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Natural Product Modulators of Adipokine Signaling: A New Frontier in Obesity-Associated Cancer Therapy

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ABSTRACT

Obesity is a recognized risk factor for several cancers, including breast, colon, pancreatic, and endometrial cancers. A critical mechanistic link between obesity and tumorigenesis lies in adipose-derived hormones known as adipokines, particularly leptin, adiponectin, and resistin. These adipokines exert profound effects on cell proliferation, inflammation, angiogenesis, and insulin resistance processes central to both metabolic dysregulation and cancer progression. Recent evidence highlights the capacity of natural products and phytochemicals to modulate adipokine signaling pathways, offering a promising avenue for dual intervention in obesity and cancer. This review explores the molecular mechanisms by which key phytochemicals, including curcumin, resveratrol, quercetin, and berberine, modulate leptin, adiponectin, and resistin signaling. We also discuss how these natural compounds influence downstream oncogenic pathways such as JAK/STAT, AMPK, and NF-κB. The emerging role of natural product modulators in reprogramming the tumor-promoting adipokine milieu of obese individuals holds therapeutic potential. A better understanding of these bioactive compounds may pave the way for novel integrative strategies targeting obesity-driven cancers. Further preclinical and clinical research is needed to validate efficacy and optimize bioavailability.

Keywords: Adipokines, Obesity, Natural Products, Cancer, Phytochemicals

INTRODUCTION

Obesity has reached pandemic proportions globally, with the World Health Organization estimating that over 1.9 billion adults are overweight and more than 650 million are classified as obese[1–3]. This alarming rise in obesity rates has profound public health implications, as obesity is not only a leading contributor to metabolic disorders such as type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular disease, but also plays a pivotal role in the development and progression of various cancers[4–8]. Epidemiological studies have consistently demonstrated a strong correlation between obesity and increased incidence and mortality in cancers such as breast (especially postmenopausal), colorectal, pancreatic, liver, endometrial, and prostate cancers[9, 10]. The mechanisms underlying this association are multifactorial and remain an area of intense scientific investigation.

At the heart of the obesity–cancer link is a complex biological interplay involving systemic and tissue-specific alterations, including chronic low-grade inflammation, hyperinsulinemia, insulin resistance, increased bioavailability of sex hormones, oxidative stress, and deregulated lipid metabolism[11, 12]. Among these, the endocrine function of adipose tissue—particularly the dysregulated secretion of adipokines—has emerged as a key player. Adipokines are bioactive peptides predominantly secreted by white adipose tissue and are central to energy homeostasis, appetite regulation, and immune modulation. In obesity, the quantitative and qualitative profiles of adipokines are markedly altered, creating a pro-tumorigenic microenvironment that favors cancer initiation, promotion, and progression[9, 13].

Among the numerous adipokines identified, leptin, adiponectin, and resistin have been the most extensively studied for their dual roles in obesity and cancer[14, 15]. Leptin, often elevated in obese individuals, promotes tumorigenesis by activating signaling cascades such as JAK/STAT, PI3K/Akt, and MAPK, which are involved in cell proliferation, survival, and angiogenesis. In contrast, adiponectin generally reduced in obesity exerts anti-inflammatory and anti-proliferative effects through AMPK activation and inhibition of oncogenic pathways. Resistin, although initially linked to insulin resistance, has also been implicated in cancer development through its pro-inflammatory actions and activation of NF-κB and STAT3 pathways. The dysregulation of these

adipokines and their downstream signaling networks contributes significantly to the establishment of a tumor-promoting environment in obese individuals[14, 16].
In recent years, natural products, especially phytochemicals derived from medicinal plants, fruits, vegetables, and herbs, have gained considerable attention for their potential to modulate adipokine expression and activity[17]. These bioactive compounds possess pleiotropic properties, including anti-inflammatory, antioxidant, and anticancer effects, which make them attractive candidates for adjunct therapy in obesity-associated cancers. Numerous in vitro and in vivo studies have demonstrated that certain polyphenols, flavonoids, alkaloids, terpenes, and other phytoconstituents can influence adipokine signaling pathways and reverse their oncogenic effects. For instance, curcumin, resveratrol, quercetin, and genistein have shown promise in restoring adipokine balance and inhibiting tumor progression[18, 19].

Given the urgent need for novel, safe, and effective strategies to combat the growing burden of obesity-linked cancers, the therapeutic targeting of adipokine pathways using natural products offers a compelling and underexplored avenue. Understanding the molecular mechanisms through which phytochemicals regulate leptin, adiponectin, and resistin signaling may pave the way for innovative interventions that bridge the gap between metabolic health and cancer prevention[10].

2. Adipokine Signaling and Cancer: An Overview

2.1 Leptin: Leptin is a hormone primarily secreted by white adipose tissue that plays a critical role in regulating energy homeostasis, satiety, and metabolism by acting on the hypothalamus[5, 20]. Under normal physiological conditions, leptin suppresses appetite and promotes energy expenditure. However, in obesity, a paradoxical state of hyperleptinemia coupled with leptin resistance emerges, whereby elevated circulating leptin fails to elicit its normal regulatory effects[21, 22]. This leptin resistance is implicated not only in metabolic disturbances but also in cancer development and progression. Elevated leptin levels in obese individuals activate several oncogenic pathways, notably the JAK2/STAT3, PI3K/Akt, and MAPK pathways. These pathways collectively contribute to enhanced cellular proliferation, inhibition of apoptosis, increased angiogenesis, and metastasis in various cancers, including breast, colorectal, prostate, and ovarian cancers[23, 24]. Leptin can also modulate the tumor microenvironment by promoting inflammatory cytokine production, macrophage recruitment, and immune evasion, thereby creating a pro-tumorigenic niche. Additionally, leptin cross-talks with estrogen signaling in hormone-dependent cancers like breast cancer, further exacerbating tumor growth. The dual metabolic and mitogenic effects of leptin underscore its significance as a molecular link between obesity and cancer, and targeting leptin signaling holds promise for novel therapeutic strategies in obesity-associated malignancies[25, 26].
2.2 Adiponectin: Adiponectin is a protective adipokine predominantly secreted by adipocytes, known for its insulin-sensitizing, anti-inflammatory, and anti-cancer properties[20]. Unlike leptin, adiponectin levels are inversely correlated with fat mass; thus, they are significantly reduced in obese individuals. Adiponectin mediates its beneficial effects primarily through the activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPARα) pathways, both of which are crucial in maintaining metabolic homeostasis[27]. These pathways inhibit gluconeogenesis, promote fatty acid oxidation, and enhance insulin sensitivity. In the context of cancer, adiponectin exerts anti-proliferative, pro-apoptotic, and anti-angiogenic effects[20]. It downregulates several tumor-promoting signaling cascades, including PI3K/Akt and NF-κB, while also reducing the production of inflammatory cytokines such as TNF-α and IL-6. Low adiponectin levels have been associated with increased risk and poor prognosis in cancers such as breast, endometrial, prostate, and colorectal cancers. Furthermore, adiponectin can counteract the oncogenic effects of leptin and resistin, highlighting its antagonistic role in the obesity–cancer axis[20]. Restoration of adiponectin levels or sensitization of its signaling pathways is therefore a promising therapeutic strategy in combating obesity-induced tumorigenesis and metabolic disorders.
2.3 Resistin: Resistin is a cysteine-rich pro-inflammatory adipokine primarily produced by macrophages in humans and adipocytes in rodents[28]. It plays a central role in the development of insulin resistance, low-grade chronic inflammation, and metabolic dysregulation commonly seen in obesity. Elevated resistin levels are associated with increased circulating inflammatory cytokines, such as IL-6, TNF-α, and CRP, linking it directly to systemic inflammation[28]. In cancer, resistin acts as a potent mediator of tumorigenesis through its activation of oncogenic signaling pathways such as nuclear factor-kappa B (NF-κB), extracellular signal-regulated kinase (ERK1/2), and signal transducer and activator of transcription 3 (STAT3)[29]. These pathways facilitate cancer cell proliferation, migration, invasion, and angiogenesis. High resistin expression has been observed in various malignancies, including colorectal, breast, pancreatic, and prostate cancers. Moreover, resistin contributes to a tumor-supportive microenvironment by enhancing matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), and epithelial-mesenchymal transition (EMT)[29]. The inflammatory and mitogenic influence of resistin underscores its potential as both a biomarker and therapeutic target in obesity-associated cancers. Strategies aimed at suppressing resistin expression or interrupting its

downstream signaling may yield novel interventions in the management of inflammation-driven malignancies[29].

3.1 Curcumin: Curcumin is a bioactive polyphenolic compound derived from the rhizome of *Curcuma longa* (turmeric), extensively studied for its anti-inflammatory, antioxidant, and anti-cancer effects. In the context of adipokine signaling, curcumin modulates multiple targets associated with obesity and tumorigenesis[30, 31]. It significantly downregulates leptin expression and its receptor (Ob-R) in various cancer models, including breast and pancreatic cancers, thereby interrupting leptin-induced JAK2/STAT3 and PI3K/Akt activation. Additionally, curcumin enhances adiponectin levels and sensitizes cells to adiponectin signaling through AMPK activation, contributing to reduced tumor cell proliferation and enhanced apoptosis. Curcumin also antagonizes the effects of resistin by inhibiting the NF-κB pathway, a central mediator of inflammation and cancer progression[32–34]. It suppresses pro-inflammatory cytokine expression, reduces oxidative stress, and modulates the tumor microenvironment to favor anti-tumor immunity[31, 35, 36]. Furthermore, curcumin interferes with angiogenesis and metastasis by downregulating VEGF and MMPs. Its ability to concurrently regulate leptin, adiponectin, and resistin pathways highlights its potential as a natural multi-targeted agent against obesity-associated cancers. However, challenges such as poor bioavailability have prompted the development of curcumin analogs and nano-formulations to enhance its therapeutic efficacy[37].

3.2 Resveratrol: Resveratrol is a naturally occurring polyphenol found abundantly in grapes, berries, red wine, and peanuts. It has gained attention for its potent anti-inflammatory, anti-obesity, and anti-cancer properties[38, 39]. Resveratrol exerts its beneficial effects partly by modulating adipokine signaling pathways. It reduces leptin secretion and downregulates leptin receptor expression, thereby attenuating leptin-induced JAK2/STAT3 and PI3K/Akt signaling[40]. This results in suppressed cancer cell proliferation, reduced angiogenesis, and enhanced apoptosis[41, 42]. Resveratrol also upregulates adiponectin levels and enhances its downstream signaling through AMPK and SIRT1 activation, promoting anti-proliferative and insulin-sensitizing effects. In addition, resveratrol inhibits the pro-inflammatory actions of resistin by suppressing NF-κB and ERK1/2 pathways, leading to decreased expression of inflammatory cytokines and matrix-degrading enzymes such as MMP-9. These effects collectively reduce tumor invasiveness and metastatic potential[43]. Resveratrol has shown efficacy in multiple cancer models, including breast, prostate, colorectal, and liver cancers. It also improves metabolic parameters in obese individuals, making it a promising candidate for integrative cancer therapy. Despite its low bioavailability, various formulations such as resveratrol-loaded nanoparticles and liposomes are being explored to enhance its stability and systemic delivery in clinical settings.

3.3 Quercetin: Quercetin is a dietary flavonoid commonly found in apples, onions, tea, and capers, known for its strong antioxidant and anti-inflammatory effects[44, 45]. It plays a regulatory role in adipokine expression, particularly in obesity and cancer-related pathways. Quercetin suppresses leptin expression and signaling, thereby reducing leptin-induced activation of JAK2/STAT3 and PI3K/Akt pathways that contribute to cancer cell survival, proliferation, and metastasis[46, 47]. Simultaneously, quercetin enhances adiponectin secretion and amplifies AMPK signaling, which inhibits cancer cell growth and improves insulin sensitivity. Quercetin also exhibits significant antagonistic activity against resistin-mediated signaling by inhibiting ERK1/2 and NF-κB pathways, resulting in decreased pro-inflammatory cytokine production and lower metastatic potential of cancer cells[48, 49]. Furthermore, quercetin modulates the tumor microenvironment by reducing oxidative stress, suppressing angiogenic factors like VEGF, and inhibiting epithelial-mesenchymal transition (EMT). These effects make quercetin an attractive compound for preventing and managing obesity-associated malignancies. Its synergistic action on multiple adipokines underscores its potential as a dietary supplement in integrative oncology[44]. However, like other polyphenols, the clinical translation of quercetin is limited by its poor solubility and bioavailability, prompting ongoing research into nano-formulations and structural analogs for enhanced efficacy.

3.4 Berberine: Berberine is an isoquinoline alkaloid extracted from plants such as *Berberis vulgaris*, with a long history of use in traditional[50, 51] Chinese medicine. It has emerged as a promising natural compound for metabolic and cancer-related disorders due to its multifaceted pharmacological effects. Berberine positively influences adipokine signaling by enhancing adiponectin secretion and promoting AMPK pathway activation, which contributes to improved insulin sensitivity, anti-proliferative activity, and apoptosis in cancer cells[50, 52]. Simultaneously, berberine reduces leptin levels and mitigates leptin resistance by downregulating Ob-R expression and interfering with leptin-mediated STAT3 signaling. This attenuation of leptin signaling results in decreased tumor growth and angiogenesis, particularly in breast, colon, and liver cancer models[53]. Berberine also suppresses resistin expression and downstream inflammatory cascades, including the NF-κB and ERK1/2 pathways, thereby reducing pro-inflammatory cytokine production and tumor invasiveness[54]. Additionally, berberine modulates the gut microbiota and reduces systemic inflammation, which indirectly contributes to favorable adipokine balance. Despite its strong therapeutic potential, the clinical use of berberine

is hindered by limited oral bioavailability, prompting the development of novel delivery systems such as lipid-based carriers and synthetic derivatives to enhance its absorption and systemic effects.

4. Mechanistic Insights: Downstream Signaling Modulation

Natural products have garnered significant attention in recent years for their potential to modulate adipokine signaling pathways that contribute to cancer progression, particularly in obesity-related malignancies[55–57]. One such pathway influenced by natural compounds is the JAK2/STAT3 signaling cascade, which is commonly activated by the pro-inflammatory adipokine leptin. This pathway promotes tumor cell proliferation, survival, and angiogenesis. Phytochemicals such as resveratrol and curcumin have been shown to inhibit leptin-induced STAT3 phosphorylation, thereby disrupting oncogenic signaling[58, 59]. By attenuating this cascade, these natural agents reduce cancer cell viability and impair tumor growth, demonstrating their promise as adjunct therapies in cancers associated with leptin overexpression and chronic inflammation.

Another critical downstream effector modulated by natural products is the AMP-activated protein kinase (AMPK) pathway, which is primarily associated with the tumor-suppressive actions of adiponectin. In obesity, adiponectin levels are diminished, weakening its protective effects. However, natural compounds such as berberine and quercetin have been observed to enhance adiponectin-mediated AMPK activation[60]. This upregulation leads to the induction of apoptosis, inhibition of cell proliferation, and a decrease in lipid accumulation within tumor microenvironments. These effects contribute not only to a reduction in tumor burden but also to a reprogramming of metabolic pathways that support malignancy, highlighting the role of phytochemicals in restoring metabolic homeostasis through AMPK modulation.

The NF-κB pathway, another critical signaling route implicated in cancer-related inflammation, is often activated by resistin, a pro-inflammatory adipokine elevated in obese individuals[29]. NF-κB drives the expression of numerous genes involved in inflammation, survival, and metastasis. Curcumin and quercetin have demonstrated efficacy in suppressing resistin-mediated NF-κB activation, thereby reducing the inflammatory milieu that fosters tumor development[61]. By targeting this axis, these natural agents not only inhibit tumor-promoting inflammation but also help shift the adipokine signaling profile from one that supports malignancy to one that restrains it. Collectively, these findings underscore the therapeutic potential of natural product modulators in influencing key adipokine signaling pathways, offering a promising strategy for cancer prevention and treatment, particularly in the context of obesity-driven carcinogenesis[61].

5. Clinical and Translational Perspectives

While preclinical studies highlight the promise of phytochemicals in modulating adipokine signaling pathways, particularly in the context of obesity-related cancer, clinical validation remains limited[62]. Numerous plant-derived compounds, such as curcumin, resveratrol, quercetin, and berberine, have demonstrated efficacy in vitro and in animal models by targeting pathways like JAK2/STAT3, AMPK, and NF-κB. Despite these encouraging results, several challenges hinder their successful translation into clinical practice[62, 63]. Chief among these are poor bioavailability, rapid metabolism, and limited systemic distribution of many phytochemicals [64]. Additionally, the variability in phytochemical content due to differences in plant source, extraction methods, and formulation contributes to inconsistent therapeutic outcomes. A major bottleneck is the lack of large-scale, randomized, and well-controlled clinical trials that can confirm efficacy and safety in diverse human populations. To overcome these limitations, innovative drug delivery systems are being explored to enhance the pharmacokinetics and tissue targeting of phytochemicals. These include nanocarriers such as nanoparticles, liposomes, micelles, and phytochemical-polymer conjugates [65]. Recent clinical trials using advanced formulations of curcumin and resveratrol have shown promising results in reducing systemic inflammation and improving insulin sensitivity, lipid profiles, and oxidative stress markers in obese cancer patients. These findings underscore the potential of integrating bioenhanced phytochemicals into future therapeutic strategies for obesity-associated malignancies.

6. Future Directions and Challenges

Future research in the field of obesity-associated cancers must prioritize high-quality, large-scale clinical trials that rigorously assess the therapeutic efficacy of natural products. While numerous preclinical studies have demonstrated the anti-inflammatory, anti-proliferative, and pro-apoptotic properties of phytochemicals such as curcumin, resveratrol, quercetin, and berberine, their translation into clinical practice remains limited due to a lack of robust human studies. Clinical trials should be well-designed, randomized, and placebo-controlled, with clearly defined endpoints, biomarkers, and long-term follow-up to establish safety and therapeutic benefit. Moreover, stratification of participants based on obesity status and adipokine profiles will enhance our understanding of how these compounds affect tumor biology in obese versus non-obese individuals. Such personalized clinical investigations could offer insight into the therapeutic potential of phytochemicals in modulating adipokine-driven oncogenic signaling.

A promising direction involves the development of combinatorial therapies that integrate natural products with existing chemotherapeutic agents. Synergistic interactions between bioactive plant compounds and

conventional drugs may enhance therapeutic efficacy while reducing drug resistance and toxicity. For instance, combining curcumin or EGCG (epigallocatechin gallate) with chemotherapy has shown improved outcomes in various cancer models. However, a major hurdle is the poor bioavailability of many phytochemicals due to their rapid metabolism, low solubility, and limited absorption. To overcome this, innovative delivery systems such as nanoformulations, liposomes, and conjugates are being explored. These advanced drug delivery platforms can increase systemic circulation time, targeted delivery to tumor tissues, and overall therapeutic impact. Simultaneously, high-throughput screening and structure-activity relationship studies are needed to identify novel phytochemicals with potent activity against adipokine-mediated signaling pathways implicated in tumorigenesis.

In addition to therapeutic development, a deeper mechanistic understanding of the interplay between natural products, adipokines, and cancer progression is critical. Emerging multi-omics technologies, such as transcriptomics, proteomics, metabolomics, and epigenomics, offer a systems-level approach to unraveling the complex regulatory networks involved. These approaches can help identify key molecular targets, biomarkers of response, and pathways disrupted in obesity-linked malignancies. Furthermore, integrating artificial intelligence and machine learning into multi-omics data analysis can accelerate the discovery of predictive biomarkers and therapeutic candidates. By mapping the molecular crosstalk between phytochemicals and adipokine signaling networks, researchers can pave the way for precision oncology tailored to obese patients. Ultimately, future research must adopt an interdisciplinary approach—combining clinical science, pharmacology, systems biology, and bioinformatics—to harness the full potential of natural products in combating obesity-driven cancers. This will not only improve therapeutic options but also contribute to a more holistic and individualized strategy in cancer care.

CONCLUSION

Natural product modulators offer a promising strategy to target the adipokine-cancer axis, especially in the context of obesity-driven malignancies. By restoring adipokine balance and disrupting tumor-promoting signaling pathways, phytochemicals such as curcumin, resveratrol, quercetin, and berberine represent a novel frontier in integrative cancer therapy. Bridging the gap between traditional natural medicine and modern oncology could yield effective and safer therapeutic interventions.

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