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Adipokine-Modulating Natural Products: Bridging Obesity, Insulin Resistance, and Type 2 Diabetes

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ABSTRACT

Obesity a global health crisis, is closely linked to insulin resistance (IR) and the development of Type 2 diabetes mellitus (T2DM). Adipokines, hormones secreted from adipose tissue (such as adiponectin, leptin, resistin, visfatin, and others), are critical regulators of energy balance, metabolic function, and inflammatory processes. Dysregulation in their secretion and function contributes to obesity-related IR and T2DM. Natural products (phytochemicals and botanical extracts) have emerged as promising modulators of adipokine activity, offering complementary therapeutic opportunities. This review comprehensively examines the impact of selected natural compounds (e.g., resveratrol, curcumin, berberine, green tea catechins, genistein, and others) on adipokine profiles, underlying molecular mechanisms, and their translational potential in human metabolic disease. We summarize preclinical and clinical findings, highlight key challenges, and suggest future research directions aimed at bridging traditional metabolic therapy with adipokine-targeted natural interventions.

Keywords: Adipokines; Obesity; Insulin Resistance; Type 2 Diabetes; Resveratrol

INTRODUCTION

The global obesity epidemic has emerged as one of the most pressing public health challenges of the 21st century, and it is closely linked to a dramatic rise in insulin resistance (IR) and Type 2 diabetes mellitus (T2DM)[1, 2]. These metabolic disorders are now reaching pandemic proportions, imposing significant morbidity, mortality, and economic burdens worldwide[3, 4]. Central to the pathogenic nexus connecting obesity, IR, and T2DM is the dysfunction of adipose tissue. Long viewed as merely a passive reservoir for energy storage, adipose tissue is now recognized as a dynamic and metabolically active endocrine organ[5–7]. It exerts profound influence on whole-body metabolism through the secretion of adipokines bioactive peptides and proteins that regulate energy balance, lipid and glucose metabolism, and inflammatory responses[8, 9].

Under physiological conditions, adipokines help maintain metabolic homeostasis by orchestrating complex interactions between various tissues, including the liver, skeletal muscle, pancreas, and central nervous system[10, 11]. Key adipokines such as adiponectin and leptin play pivotal roles in insulin sensitivity, appetite regulation, and lipid oxidation[12–14]. Adiponectin, for instance, enhances insulin sensitivity and exerts potent anti-inflammatory and anti-atherogenic effects[13]. In contrast, leptin primarily regulates satiety and energy expenditure but also contributes to glucose metabolism[14–16]. However, in the context of obesity, the functional integrity of adipose tissue becomes compromised due to adipocyte hypertrophy, hypoxia, immune cell infiltration, and oxidative stress[17, 18]. This leads to a dysregulated adipokine secretion profile characterized by decreased adiponectin and increased levels of leptin, resistin, visfatin, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6)[12].

Such an imbalance in adipokine signaling fosters a pro-inflammatory, insulin-resistant state, which constitutes a core pathophysiological mechanism underlying the development and progression of T2DM[15]. The chronic low-grade inflammation mediated by these altered adipokine levels contributes to impaired insulin receptor signaling in target tissues, further aggravating metabolic dysfunction[19, 20]. Hence, targeting adipokine pathways presents an attractive and promising strategy for the prevention and treatment of T2DM in obese individuals.

Pharmacological agents currently used in the management of T2DM, such as metformin and thiazolidinediones (TZDs), have shown partial efficacy in modulating adipokine profiles[21]. For instance, TZDs activate peroxisome proliferator-activated receptor-gamma (PPAR-γ), leading to improved insulin sensitivity and increased adiponectin levels[21]. However, their use is often limited by undesirable side effects, including

weight gain, fluid retention, and cardiovascular risks[21]. Therefore, there is an increasing need for safer and more holistic interventions that can effectively restore adipokine balance without inducing adverse effects.

In this context, natural products derived from dietary sources or traditional medicinal plants—are gaining attention as complementary or alternative strategies. These compounds are typically associated with minimal toxicity and have been consumed by humans for centuries. Importantly, many natural products are rich in phytochemicals such as flavonoids, polyphenols, alkaloids, terpenoids, and saponins, which have demonstrated the ability to modulate adipokine expression and activity at the molecular level[22].

Several plant-derived compounds have shown promising results in experimental and clinical studies. For example, resveratrol, a polyphenol found in grapes and berries, has been reported to upregulate adiponectin levels and improve insulin sensitivity through the activation of AMP-activated protein kinase (AMPK) and SIRT1 signaling pathways[23–25]. Similarly, curcumin, the active constituent of turmeric, exhibits potent anti-inflammatory properties and has been shown to reduce levels of TNF-α and IL-6 while enhancing adiponectin expression[26–28]. Other phytochemicals such as quercetin, genistein, catechins, and berberine have also been implicated in adipokine regulation and the amelioration of IR[22].

The mechanisms by which these compounds exert their effects are diverse and multifaceted. They may influence transcription factors such as PPARs, nuclear factor-kappa B (NF-κB), and CCAAT/enhancer-binding proteins (C/EBPs), or modulate key signaling pathways including PI3K/Akt, JNK, and STAT3[22]. These molecular actions culminate in improved insulin sensitivity, reduced inflammation, and enhanced lipid metabolism.

Importantly, clinical studies investigating the effects of natural products on adipokine levels and glycemic control have begun to yield encouraging results. For instance, supplementation with green tea catechins or cinnamon extracts has been associated with improved fasting glucose levels and favorable changes in adipokine profiles in individuals with T2DM or metabolic syndrome[29]. Nonetheless, variability in study design, dosage, bioavailability, and population characteristics calls for more rigorous, large-scale clinical trials to confirm these findings and establish standardized guidelines for use.

In sum, the dysregulation of adipokines represents a key link between obesity and T2DM. While conventional pharmacological therapies offer some benefits, their limitations highlight the need for complementary approaches. Natural products, with their ability to modulate adipokine function and improve metabolic health, offer a promising avenue for therapeutic intervention. A deeper understanding of the molecular interactions between phytochemicals and adipokine signaling pathways may pave the way for novel, safe, and effective strategies in the battle against obesity-related insulin resistance and T2DM.

Adipokines: Biological Roles and Dysregulation

Adiponectin

Adiponectin is a key adipokine secreted predominantly by adipose tissue, and it plays a vital role in maintaining metabolic homeostasis[12]. It enhances hepatic insulin sensitivity and promotes fatty acid oxidation in skeletal muscles, making it a critical factor in glucose and lipid metabolism[14]. Mechanistically, adiponectin exerts its effects through its receptors, AdipoR1 and AdipoR2, which activate signaling pathways involving AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR-α)[30]. These pathways lead to increased glucose uptake and enhanced β-oxidation of fatty acids, thereby improving insulin sensitivity and energy expenditure[30]. Beyond metabolic regulation, adiponectin has notable anti-inflammatory and anti-atherogenic properties[13]. It inhibits the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), while enhancing the production of anti-inflammatory cytokines like IL-10[12]. Clinically, low circulating levels of adiponectin are consistently associated with various metabolic disorders, including insulin resistance (IR), type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD). As such, adiponectin is not only a biomarker of metabolic health but also a potential therapeutic target for intervention in metabolic syndrome[13]. Restoring or enhancing adiponectin activity may help in the prevention and management of these metabolic and inflammatory diseases.

Leptin: Leptin is an essential hormone predominantly produced by white adipose tissue and is primarily known for its role in regulating energy homeostasis[14, 16]. Acting through its receptors in the hypothalamus, leptin signals satiety and suppresses appetite while simultaneously stimulating energy expenditure[31]. In physiological states, leptin functions as a feedback mechanism to regulate food intake and body weight. However, in the context of obesity, a paradoxical situation arises where circulating leptin levels are elevated, yet its appetite-suppressing effects are diminished—a condition referred to as leptin resistance[31]. This resistance blunts the central nervous system's response to leptin, leading to continued food intake and further weight gain. Additionally, leptin plays a significant role in modulating immune and inflammatory responses[32]. It promotes the production of pro-inflammatory cytokines such as TNF-α and IL-6 and enhances the activation of immune cells including macrophages and T-cells[32]. This pro-inflammatory role is particularly prominent in obesity, where elevated leptin levels contribute to chronic low-grade inflammation. As such, leptin is both a metabolic and immunological mediator, with its dysregulation implicated in various conditions such as metabolic

syndrome, cardiovascular diseases, and autoimmune disorders[32]. Understanding leptin biology is crucial for developing therapeutic strategies aimed at mitigating leptin resistance and its associated complications.

Resistin, Visfatin, and Other Pro-inflammatory Adipokines: Resistin and visfatin are two prominent adipokines implicated in the development of insulin resistance and metabolic inflammation. Resistin, primarily secreted by macrophages in humans, has been shown to promote hepatic glucose production, thereby impairing insulin sensitivity[33]. It exerts its effects through activation of inflammatory signaling pathways, including nuclear factor-kappa B (NF-κB), leading to the upregulation of pro-inflammatory cytokines. Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT), exhibits insulin-mimetic properties by binding to the insulin receptor and promoting glucose uptake[33]. However, despite these insulin-like actions, visfatin is paradoxically associated with elevated inflammation and metabolic dysregulation, especially in obesity and type 2 diabetes mellitus (T2DM). In addition to resistin and visfatin, adipose tissue also secretes a range of classical pro-inflammatory cytokines such as TNF-α and interleukin-6 (IL-6), which exacerbate insulin resistance by activating serine kinases that phosphorylate insulin receptor substrate-1 (IRS-1) on serine residues[33]. This phosphorylation impairs insulin signaling, contributing to systemic insulin resistance. The collective impact of these pro-inflammatory adipokines promotes a state of chronic low-grade inflammation, a key pathological feature of obesity-linked metabolic disorders. Therapeutic strategies aimed at modulating these adipokines or their signaling pathways hold promise in combating obesity-associated insulin resistance and related complications.

Natural Products Modulating Adipokines: Several natural products and phytochemicals have demonstrated promising potential in modulating adipokine expression and function, thereby offering therapeutic avenues for managing metabolic disorders[22]. Resveratrol, a polyphenol found in grapes and red wine, enhances adiponectin expression while suppressing pro-inflammatory cytokines like TNF-α[23, 24]. Curcumin, the active compound in turmeric, exhibits anti-inflammatory properties and has been shown to increase adiponectin levels and reduce leptin resistance in obese models[27, 34–36]. Berberine, an isoquinoline alkaloid found in goldenseal and Chinese goldthread, modulates glucose metabolism and has been reported to upregulate adiponectin while downregulating resistin and visfatin[37, 38]. Green tea catechins, particularly epigallocatechin gallate (EGCG), have antioxidant and anti-inflammatory effects and enhance adiponectin expression while reducing circulating leptin and TNF-α levels[39–41]. Genistein, a soy-derived isoflavone, improves insulin sensitivity and modulates adipokines by increasing adiponectin and lowering inflammatory markers. Quercetin, a flavonoid present in onions and apples, similarly improves adipokine profiles by enhancing adiponectin and inhibiting IL-6 and TNF-α production[42, 43]. Additionally, omega-3 polyunsaturated fatty acids (EPA and DHA) possess anti-inflammatory properties that improve leptin and adiponectin signaling. Together, these natural compounds represent valuable adjuncts to conventional therapies, capable of restoring a healthy adipokine balance, mitigating inflammation, and improving metabolic outcomes in conditions such as obesity, insulin resistance, and type 2 diabetes.

Resveratrol: Resveratrol, a polyphenolic compound found in grapes and berries, has demonstrated significant effects in adipocytes and high-fat-fed rodent models[23, 44]. Studies indicate that resveratrol administration increases adiponectin levels, decreases resistin and TNF-α, and improves glucose homeostasis[45, 46]. These effects are primarily mediated through the activation of the SIRT1/AMPK pathway, which enhances mitochondrial function and energy metabolism. Resveratrol activates SIRT1, a NAD+-dependent deacetylase, leading to the deacetylation of PGC-1α, a key regulator of mitochondrial biogenesis[25, 46]. This process boosts mitochondrial function and promotes oxidative metabolism. Additionally, resveratrol increases adiponectin expression at the transcriptional level, contributing to improved insulin sensitivity and anti-inflammatory effects. Meta-analyses have shown that resveratrol supplementation leads to modest improvements in insulin sensitivity and increases in adiponectin levels[47]. Doses ranging from 150 to 2000 mg/day have been well-tolerated in clinical trials. However, the bioavailability of resveratrol remains a concern, as it is rapidly metabolized and eliminated from the body. Strategies to enhance its bioavailability, such as using nanoparticles or co-administration with other compounds, are under investigation [47].

Curcumin: Curcumin, the active compound in turmeric, has been shown to upregulate adiponectin and downregulate leptin, resistin, and inflammatory cytokines in adipocytes[28, 48]. These effects contribute to reduced adipose tissue inflammation and improved insulin resistance. The underlying mechanism involves the inhibition of the NF-κB pathway, a key regulator of inflammation. Randomized controlled trials (RCTs) have demonstrated that curcumin supplementation increases adiponectin levels and reduces fasting glucose and HOMA-IR, indicating improved insulin sensitivity[49]. Commonly used doses range from 500 mg to 2 g/day. These studies suggest that curcumin may be a beneficial adjunct in managing metabolic disorders. Despite its promising effects, curcumin has low bioavailability due to poor absorption and rapid metabolism[50]. To overcome this limitation, researchers are exploring improved delivery systems, such as nanoparticles and turmeric phytosome formulations, which enhance curcumin's stability and absorption.

Berberine: Berberine, a natural alkaloid found in several plants, has been shown to increase adiponectin and PPARγ expression, enhancing lipid metabolism and insulin receptor activity[38, 51]. These effects contribute to improved glucose and lipid homeostasis in preclinical models. Berberine activates AMP-activated protein kinase (AMPK), a key energy sensor that regulates metabolic pathways. Activation of AMPK leads to the upregulation of adiponectin via PPARγ agonism, promoting insulin sensitivity and reducing inflammation. Clinical trials comparing berberine (~500 mg, 2–3 times/day) to metformin have shown comparable reductions in fasting glucose, postprandial glucose[52], HbA1c, and HOMA-IR. Additionally, berberine supplementation has been associated with increased adiponectin levels, suggesting its potential as an effective alternative to conventional diabetes medications .

Green Tea Catechins (EGCG): Epigallocatechin gallate (EGCG), a major catechin in green tea, has been shown to elevate adiponectin levels, suppress leptin, TNF-α, and IL-6, and enhance thermogenesis[41, 53]. These effects contribute to reduced adipose oxidative stress and improved metabolic function[41, 54]. Some clinical trials have demonstrated that EGCG supplementation leads to weight loss, improved insulin sensitivity, and a favorable inflammatory profile. However, results vary due to differences in dosing (300–800 mg EGCG daily) and habitual tea intake among participants.

Genistein: Genistein, a soy isoflavone, has been shown to enhance adiponectin secretion via the PPARγ pathway, reduce leptin expression, and attenuate adipogenesis and inflammation in preclinical models[55]. Interventions with soy protein or genistein have led to modest improvements in adiponectin levels, fasting insulin, and lipid profiles in peri- and post-menopausal women[55]. However, results in men have been mixed, with some studies showing no significant effects

Quercetin: Quercetin, a flavonol found in fruits and vegetables, has been shown to increase adiponectin and insulin sensitivity while decreasing leptin and pro-inflammatory markers such as NF-κB and TNF-α in preclinical studies[42, 56]. Limited data from small trials in overweight individuals suggest that quercetin supplementation may lead to decreased blood pressure and IL-6 levels[57, 58]. However, adipokine endpoints remain underexplored, and further research is needed to confirm these effects.

Omega-3 PUFAs: Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), omega-3 polyunsaturated fatty acids, have been shown to upregulate adiponectin gene expression via PPARγ, and reduce the expression of resistin and inflammatory cytokines in preclinical model[59]. Meta-analyses indicate small reductions in triglycerides and occasional improvements in adiponectin levels with omega-3 PUFA supplementation. However, results are inconsistent across studies, possibly due to variations in study design, dosing, and participant characteristics [60].

Mechanistic Insights: How Natural Products Affect Adipokines

Transcriptional Regulation

Transcriptional regulation plays a crucial role in modulating adipokine expression in adipose tissues. Various bioactive compounds, particularly phytochemicals[61], have demonstrated the ability to activate nuclear receptors such as peroxisome proliferator-activated receptor gamma (PPARγ) and related transcription factors. PPARγ is a key regulator of adipocyte differentiation and lipid metabolism, and its activation leads to improved insulin sensitivity and enhanced adiponectin production[61]. Compounds like rosiglitazone, pioglitazone, and natural ligands such as omega-3 fatty acids, flavonoids, and polyphenols (e.g., resveratrol and curcumin) act as PPARγ agonists[61]. These compounds simultaneously reduce the expression of pro-inflammatory adipokines such as leptin, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), thereby mitigating systemic inflammation[62]. Additionally, transcriptional coactivators like PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) synergize with PPARγ and SIRT1 to fine-tune adipokine gene expression. This dual effect of upregulating beneficial adipokines like adiponectin while downregulating detrimental ones contributes to an overall improvement in metabolic health. Furthermore, the modulation of transcriptional machinery by these compounds influences epigenetic markers and chromatin accessibility, adding another layer of regulatory control[62]. Overall, targeting transcriptional pathways offers a promising approach to restoring adipokine balance and alleviating metabolic disorders associated with obesity and insulin resistance.

AMPK/SIRT1 Signaling

AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) are central metabolic regulators that integrate energy balance and stress responses[63]. These signaling molecules respond to changes in cellular energy levels, promoting catabolic processes and inhibiting anabolic ones to restore homeostasis[63]. Several natural compounds—most notably resveratrol, berberine, and epigallocatechin gallate (EGCG) have been shown to activate AMPK and SIRT1. Upon activation, AMPK enhances glucose uptake, fatty acid oxidation, and mitochondrial biogenesis while suppressing lipogenesis[63]. Concurrently, SIRT1, a NAD+-dependent deacetylase, deacetylates and activates transcriptional regulators such as PGC-1α and FOXO, which contribute to improved mitochondrial function and oxidative stress resistance. Both AMPK and SIRT1 activation lead to increased expression of adiponectin, an insulin-sensitizing adipokine, and reduced levels of leptin and pro-inflammatory mediators[63]. These pathways are also interlinked; for instance, AMPK activation can increase

NAD+ levels, further stimulating SIRT1 activity, creating a positive feedback loop. Activation of these signaling cascades improves insulin sensitivity, reduces inflammation, and supports metabolic flexibility in adipose tissues. Therefore, targeting the AMPK/SIRT1 axis represents a strategic therapeutic approach for combating obesity-induced metabolic disorders and for restoring adipokine homeostasis disrupted in conditions such as type 2 diabetes and metabolic syndrome.

NF-κB Inhibition

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway is a pivotal regulator of inflammatory responses within adipose tissue[64]. Chronic activation of NF-κB in obesity leads to elevated expression and release of pro-inflammatory cytokines and adipokines, including TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1)[64]. This state of low-grade chronic inflammation contributes significantly to insulin resistance and metabolic dysfunction. Phytochemicals such as curcumin, quercetin, and EGCG have demonstrated potent anti-inflammatory properties through their ability to suppress NF-κB activation[65]. These compounds inhibit IκB kinase (IKK), preventing the degradation of IκBα and thus hindering NF-κB's translocation into the nucleus. By blocking this pathway, the release of inflammatory adipokines is significantly reduced, mitigating inflammation in adipose tissue[65]. Additionally, NF-κB suppression enhances the expression of anti-inflammatory mediators like adiponectin, further contributing to improved metabolic outcomes. Inhibition of NF-κB also indirectly reduces oxidative stress, another key driver of adipocyte dysfunction[66]. Collectively, the downregulation of NF-κB signaling by natural compounds provides a multifaceted benefit: attenuating inflammation, restoring adipokine balance, and enhancing insulin sensitivity. This makes NF-κB a critical target in therapeutic interventions aimed at obesity-associated metabolic and inflammatory disorders.

Oxidative Stress Reduction

Oxidative stress, characterized by excessive generation of reactive oxygen species (ROS), plays a crucial role in disrupting adipocyte function and suppressing beneficial adipokines like adiponectin. Elevated ROS levels in adipose tissue are often associated with obesity, inflammation, and insulin resistance. These oxidative molecules damage cellular structures and impair insulin signaling pathways, exacerbating metabolic dysfunction. Antioxidant phytochemicals—such as resveratrol, curcumin, EGCG, and quercetin—have been shown to enhance the cellular antioxidant defense system by upregulating enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase. This enzymatic defense reduces oxidative burden, protects mitochondrial integrity, and restores redox balance. As a result, these compounds alleviate ROS-induced suppression of adiponectin expression, promoting a favorable adipokine profile. Additionally, by minimizing oxidative stress, these phytochemicals reduce NF-κB activation and subsequent inflammatory responses, creating a synergistic anti-inflammatory and antioxidant effect. Moreover, improved redox status enhances insulin sensitivity and supports metabolic homeostasis. The reduction of oxidative stress also plays a role in preserving preadipocyte differentiation and preventing adipocyte hypertrophy. Therefore, targeting oxidative stress with natural antioxidants offers a promising strategy to counteract the deleterious effects of metabolic syndrome and promote healthy adipose tissue function and adipokine secretion.

Modulation of Adipocyte Differentiation

Adipocyte differentiation, also known as adipogenesis, is a tightly regulated process crucial for healthy adipose tissue development and function. Dysregulated adipogenesis contributes to ectopic fat deposition, adipocyte hypertrophy, and altered adipokine secretion, often seen in obesity and related metabolic diseases. Natural compounds such as genistein (a soy isoflavone), curcumin, resveratrol, and EGCG have been reported to modulate adipocyte differentiation. These compounds influence key transcription factors, including PPARγ, C/EBPα (CCAAT/enhancer-binding protein alpha), and SREBP-1c (sterol regulatory element-binding protein 1c), which are essential for the maturation of preadipocytes into functional adipocytes. For instance, genistein can inhibit excessive adipocyte formation while promoting the development of metabolically active beige adipocytes, which are associated with increased energy expenditure. Curcumin, on the other hand, promotes a balanced differentiation process that enhances adiponectin secretion and reduces pro-inflammatory cytokines. By regulating adipogenesis, these phytochemicals help maintain an optimal number and size of adipocytes, prevent adipose tissue inflammation, and restore the balance between beneficial (adiponectin) and harmful (leptin, resistin) adipokines. Additionally, proper adipocyte differentiation supports lipid storage capacity and insulin responsiveness. Thus, the modulation of adipogenesis by natural compounds is a vital mechanism for sustaining metabolic health and combating obesity-related complications.

Challenges, Limitations, and Future Perspectives

Bioavailability: The therapeutic efficacy of many natural adipokine modulators is often compromised due to poor bioavailability, primarily stemming from low water solubility, poor absorption, and rapid metabolism in the gastrointestinal tract and liver. These pharmacokinetic limitations hinder their systemic circulation and therapeutic action. Recent advances in delivery systems such as nano-formulations, liposomes, micelles, and phytosome-based carriers are showing promise in overcoming these challenges. These technologies enhance

solubility, protect bioactive compounds from degradation, and improve cellular uptake and sustained release. Future research should optimize these novel delivery systems and evaluate their long-term safety, efficacy, and scalability for clinical use.

Dosing and Standardization: Natural compounds often lack standardized dosing regimens, which complicates reproducibility across studies and clinical applications. The concentration of bioactive constituents can vary significantly due to differences in plant origin, extraction methods, processing, and formulation. Inconsistent product quality leads to variable therapeutic outcomes, reducing the reliability of clinical evidence. To address this, rigorous quality control, batch-to-batch consistency, and standardization of active ingredients are essential. Establishing evidence-based dosing protocols through pharmacokinetic and pharmacodynamic studies will further support effective clinical application. Regulatory frameworks should enforce manufacturing standards to ensure uniformity and safety of commercially available natural health products.

Patient Heterogeneity: Individual responses to adipokine-targeting natural therapies vary significantly due to patient heterogeneity. Factors such as sex, age, genetic polymorphisms, baseline metabolic state (e.g., insulin resistance, lipid profile), gut microbiota composition, ethnicity, and comorbidities influence treatment outcomes. For instance, genetic variants in adipokine receptors or metabolic enzymes may modulate responsiveness. This diversity complicates clinical trial interpretations and generalizability of findings. Personalized approaches that consider these variables are necessary to optimize therapy. Future studies should stratify participants based on key biomarkers or genetic profiles to better understand subgroup-specific responses and to guide precision medicine strategies in adipokine modulation.

Endpoint Selection: Clinical trials investigating natural compounds that modulate adipokines often use broad metabolic endpoints such as body weight, glucose levels, or lipid profiles. While informative, these do not capture the direct effects on specific adipokines or their signaling pathways. This makes it challenging to establish a causal relationship between intervention and adipokine modulation. Future studies should include targeted endpoint selection, such as serum levels of leptin, adiponectin, resistin, and inflammatory markers, alongside mechanistic biomarkers like mRNA expression or pathway activity. Incorporating omics-based approaches and systems biology can offer deeper insights into molecular mechanisms and therapeutic potential.

Synergistic Combinations: Combining natural compounds with complementary mechanisms offers a promising strategy to enhance therapeutic efficacy in adipokine modulation. For example, berberine improves insulin sensitivity, curcumin reduces inflammation, and resveratrol activates sirtuins—together potentially providing a multi-targeted effect on adipokine regulation. Synergistic combinations can enhance bioavailability, minimize required doses, and reduce adverse effects. However, few well-designed randomized controlled trials (RCTs) have rigorously tested such combinations. Future research should explore optimal dosing, interaction effects, and mechanism-based synergy using in vitro, in vivo, and clinical models. Standardized multi-component formulations may become the next frontier in natural metabolic therapeutics.

Regulatory and Safety Considerations: Despite being of natural origin, adipokine-modulating supplements are not inherently safe, especially at high doses or when combined with other therapies. Compounds like berberine can inhibit cytochrome P450 enzymes, notably CYP3A4, potentially altering drug metabolism and increasing the risk of adverse drug interactions. Moreover, long-term safety data for many natural products remain limited. Regulatory oversight is often inconsistent across regions, allowing for variability in product composition and safety standards. To ensure patient safety and therapeutic consistency, clear regulatory frameworks must be established, including mandatory toxicological evaluations, safety assessments, and post-market surveillance for dietary and herbal supplements.

Bridging to Complementary and Integrative Care: Integrating adipokine-modulating phytochemicals into lifestyle-based approaches (diet, exercise, sleep, stress management) may significantly enhance metabolic outcomes by targeting key hormone regulators like adiponectin, leptin, resistin, and visfatin. Clinicians should begin with well-studied compounds such as curcumin and berberine at moderate, standardized doses—curcumin 1 g/day has been shown to raise adiponectin and lower leptin in metabolic-syndrome patients, while berberine has demonstrated improvements in insulin sensitivity, liver enzymes, and lipid profiles in non-alcoholic fatty liver disease. Regular monitoring of glycemia, lipid panels, liver function tests, and potential interactions—especially in polypharmacy—is essential, as berberine may alter hepatic enzyme activity and potentiate effects of antidiabetic or anticoagulant agents. Encouraging patients to adopt dietary patterns naturally rich in these compounds—such as Mediterranean-style eating with turmeric, whole grains, and colorful produce—reinforces both nutritional and behavioral aspects. Lastly, personalization based on patient phenotype (e.g., obesity, fatty liver, insulin resistance), tolerability, and observed response allows for tailored adjustments. By integrating phytochemical supplementation into comprehensive lifestyle protocols and diligently monitoring safety and efficacy, clinicians can enhance metabolic regulation while minimizing risks.

CONCLUSION

Altering adipokine secretion and function is a promising strategy for intervening in obesity-associated IR and T2DM. Natural products—especially resveratrol, curcumin, and berberine—show preclinical and emerging clinical efficacy in modulating adiponectin and inflammatory adipokines, thereby improving metabolic outcomes.

However, challenges in formulation, dose, and trial design remain. Thoughtfully designed, longer-term, adequately powered studies with standardized preparations and adipokine-focused endpoints are warranted. Integration of these agents into a holistic metabolic care framework could enrich current therapeutic paradigms.

Future Directions

Recent advancements in phytochemical therapies aim to tackle longstanding challenges in bioavailability and therapeutic consistency. Innovations such as nanoparticles, phytosomes, and sustained-release formulations are being developed to enhance absorption and extend release profiles. At the same time, robust large-scale randomized controlled trials, lasting six to twelve months and enrolling over 300 participants, are examining both underlying biological mechanisms (adipokine levels and adipose tissue imaging) and cardiometabolic outcomes. Concurrently, research is delving into synergistic, multi-component formulations designed to activate key metabolic regulators including AMPK, SIRT1, and PPARγ. To further tailor interventions, precision nutrition strategies are emerging, using genetic and metabolomic profiling to personalize phytochemical regimens. Complementing this approach, mechanistic studies leveraging transcriptomic and metabolomic tools are mapping molecular responses within adipose tissue, clarifying how different formulations exert their effects. Finally, clear global regulatory frameworks are being proposed to standardize quality control, verify safety, and substantiate therapeutic claims. Together, these strategies form a multifaceted roadmap aimed at optimizing phytochemical therapies, enhancing their scientific rigor, and ensuring they achieve measurable health benefits in metabolic and cardiometabolic contexts.

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