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Natural Products Targeting Adipokine Regulation in Obesity-Induced Type 2 Diabetes

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ABSTRACT

Obesity-induced type 2 diabetes (T2D) is a complex metabolic disorder characterized by insulin resistance and chronic low-grade inflammation. Adipokines bioactive peptides secreted by adipose tissue play a pivotal role in modulating glucose homeostasis, lipid metabolism, and inflammation. Dysregulation of adipokines such as adiponectin, leptin, resistin, and visfatin contributes significantly to the pathogenesis of obesity-induced T2D. Recently, natural products derived from plants, fungi, and marine sources have garnered attention for their potential to modulate adipokine expression and activity. These bioactive compounds, including polyphenols, flavonoids, terpenoids, and alkaloids, demonstrate promising therapeutic effects by restoring adipokine balance, improving insulin sensitivity, and mitigating metabolic inflammation. This review critically examines the current knowledge of adipokine biology in obesity-associated T2D and highlights the emerging role of natural products in targeting adipokine dysregulation as a novel therapeutic strategy.

Keywords: Adipokines; Natural products; Obesity; Type 2 diabetes; Insulin resistance; Inflammation; Phytochemicals; Metabolic syndrome

INTRODUCTION

The escalating prevalence of obesity has emerged as a major public health concern globally, with profound implications for the development of numerous metabolic diseases[1–4]. Among these, type 2 diabetes mellitus (T2D) has shown a particularly strong epidemiological and pathophysiological link to obesity[5–8]. The co-existence of obesity and T2D, often termed "diabesity," has reached epidemic proportions, posing significant challenges to healthcare systems worldwide[9, 10]. This metabolic condition is characterized by insulin resistance, pancreatic β-cell dysfunction, low-grade chronic inflammation, and dysregulated lipid and glucose metabolism[5, 11, 12]. The pathogenesis of diabesity is multifactorial, involving genetic, epigenetic, behavioral, and environmental components. However, at the center of this complex interplay lies adipose tissue, which has evolved from being viewed solely as an inert energy storage depot to being recognized as a metabolically active and highly dynamic endocrine organ[13, 14].

Adipose tissue secretes a wide array of bioactive molecules known as adipokines**,** which play crucial roles in regulating energy homeostasis, insulin sensitivity, inflammation, appetite, and lipid metabolism[15–18]. In a healthy metabolic state, adipokines such as adiponectin**,** leptin**,** resistin**,** visfatin**,** chemerin**,** and tumor necrosis factor-alpha (TNF-α) maintain a delicate balance to support normal physiological functions[11, 18, 19]. However, in obesity, the adipose tissue expands through both hypertrophy (increase in adipocyte size) and hyperplasia (increase in adipocyte number), leading to adipose tissue dysfunction. This dysfunctional state is marked by hypoxia, macrophage infiltration, oxidative stress, and an aberrant adipokine secretion profile characterized by decreased anti-inflammatory adipokines (e.g., adiponectin) and increased pro-inflammatory ones (e.g., TNF-α, IL-6, and resistin)[11, 13, 20].

This altered adipokine profile contributes directly to the pathogenesis of insulin resistance and chronic inflammation, which are hallmarks of T2D. For instance, low adiponectin levels are associated with reduced insulin sensitivity, impaired fatty acid oxidation, and increased gluconeogenesis[11, 13, 20]. Conversely, elevated levels of leptin and resistin promote inflammation and hepatic insulin resistance. Moreover, the recruitment of immune cells, particularly macrophages, into adipose tissue during obesity further amplifies this

inflammatory response through the release of cytokines and chemokines. This chronic low-grade inflammation perpetuates metabolic derangements, establishing a vicious cycle that underpins the progression of diabesity[4, 21–23].

Given the central role of adipokines in bridging obesity and T2D, targeting adipokine signaling pathways has emerged as a promising therapeutic strategy. Modulation of adipokine expression or function can potentially restore metabolic balance, reduce inflammation, and improve insulin sensitivity[24–26]. Traditional pharmacological approaches, including the use of insulin sensitizers such as thiazolidinediones and metformin, have shown some efficacy in modulating adipokine levels, but they are often associated with side effects, limited long-term efficacy, and poor patient adherence[27–29]. This has spurred interest in exploring alternative, more holistic interventions with fewer adverse effects.

In this context, natural products derived from medicinal plants, dietary sources, and traditional herbal medicines have garnered considerable attention for their potential to regulate adipokine signaling[30]. These natural compounds often possess anti-inflammatory, antioxidant, and insulin-sensitizing properties, which can positively influence adipokine secretion and action. For example, polyphenols such as resveratrol, curcumin, quercetin, and catechins have been shown to upregulate adiponectin, downregulate pro-inflammatory adipokines, and improve insulin sensitivity in various preclinical models[31–34]. Similarly, flavonoids, alkaloids, terpenoids, and other phytochemicals exhibit multi-targeted mechanisms that make them suitable candidates for the management of complex disorders like diabesity[35–38].

Furthermore, natural products have the advantage of being part of traditional dietary and medicinal systems across cultures, which supports their long-term safety and acceptability[39–41]. Emerging evidence from both animal studies and human clinical trials suggests that these compounds may provide effective adjunctive or even standalone therapies for managing obesity-induced T2D through modulation of adipokine-mediated pathways. However, despite promising preclinical data, more rigorous clinical investigations are needed to establish their efficacy, safety, bioavailability, and mechanisms of action in human populations[42]. This review aims to provide a comprehensive overview of the role of key adipokines in the pathophysiology of obesity-induced T2D and highlight the therapeutic potential of natural products in regulating adipokine function. By bridging the gap between molecular understanding and translational application, this work seeks to underscore the importance of adipokines as viable targets and natural compounds as valuable resources in the ongoing fight against diabesity. Ultimately, a deeper insight into adipokine biology and its modulation by natural agents could pave the way for innovative and integrative approaches to diabetes prevention and management.

2. Adipokines and Their Roles in Obesity-Induced Type 2 Diabetes

2.1. Adiponectin

Adiponectin is a key anti-inflammatory and insulin-sensitizing adipokine primarily secreted by adipocytes, particularly in subcutaneous adipose tissue[43–46]. It plays a crucial role in maintaining metabolic homeostasis by enhancing insulin sensitivity, promoting glucose uptake, and stimulating fatty acid oxidation, particularly in skeletal muscle and liver. Additionally, adiponectin suppresses hepatic gluconeogenesis and contributes to improved lipid profiles by increasing HDL cholesterol and reducing triglyceride levels[44–46]. In healthy individuals, circulating adiponectin levels are high and inversely correlated with body fat percentage. However, in obesity and obesity-related type 2 diabetes (T2D), adiponectin levels are markedly decreased[6, 33, 47]. This reduction contributes to systemic insulin resistance, chronic low-grade inflammation, and the development of metabolic syndrome. Low adiponectin levels are also associated with endothelial dysfunction and increased cardiovascular risk. Research indicates that therapeutic strategies aimed at enhancing adiponectin levels either through pharmacological agents, lifestyle interventions, or natural products can significantly improve insulin sensitivity and reduce the risk of T2D[48–50]. Some plant-derived compounds such as resveratrol and berberine have been shown to upregulate adiponectin expression[51, 52]. Thus, adiponectin is not only a biomarker for metabolic health but also a promising therapeutic target for the prevention and management of obesity-induced metabolic disorders.

2.2. Leptin

Leptin is a hormone predominantly produced by white adipose tissue and plays a central role in regulating energy homeostasis, appetite, and glucose metabolism[22, 24, 25]. It acts on the hypothalamus in the brain to suppress hunger and increase energy expenditure. In lean individuals, leptin serves as a feedback signal to prevent excessive food intake and maintain body weight. However, in obesity, leptin levels are chronically elevated due to increased adipose mass. Paradoxically, this does not lead to decreased food intake—a phenomenon termed leptin resistance, in which the hypothalamic neurons become less responsive to leptin signaling. As a result, appetite remains high despite sufficient energy stores, perpetuating weight gain and metabolic dysregulation[24, 26, 53, 54]. Leptin resistance is associated with increased insulin resistance, impaired glucose tolerance, and heightened inflammatory responses, all of which contribute to the pathogenesis of type 2 diabetes. Furthermore, leptin has immunomodulatory effects, promoting the secretion of pro-inflammatory cytokines such as TNF-α and IL-6. These effects exacerbate the chronic low-grade inflammation

observed in obesity. Although leptin therapy has shown promise in rare cases of leptin deficiency, its efficacy in common obesity is limited due to resistance[55, 56]. Understanding and overcoming leptin resistance remains a critical focus for therapeutic strategies targeting obesity and T2D.

2.3. Resistin

Resistin, a cysteine-rich polypeptide, was first identified in rodents as a hormone secreted by adipocytes, but in humans, it is mainly produced by mononuclear immune cells such as macrophages[57, 58]. It derives its name from its ability to induce resistance to insulin, thereby implicating it in the pathophysiology of type 2 diabetes and other metabolic disorders. Resistin exerts pro-inflammatory and insulin-antagonistic effects by promoting the secretion of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. These cytokines interfere with insulin signaling pathways, particularly in the liver, contributing to hepatic insulin resistance and impaired glucose metabolism[11, 59]. In obese individuals, serum resistin levels are typically elevated and strongly correlate with increased visceral fat mass, systemic inflammation, and a heightened risk of developing T2D[37, 60–62]. Moreover, resistin has been linked to endothelial dysfunction and atherosclerosis, suggesting a role in cardiovascular complications associated with metabolic diseases. Its expression is upregulated by inflammatory stimuli, creating a vicious cycle of inflammation and insulin resistance. Natural products with anti-inflammatory properties such as curcumin and quercetin may help reduce resistin expression and its deleterious metabolic effects. Given its dual role in inflammation and insulin resistance, resistin is a potential biomarker and therapeutic target in obesity-induced diabetes.

2.4. Visfatin

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT) or pre-B-cell colony-enhancing factor (PBEF), is an adipokine predominantly secreted by visceral adipose tissue[63]. It has garnered significant interest due to its insulin-mimetic properties, particularly its ability to bind to the insulin receptor and activate downstream signaling pathways that enhance glucose uptake in peripheral tissues. In obesity and type 2 diabetes, visfatin levels are typically elevated and correlate with visceral fat accumulation and insulin resistance. However, the role of visfatin in metabolic regulation remains controversial and complex[64]. While some studies suggest it enhances insulin sensitivity, others report that high visfatin levels contribute to inflammation, oxidative stress, and β-cell dysfunction. Visfatin also plays a role in NAD+ biosynthesis, which is essential for cellular energy metabolism and stress responses. Additionally, visfatin can activate inflammatory pathways, such as NF-κB, and upregulate the production of cytokines like IL-6 and TNF-α, thereby linking it to obesity-associated chronic inflammation[64]. Elevated visfatin has also been implicated in cardiovascular diseases and metabolic syndrome. Due to its dual nature, further research is needed to clarify its exact physiological and pathological roles. Nonetheless, visfatin remains a potential target for therapeutic intervention in obesity-related metabolic disorders.

2.5. Other Adipokines

In addition to adiponectin, leptin, resistin, and visfatin, several other adipokines have emerged as important modulators of metabolic function and inflammation in obesity-induced type 2 diabetes (T2D). Omentin, primarily expressed in visceral fat, exhibits insulin-sensitizing and anti-inflammatory properties[65]. Its levels are decreased in obesity and T2D, and low omentin levels are associated with insulin resistance and cardiovascular risk. Chemerin is a chemoattractant adipokine involved in adipogenesis, inflammation, and glucose homeostasis[65]. Elevated chemerin levels correlate with increased adiposity, insulin resistance, and systemic inflammation. Apelin, another adipokine, acts through the APJ receptor and has been shown to regulate glucose and lipid metabolism, improve insulin sensitivity, and exert cardiovascular protective effects. In obesity and T2D, apelin levels can vary, but studies suggest that enhancing apelin signaling may ameliorate metabolic dysfunction[66]. These adipokines, while less extensively studied than leptin and adiponectin, contribute significantly to the complex crosstalk between adipose tissue and other organs. Dysregulation of their expression and signaling pathways plays a key role in the development and progression of metabolic syndrome and T2D. Targeting these novel adipokines through dietary, pharmacological, or natural-product-based approaches may offer new strategies for managing obesity-related metabolic disorders.

3. Mechanisms of Adipokine Dysregulation in Obesity-Induced T2D

Obesity induces a chronic low-grade inflammatory state within adipose tissue, which plays a central role in the development of insulin resistance and metabolic dysfunction[4, 43, 67]. This inflammation is primarily driven by the infiltration of immune cells, particularly macrophages, into adipose tissue depots. In lean individuals, adipose tissue predominantly contains anti-inflammatory M2 macrophages, which help maintain metabolic homeostasis. However, in obesity, there is a phenotypic switch towards pro-inflammatory M1 macrophages. These M1 macrophages release high levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). These cytokines contribute to a sustained inflammatory environment that interferes with normal adipocyte function and disrupts adipokine secretion patterns.

Adipokines, such as adiponectin and leptin, are crucial regulators of glucose and lipid metabolism. In obesity, adiponectin levels are significantly decreased, while leptin levels are elevated but accompanied by leptin resistance[55, 56]. This imbalance promotes insulin resistance and further contributes to systemic metabolic dysfunction. Moreover, obesity-associated inflammation is compounded by oxidative stress, resulting from excessive reactive oxygen species (ROS) production, and endoplasmic reticulum (ER) stress, which arises due to the increased demand on protein-folding machinery in hypertrophic adipocytes. Both oxidative and ER stress activate intracellular signaling pathways such as JNK and IKKβ/NF-κB, which further amplify cytokine production and insulin resistance[68, 69].

These pathological mechanisms converge to impair insulin signaling in peripheral tissues, such as skeletal muscle and the liver, by inhibiting key components of the insulin signaling cascade. As a result, glucose uptake is reduced, and hepatic glucose production remains elevated, ultimately leading to hyperglycemia and type 2 diabetes[68]. Therefore, obesity-induced inflammation, oxidative stress, and ER stress create a vicious cycle that perpetuates adipokine dysregulation and metabolic disease progression.

4. Natural Products Modulating Adipokine Regulation

4.1. Polyphenols: Polyphenols are a diverse class of natural compounds known for their potent antioxidant and anti-inflammatory properties, which contribute significantly to their beneficial effects on metabolic health[31, 33, 34]. Key polyphenols such as resveratrol, curcumin, and epigallocatechin gallate (EGCG) have been shown to modulate adipokine secretion, thereby exerting anti-diabetic effects. Resveratrol, predominantly found in grapes, berries, and red wine, enhances adiponectin levels while simultaneously suppressing tumor necrosis factor-alpha (TNF-α), a major pro-inflammatory cytokine[52, 70]. This contributes to improved insulin sensitivity and reduced systemic inflammation. Curcumin, the principal curcuminoid in turmeric, exerts regulatory effects on both leptin and adiponectin expression. It lowers the levels of inflammatory cytokines such as interleukin-6 (IL-6) and TNF-α, improving metabolic parameters in obese and diabetic models. EGCG, the most abundant catechin in green tea, has been shown to reduce leptin resistance and elevate adiponectin levels, thereby contributing to improved glucose homeostasis and insulin signaling[71, 72]. Collectively, these polyphenols enhance adipokine balance by upregulating beneficial adipokines and downregulating those associated with inflammation and insulin resistance. Their pleiotropic mechanisms include modulation of AMP-activated protein kinase (AMPK), nuclear factor-kappa B (NF-κB), and peroxisome proliferator-activated receptors (PPARs), making them promising agents for therapeutic interventions in obesity-induced type 2 diabetes.

4.2. Flavonoids: Flavonoids are a prominent subclass of polyphenols widely found in fruits, vegetables, and medicinal plants, recognized for their anti-inflammatory, antioxidant, and adipokine-modulating properties[35, 36, 73]. Compounds like quercetin, naringenin, and kaempferol have been extensively studied for their roles in regulating adipocyte function and improving metabolic profiles[74]. Quercetin, naturally present in apples, onions, and berries, significantly lowers leptin and resistin levels, while increasing the secretion of adiponectin[70, 75]. This shift in adipokine balance is beneficial for enhancing insulin sensitivity and reducing systemic inflammation. Quercetin also inhibits nuclear factor-kappa B (NF-κB) signaling, thereby attenuating the expression of pro-inflammatory cytokines such as TNF-α and IL-6. Naringenin, a citrus-derived flavonoid, has demonstrated the ability to downregulate pro-inflammatory adipokines while upregulating adiponectin expression[76, 77]. It also enhances insulin receptor signaling, thereby improving glucose uptake in peripheral tissues. Kaempferol, found in leafy greens and tea, improves lipid metabolism and reduces oxidative stress in adipose tissue. These flavonoids act through multiple molecular targets, including AMPK activation, inhibition of oxidative stress pathways, and modulation of adipogenic gene expression. Overall, flavonoids represent a promising class of natural products for managing obesity and its metabolic complications through their effects on adipokine secretion and systemic inflammation.

4.3. Terpenoids: Terpenoids are a large and structurally diverse class of phytochemicals that possess a wide range of biological activities, including anti-inflammatory, antioxidant, and metabolic regulatory effects[78–80]. Among them, ginsenosides and oleanolic acid have been particularly noted for their capacity to modulate adipokine expression and improve glucose metabolism. Ginsenosides, the major active components of *Panax ginseng*, significantly elevate adiponectin levels and enhance glucose uptake in adipocytes and muscle cells. These effects are mediated through the activation of AMPK and enhancement of insulin receptor sensitivity, making them effective in countering insulin resistance[81, 82]. Ginsenosides also reduce inflammatory cytokines such as TNF-α and IL-6, contributing to improved adipose tissue function. Oleanolic acid, a pentacyclic triterpenoid found in olive oil, rosemary, and other medicinal plants, has demonstrated similar effects by decreasing leptin expression and increasing adiponectin production. It also exerts hepatoprotective and lipid-lowering effects, which are crucial in managing metabolic syndrome[81]. These terpenoids work synergistically by targeting key signaling pathways such as PPAR-γ, AMPK, and NF-κB, thereby reducing inflammation, promoting insulin

sensitivity, and restoring adipokine homeostasis. Their natural origin and multitargeted effects make terpenoids valuable candidates for the prevention and treatment of obesity-induced type 2 diabetes.

4.4. Alkaloids: Alkaloids are nitrogen-containing bioactive compounds derived from plants and are known for their diverse pharmacological properties, including anti-diabetic and anti-inflammatory effects[83, 84]. Two notable alkaloids, berberine and capsaicin, have shown remarkable efficacy in modulating adipokine secretion and improving metabolic outcomes in obesity-associated type 2 diabetes. Berberine, isolated from *Berberis* species, increases adiponectin levels and decreases resistin expression, thereby enhancing insulin sensitivity and reducing chronic inflammation[28, 85]. It also suppresses the expression of inflammatory cytokines such as TNF-α and IL-6 through inhibition of NF-κB signaling. Furthermore, berberine activates AMPK, which facilitates glucose uptake and lipid metabolism. Capsaicin, the pungent compound found in chili peppers, modulates leptin signaling by reducing leptin resistance and suppressing leptin-induced inflammatory responses[28, 86]. It also lowers the expression of pro-inflammatory cytokines and improves mitochondrial function in adipose tissue. These alkaloids interact with key metabolic regulators, including AMPK, PPAR-γ, and TRPV1 channels, leading to favorable changes in energy expenditure, adipokine balance, and insulin action. The capacity of berberine and capsaicin to influence both hormonal and inflammatory pathways underscores their therapeutic potential in correcting metabolic dysfunctions linked to obesity and type 2 diabetes, particularly through targeted regulation of adipokine secretion and signaling.

4.5. Marine-Derived Compounds: Marine ecosystems are an abundant source of structurally unique bioactive compounds with significant therapeutic potential. Marine-derived compounds such as fucoxanthin and phlorotannins have gained attention for their role in modulating adipokine secretion and improving metabolic health in obesity and type 2 diabetes[87–89]. Fucoxanthin, a marine carotenoid derived from brown seaweeds like *Undaria pinnatifida*, has been shown to significantly increase adiponectin levels while decreasing visceral fat accumulation and plasma glucose levels. It also activates the AMPK signaling pathway and enhances lipid oxidation, contributing to improved insulin sensitivity[90, 91]. Moreover, fucoxanthin inhibits inflammatory cytokine production in adipose tissue, thereby reducing systemic inflammation. Phlorotannins, a group of polyphenolic compounds unique to brown algae, exhibit strong antioxidant and anti-inflammatory properties. They have been reported to restore normal adipokine profiles by upregulating adiponectin and downregulating leptin and other pro-inflammatory markers[92]. These marine-derived agents target various molecular mechanisms, including suppression of NF-κB activation, enhancement of insulin receptor sensitivity, and modulation of gene expression related to lipid metabolism and adipogenesis. The pharmacological potential of these compounds makes them valuable additions to the arsenal of natural products aimed at managing obesity-induced metabolic dysfunctions and offers promising prospects for novel anti-diabetic therapeutics.

5. Challenges and Future Directions

Despite promising preclinical findings, the clinical translation of natural products targeting adipokines faces several challenges:

i. **Bioavailability and pharmacokinetics**: Many natural products suffer from low bioavailability, rapid metabolism, and limited tissue distribution.
ii. **Standardization**: Variability in plant source, extraction methods, and formulation can affect the reproducibility of results.
iii. **Mechanistic clarity**: The pleiotropic effects of natural products make it difficult to attribute therapeutic benefits to adipokine modulation alone.
iv. **Clinical evidence**: More well-designed clinical trials are needed to validate efficacy and safety in human populations.

Future research should focus on:

- Developing novel delivery systems (e.g., nanoparticles, liposomes) to enhance bioavailability.
- Identifying synergistic combinations of natural compounds for multi-targeted effects.
- Elucidating molecular pathways through integrative omics and systems biology approaches.
- Conducting long-term clinical trials to confirm efficacy in obese and diabetic populations.

CONCLUSION

Adipokines are critical regulators of metabolic homeostasis, and their dysregulation is central to the development of obesity-induced T2D. Natural products offer a promising therapeutic avenue for modulating adipokine expression, improving insulin sensitivity, and alleviating chronic inflammation. While the evidence supporting their efficacy is growing, rigorous clinical studies and mechanistic investigations are essential to fully realize their potential in metabolic disease management. Integrating natural product-based strategies with lifestyle interventions and conventional therapies could provide a holistic approach to combating diabesity.

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