, A.M., Ngwueche, W., Egwu, C.O., Tusubira, D., Ross, K.: RNA research for drug discovery: Recent advances and critical insight. Gene. 947, 149342 (2025). https://doi.org/10.1016/j.gene.2025.149342
35. Kim, M.: DNA methylation: a cause and consequence of type 2 diabetes. Genomics Inform. 17, e38 (2019). https://doi.org/10.5808/GI.2019.17.4.e38
36. Ahmed, S.A.H., Ansari, S.A., Mensah-Brown, E.P.K., Emerald, B.S.: The role of DNA methylation in the pathogenesis of type 2 diabetes mellitus. Clin Epigenetics. 12, 104 (2020). https://doi.org/10.1186/s13148-020-00896-4
37. Tiffon, C.: The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. Int J Mol Sci. 19, 3425 (2018). https://doi.org/10.3390/ijms19113425
38. Raciti, G.A., Desiderio, A., Longo, M., Leone, A., Zatterale, F., Prevenzano, I., Miele, C., Napoli, R., Beguinot, F.: DNA Methylation and Type 2 Diabetes: Novel Biomarkers for Risk Assessment? Int J Mol Sci. 22, 11652 (2021). https://doi.org/10.3390/ijms222111652

39. Liu, R., Wu, J., Guo, H., Yao, W., Li, S., Lu, Y., Jia, Y., Liang, X., Tang, J., Zhang, H.: Post-translational modifications of histones: Mechanisms, biological functions, and therapeutic targets. MedComm (2020). 4, e292 (2023). https://doi.org/10.1002/mco2.292
40. Park, S.-Y., Kim, J.-S.: A short guide to histone deacetylases including recent progress on class II enzymes. Exp Mol Med. 52, 204–212 (2020). https://doi.org/10.1038/s12276-020-0382-4
41. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. Obesity Medicine. 100623 (2025). https://doi.org/10.1016/j.obmed.2025.100623
42. Wu, Y.-L., Lin, Z.-J., Li, C.-C., Lin, X., Shan, S.-K., Guo, B., Zheng, M.-H., Li, F., Yuan, L.-Q., Li, Z.: Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. Sig Transduct Target Ther. 8, 98 (2023). https://doi.org/10.1038/s41392-023-01333-7
43. Axsom, J.E., Schmidt, H.D., Matura, L.A., Libonati, J.R.: The Influence of Epigenetic Modifications on Metabolic Changes in White Adipose Tissue and Liver and Their Potential Impact in Exercise. Front Physiol. 12, 686270 (2021). https://doi.org/10.3389/fphys.2021.686270
44. Mattick, J.S., Amaral, P.P., Carninci, P., Carpenter, S., Chang, H.Y., Chen, L.-L., Chen, R., Dean, C., Dinger, M.E., Fitzgerald, K.A., Gingeras, T.R., Guttman, M., Hirose, T., Huarte, M., Johnson, R., Kanduri, C., Kapranov, P., Lawrence, J.B., Lee, J.T., Mendell, J.T., Mercer, T.R., Moore, K.J., Nakagawa, S., Rinn, J.L., Spector, D.L., Ulitsky, I., Wan, Y., Wilusz, J.E., Wu, M.: Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 24, 430–447 (2023). https://doi.org/10.1038/s41580-022-00566-8
45. O'Brien, J., Hayder, H., Zayed, Y., Peng, C.: Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front Endocrinol (Lausanne). 9, 402 (2018). https://doi.org/10.3389/fendo.2018.00402
46. Hashimoto, N., Tanaka, T.: Role of miRNAs in the pathogenesis and susceptibility of diabetes mellitus. J Hum Genet. 62, 141–150 (2017). https://doi.org/10.1038/jhg.2016.150
47. Hu, G., Niu, F., Humburg, B.A., Liao, K., Bendi, S., Callen, S., Fox, H.S., Buch, S.: Molecular mechanisms of long noncoding RNAs and their role in disease pathogenesis. Oncotarget. 9, 18648–18663 (2018). https://doi.org/10.18632/oncotarget.24307
48. Yang, Y., Cheng, H.: Emerging Roles of ncRNAs in Type 2 Diabetes Mellitus: From Mechanisms to Drug Discovery. Biomolecules. 14, 1364 (2024). https://doi.org/10.3390/biom14111364
49. Wang(a), J., Wang, S., Wang(b), J., Xiao, M., Guo, Y., Tang, Y., Zhang, J., Gu, J.: Epigenetic Regulation Associated with Sirtuin 1 in Complications of Diabetes Mellitus. Front Endocrinol (Lausanne). 11, 598012 (2021). https://doi.org/10.3389/fendo.2020.598012
50. Tabanelli, R., Brogi, S., Calderone, V.: Improving Curcumin Bioavailability: Current Strategies and Future Perspectives. Pharmaceutics. 13, 1715 (2021). https://doi.org/10.3390/pharmaceutics13101715
51. Puspadewi, R., Milanda, T., Muhaimin, M., Chaerunisaa, A.Y.: Nanoparticle-Encapsulated Plant Polyphenols and Flavonoids as an Enhanced Delivery System for Anti-Acne Therapy. Pharmaceuticals. 18, 209 (2025). https://doi.org/10.3390/ph18020209
52. Vauzour, D., Rodriguez-Mateos, A., Corona, G., Oruna-Concha, M.J., Spencer, J.P.E.: Polyphenols and Human Health: Prevention of Disease and Mechanisms of Action. Nutrients. 2, 1106–1131 (2010). https://doi.org/10.3390/nu2111106
53. Fatima, N., Baqri, S.S.R., Bhattacharya, A., Koney, N.K.-K., Husain, K., Abbas, A., Ansari, R.A.: Role of Flavonoids as Epigenetic Modulators in Cancer Prevention and Therapy. Front. Genet. 12, (2021). https://doi.org/10.3389/fgene.2021.758733
54. Aghababaei, F., Hadidi, M.: Recent Advances in Potential Health Benefits of Quercetin. Pharmaceuticals (Basel). 16, 1020 (2023). https://doi.org/10.3390/ph16071020
55. Chiang, M.-C., Tsai, T.-Y., Wang, C.-J.: The Potential Benefits of Quercetin for Brain Health: A Review of Anti-Inflammatory and Neuroprotective Mechanisms. Int J Mol Sci. 24, 6328 (2023). https://doi.org/10.3390/ijms24076328
56. Mahadev, M., Nandini, H.S., Ramu, R., Gowda, D.V., Almarhoon, Z.M., Al-Ghorbani, M., Mabkhot, Y.N.: Fabrication and Evaluation of Quercetin Nanoemulsion: A Delivery System with Improved Bioavailability and Therapeutic Efficacy in Diabetes Mellitus. Pharmaceuticals (Basel). 15, 70 (2022). https://doi.org/10.3390/ph15010070
57. Odabaş Köse, E., Koyuncu Özyurt, Ö., Bilmen, S., Er, H., Kilit, C., Aydemir, E.: Quercetin: Synergistic Interaction with Antibiotics against Colistin-Resistant Acinetobacter baumannii. Antibiotics. 12, 739 (2023). https://doi.org/10.3390/antibiotics12040739
58. Adhikari, B.: Roles of Alkaloids from Medicinal Plants in the Management of Diabetes Mellitus. Journal of Chemistry. 2021, 2691525 (2021). https://doi.org/10.1155/2021/2691525
59. Dhalsamant, K., Singh, C.B., Lankapalli, R.: A Review on Greening and Glycoalkaloids in Potato Tubers: Potential Solutions. J Agric Food Chem. 70, 13819–13831 (2022). https://doi.org/10.1021/acs.jafc.2c01169

60. Ai, X., Yu, P., Peng, L., Luo, L., Liu, J., Li, S., Lai, X., Luan, F., Meng, X.: Berberine: A Review of its Pharmacokinetics Properties and Therapeutic Potentials in Diverse Vascular Diseases. Front. Pharmacol. 12, (2021). https://doi.org/10.3389/fphar.2021.762654
61. Li, A., Liu, Q., Li, Q., Liu, B., Yang, Y., Zhang, N.: Berberine Reduces Pyruvate-driven Hepatic Glucose Production by Limiting Mitochondrial Import of Pyruvate through Mitochondrial Pyruvate Carrier 1. EBioMedicine. 34, 243–255 (2018). https://doi.org/10.1016/j.ebiom.2018.07.039
62. Parseghian, L., Kahrarian, N., Arabanian, A.S., Moradi Alvand, Z., Massudi, R., Rahimi, M., Rafati, H.: Berberine-loaded nanoemulsions as a natural food preservative; the impact of femtosecond laser irradiation on the antibacterial activity. Heliyon. 10, e37283 (2024). https://doi.org/10.1016/j.heliyon.2024.e37283
63. Zaied, H., Ashmawy, M.I., Abdel Karim, A.E., Ghareeb, D.A., El Wakil, A.: Berberine-loaded albumin nanoparticles alleviate liver damage in rats by modulating mitochondrial biogenesis and mitochondria-endoplasmic reticulum interactions. Biochem Biophys Res Commun. 754, 151555 (2025). https://doi.org/10.1016/j.bbrc.2025.151555
64. Kim, T., Song, B., Cho, K.S., Lee, I.-S.: Therapeutic Potential of Volatile Terpenes and Terpenoids from Forests for Inflammatory Diseases. Int J Mol Sci. 21, 2187 (2020). https://doi.org/10.3390/ijms21062187
65. Magadani, R., Ndinteh, D.T., Roux, S., Nangah, L.P., Atangwho, I.J., Uti, D.E., Alum, E.U., Egba, S.I.: Cytotoxic Effects of Lecaniodiscus Cupanioides (Planch.) Extract and Triterpenoids-derived Gold Nanoparticles On MCF-7 Breast Cancer Cell Lines. Anticancer Agents Med Chem. (2025). https://doi.org/10.2174/0118715206325529241004064307
66. Park, J.D.: Metabolism and drug interactions of Korean ginseng based on the pharmacokinetic properties of ginsenosides: Current status and future perspectives. J Ginseng Res. 48, 253–265 (2024). https://doi.org/10.1016/j.jgr.2024.02.003
67. Ogunyemi, O.M., Gyebi, G.A., Olawale, F., Ibrahim, I.M., Iwaloye, O., Fabusiwa, M.M., Omowaye, S., Oloyede, O.I., Olaiya, C.O.: Identification of promising dipeptidyl peptidase-4 and protein tyrosine phosphatase 1B inhibitors from selected terpenoids through molecular modeling. Bioinform Adv. 5, vbae205 (2024). https://doi.org/10.1093/bioadv/vbae205
68. Chen, P., Wang, Y., Chen, F., Zhou, B.: Epigenetics in obesity: Mechanisms and advances in therapies based on natural products. Pharmacol Res Perspect. 12, e1171 (2024). https://doi.org/10.1002/prp2.1171
69. Chen, H.P., Zhao, Y.T., Zhao, T.C.: Histone Deacetylases and Mechanisms of Regulation of Gene Expression (Histone deacetylases in cancer). Crit Rev Oncog. 20, 35–47 (2015). https://doi.org/10.1615/critrevoncog.2015012997
70. Evans, L.W., Ferguson, B.S.: Food Bioactive HDAC Inhibitors in the Epigenetic Regulation of Heart Failure. Nutrients. 10, 1120 (2018). https://doi.org/10.3390/nu10081120
71. Atangwho, I.J., Ugwu, O.P.-C., Egbung, G.E., Aja, P.M.: Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: advances in targeted delivery and precision therapeutics. J Nanobiotechnology. 23, 336 (2025). https://doi.org/10.1186/s12951-025-03412-z
72. Nurkolis, F., Taslim, N.A., Syahputra, R.A., Annette d'Arqom, Tjandrawinata, R.R., Purba, A.K.R., Mustika, A.: Food phytochemicals as epigenetic modulators in diabetes: A systematic review. Journal of Agriculture and Food Research. 21, 101873 (2025). https://doi.org/10.1016/j.jafr.2025.101873
73. Filardi, T., Sabato, C., Lubrano, C., Santangelo, C., Morano, S., Lenzi, A., Migliaccio, S., Ferretti, E., Catanzaro, G.: MicroRNA Modulation by Dietary Supplements in Obesity. Biomedicines. 8, 545 (2020). https://doi.org/10.3390/biomedicines8120545
74. de Ligt, M., Bergman, M., Fuentes, R.M., Essers, H., Moonen-Kornips, E., Havekes, B., Schrauwen-Hinderling, V.B., Schrauwen, P.: No effect of resveratrol supplementation after 6 months on insulin sensitivity in overweight adults: a randomized trial. Am J Clin Nutr. 112, 1029–1038 (2020). https://doi.org/10.1093/ajcn/nqaa125
75. Nwuruku, O.A., Ugwu, O.P.-C., Uti, D.E., Edwin, N.: Harnessing nature: plant-derived nanocarriers for targeted drug delivery in cancer therapy. Phytomedicine Plus. 5, 100828 (2025). https://doi.org/10.1016/j.phyplu.2025.100828

CITE AS: Kamanzi Ntakirutimana G. (2025). The Role of Natural Products in Epigenetic Regulation of Genes Involved in Obesity and Diabetes. EURASIAN EXPERIMENT JOURNAL OF MEDICINE AND MEDICAL SCIENCES, 6(3):73-81