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Marine-Derived Compounds as Dual Modulators of Lipid Metabolism and Tumor Suppression in Obese Cancer Models

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ABSTRACT

Obesity-associated cancers represent a significant public health burden, driven by complex metabolic and inflammatory alterations. One emerging therapeutic strategy is the use of marine-derived bioactive compounds that exhibit dual functionality in modulating lipid metabolism and exerting antitumor effects. These compounds, derived from algae, sponges, tunicates, and marine microbes, have demonstrated promise in preclinical models of obesity-related malignancies. Their mechanisms of action often involve the regulation of key lipid signaling pathways such as AMPK, PPAR, and SREBP, as well as inhibition of tumor-promoting cascades including PI3K/Akt/mTOR and NF-κB. Additionally, these marine agents influence adipokine signaling, mitigate chronic inflammation, and improve metabolic homeostasis. This review provides a comprehensive overview of marine natural products with dual modulatory roles in lipid metabolism and cancer suppression. It highlights current evidence from in vitro and in vivo studies, discusses pharmacokinetic challenges, and suggests translational strategies, including advanced delivery systems and combinatorial therapies, to enhance therapeutic outcomes. The review also emphasizes the importance of integrating multi-omics approaches to fully elucidate the bioactivity and molecular targets of these marine-derived compounds in obese cancer models.

Keywords: Marine natural products, Obesity-related cancer, Lipid metabolism, Tumor suppression, Adipokine signaling

INTRODUCTION

The global rise in obesity has been paralleled by an alarming increase in obesity-associated cancers, including breast, colorectal, liver, endometrial, and pancreatic cancers[1–3]. Obesity is no longer considered a simple metabolic disorder but a multifactorial disease that significantly increases cancer risk through complex biological pathways[3–6]. The link between obesity and cancer is underpinned by a constellation of pathological alterations, such as chronic low-grade inflammation, dyslipidemia, insulin resistance, oxidative stress, and significant changes in the secretion and function of adipokines[7]. These interconnected disturbances disrupt cellular homeostasis and promote tumor initiation, progression, and metastasis by fostering a tumor-friendly microenvironment. Adipose tissue in obese individuals acts not just as an energy reservoir but also as an active endocrine organ that releases bioactive molecules, including leptin, adiponectin, resistin, and pro-inflammatory cytokines, which influence cancer cell behavior through various signaling cascades[8, 9].

Conventional cancer therapies, including chemotherapy, radiotherapy, and targeted agents, often face significant limitations in obese cancer patients[10–12]. One major challenge is the altered pharmacokinetics and pharmacodynamics caused by obesity-related changes in drug absorption, distribution, metabolism, and excretion. Moreover, the persistent inflammatory and lipotoxic milieu associated with obesity fosters resistance to many anticancer therapies, leading to poorer clinical outcomes. As a result, conventional single-target approaches frequently fall short in adequately managing obesity-associated malignancies[9, 13]. These challenges underscore the urgent need for the development of novel therapeutic strategies that can simultaneously address both metabolic dysfunction and oncogenic signaling.

In this context, natural products have emerged as a promising resource for cancer therapeutics. Among them, marine-derived compounds have gained considerable attention due to their unparalleled chemical diversity and broad-spectrum biological activities[14–16]. The marine environment, which constitutes over 70% of the

Earth's surface, harbors a vast array of organisms such as sponges, algae, cyanobacteria, tunicates, mollusks, and soft corals that have evolved unique metabolic pathways to survive under extreme conditions[17]. These adaptations have resulted in the production of structurally novel and pharmacologically potent secondary metabolites with bioactivities that include anticancer, anti-inflammatory, antioxidant, and lipid-lowering properties[17, 18].

Marine-derived compounds are particularly attractive for their ability to act as dual modulators, targeting both metabolic derangements and oncogenic pathways concurrently. For example, several marine metabolites have been shown to reduce lipid accumulation and inflammation, while also inhibiting cancer cell proliferation, inducing apoptosis, and blocking angiogenesis[18]. Their pleiotropic mechanisms of action make them ideal candidates for tackling the multifaceted pathophysiology of obesity-related cancers. In contrast to synthetic drugs that often act on a single molecular target, marine natural products frequently exert their effects through multiple pathways, thereby enhancing therapeutic efficacy and reducing the likelihood of resistance[18].

The dual-modulatory potential of marine-derived bioactives is exemplified by compounds such as fucoxanthin (a carotenoid from brown algae), which modulates lipid metabolism via activation of AMP-activated protein kinase (AMPK), while simultaneously exerting antiproliferative effects on breast and colon cancer cells[19]. Similarly, trabectedin, derived from the sea squirt *Ecteinascidia turbinata*, is a clinically approved anticancer agent that also modulates immune and inflammatory responses, critical components of the obesity-cancer axis[20]. Other notable marine compounds, such as kahalalide F, salinosporamide A, and manoalide, continue to show promise in preclinical studies, particularly in models that mimic the metabolic conditions of obesity[20]. This review explores the current landscape of marine-derived compounds with dual modulatory functions, focusing on their capacity to regulate both lipid metabolism and tumorigenic signaling. We provide an in-depth evaluation of their mechanisms of action, preclinical and in vivo efficacy, and translational potential in obesity-associated cancer models. In doing so, we aim to shed light on the therapeutic promise of marine natural products as next-generation agents in the fight against obesity-related cancers—offering a multidimensional approach to a multidimensional problem.

2. Lipid Metabolism and Its Role in Obesity-Related Cancers

Lipid metabolism is profoundly disrupted in obese individuals, with significant implications for cancer initiation, progression, and treatment resistance[21]. Obesity is characterized by excessive accumulation of adipose tissue, which leads to a systemic imbalance in lipid handling[21]. This includes elevated circulating free fatty acids (FFAs), increased de novo lipogenesis, reduced fatty acid oxidation, and ectopic fat deposition in non-adipose tissues such as the liver, pancreas, and muscle[22]. These metabolic disturbances play a critical role in the pathogenesis of insulin resistance, a hallmark of obesity-related metabolic dysfunction. More importantly, these alterations in lipid metabolism create a pro-tumorigenic microenvironment that fosters the initiation and progression of several cancers, including breast, prostate, liver, and colorectal cancers[22].

At the molecular level, key regulatory pathways controlling lipid metabolism become aberrantly activated in obesity. Sterol regulatory element-binding proteins (SREBPs), particularly SREBP-1, are upregulated and drive increased transcription of lipogenic genes such as fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), and stearoyl-CoA desaturase-1 (SCD1)[2, 5, 23]. This enhances lipogenesis within both adipocytes and tumor cells. Similarly, peroxisome proliferator-activated receptors (PPARs), especially PPARγ, become dysregulated, influencing adipocyte differentiation, lipid storage, and inflammatory responses. Additionally, AMP-activated protein kinase (AMPK), a key energy sensor and negative regulator of lipid synthesis, is often inhibited in obesity, further promoting lipid accumulation and reducing fatty acid oxidation. The net result of these changes is the development of a metabolic environment rich in lipids and inflammatory mediators that support tumor growth, angiogenesis, immune evasion, and metastasis[22, 24, 25].

Cancer cells in obese individuals are remarkably adept at adapting to this lipid-rich environment. They increase expression of lipid uptake and utilization proteins, including CD36 (a fatty acid translocase), fatty acid-binding proteins (FABPs), and lipid droplet-associated proteins like perilipins and ADRP (adipose differentiation-related protein)[26]. This adaptation enhances their ability to import and store fatty acids in lipid droplets, which can be mobilized during metabolic stress to fuel β-oxidation or membrane biosynthesis. Additionally, elevated FASN activity in tumor cells not only supports membrane lipid production and energy storage but also contributes to oncogenic signaling and resistance to apoptosis[26].

The close link between lipid metabolic reprogramming and tumor aggressiveness in the context of obesity presents a compelling therapeutic opportunity. Targeting lipid metabolic enzymes and pathways offers a novel approach to cancer therapy, particularly in obese patients who often experience more aggressive disease and poorer outcomes[16, 27]. For instance, inhibitors of FASN have shown promise in preclinical models of breast and prostate cancer, inducing apoptosis and sensitizing tumors to chemotherapy. CD36 blockade has also been explored to reduce metastasis, particularly in cancers that rely heavily on exogenous fatty acid uptake. Furthermore, activating AMPK pharmacologically through agents like metformin or AICAR can restore lipid homeostasis and inhibit tumor growth[28, 29].

Given the growing prevalence of obesity worldwide and its established connection to cancer risk and progression, it is increasingly important to consider metabolic context in designing cancer therapies. Lipid metabolism not only supports the energetic and biosynthetic needs of tumor cells but also modulates signaling networks, immune responses, and interactions with the tumor microenvironment[4, 7, 30]. Thus, therapeutic strategies that disrupt lipid metabolic reprogramming could attenuate cancer development and progression, offering improved outcomes for obese cancer patients. Future research should prioritize the identification of lipid metabolic vulnerabilities in tumors, explore synergistic effects with existing chemotherapeutics, and develop personalized metabolic interventions that account for patient-specific lipidomic profiles.

3. Marine-Derived Compounds: An Untapped Reservoir of Dual Modulators

Marine ecosystems, encompassing a wide variety of organisms such as algae, sponges, tunicates, and mollusks, represent an untapped reservoir of chemically unique and biologically active compounds[31]. These natural products exhibit diverse pharmacological properties due to their structural novelty and the extreme conditions of their environment, including high pressure, low light, and variable salinity. Increasingly, marine-derived compounds have attracted significant attention in biomedical research for their potential dual role in modulating lipid metabolism and suppressing cancer development, especially within the context of obesity-associated malignancies[31]. Obesity not only disrupts lipid homeostasis but also creates a tumor-promoting microenvironment through chronic inflammation, insulin resistance, and dysregulated adipokine signaling[32]. Marine bioactives that target both metabolic and oncogenic pathways simultaneously offer a promising therapeutic strategy.

One of the most studied marine compounds with dual activity is fucoxanthin, a xanthophyll carotenoid found abundantly in brown seaweeds such as *Undaria pinnatifida* and *Laminaria japonica*[33]. Fucoxanthin has demonstrated strong potential in regulating lipid metabolism by activating AMP-activated protein kinase (AMPK), a central metabolic sensor that enhances energy expenditure and inhibits lipid synthesis[34]. Specifically, fucoxanthin suppresses the expression of sterol regulatory element-binding protein-1c (SREBP-1c), a master transcription factor involved in fatty acid and triglyceride biosynthesis. This leads to a reduction in hepatic lipid accumulation and overall adiposity. Simultaneously, fucoxanthin exerts anticancer effects by inhibiting the nuclear factor-kappa B (NF-κB) and phosphoinositide 3-kinase/Akt (PI3K/Akt) pathways—key signaling cascades involved in cell proliferation, survival, and inflammation[34]. These dual actions render fucoxanthin an attractive candidate for combating both obesity-related metabolic dysfunction and the progression of cancer.

Another noteworthy compound is halichondrin B, a macrolide polyether originally isolated from marine sponges such as *Halichondria okadai*. Halichondrin B and its synthetic analog, eribulin, exhibit potent antitumor activity primarily through the disruption of microtubule dynamics, leading to mitotic arrest and apoptosis in rapidly dividing cells[35]. In addition to its cytotoxic effects, emerging evidence suggests halichondrin B may influence lipid metabolism by modulating enzymes involved in fatty acid oxidation and mitochondrial energy production[35]. Through these actions, halichondrin B not only targets the structural components of cancer cells but also alters their metabolic flexibility an essential feature of tumor survival under metabolic stress, particularly in lipid-rich environments like those found in obese individuals.

Didemnin B, a cyclic depsipeptide derived from marine tunicates (ascidians), presents another example of a dual-acting marine compound[36]. It exerts strong cytotoxic effects on a wide range of cancer cell lines by inhibiting protein synthesis and inducing apoptosis. Moreover, Didemnin B targets key enzymes involved in lipid biosynthesis, particularly those regulated by the mTOR and SREBP pathways, which are often upregulated in cancer cells to meet their elevated energy and biosynthetic demands. By disrupting these lipid biosynthetic processes, Didemnin B not only inhibits tumor growth but also attenuates lipid accumulation—highlighting its potential as a compound that bridges metabolic and oncologic therapeutic strategies[37].

Marine polyphenols, particularly phlorotannins found in brown algae such as *Ecklonia cava*, also demonstrate multifaceted bioactivity. These compounds possess strong antioxidant and anti-inflammatory properties that counteract oxidative stress and chronic inflammation, both hallmarks of obesity and cancer[38]. Phlorotannins suppress adipogenesis by downregulating the expression of key adipogenic transcription factors such as PPARγ and C/EBPα, while also reducing the release of tumor-promoting cytokines like TNF-α and IL-6. Furthermore, their anticancer effects are mediated through the modulation of cell cycle regulators and apoptosis-inducing factors[38]. Phlorotannins thereby attenuate both the metabolic drivers and the inflammatory milieu that support cancer development in obese individuals.

A particularly critical aspect of marine-derived compounds is their ability to regulate adipokine signaling, a central link between obesity and cancer[39]. Adipokines such as leptin and adiponectin are hormone-like proteins secreted by adipose tissue, and they play opposing roles in tumor biology[39]. Elevated leptin levels, commonly observed in obesity, promote cancer cell proliferation, angiogenesis, and metastasis through activation of JAK2/STAT3, PI3K/Akt, and MAPK pathways. Marine compounds like fucoxanthin and phlorotannins have been shown to downregulate leptin expression and interfere with its signaling pathways, thereby attenuating its tumorigenic effects[40]. On the other hand, adiponectin, which is typically reduced in

obese individuals, exerts anti-cancer effects through the activation of AMPK and suppression of mTOR signaling[40]. Certain marine-derived agents can enhance adiponectin expression or mimic its activity, thereby restoring its protective role against cancer.

The integrative modulation of both metabolic and oncogenic axes by marine-derived compounds represents a novel therapeutic paradigm. Unlike traditional chemotherapeutics that focus solely on tumor eradication, these marine bioactives offer a systems-level approach that addresses the metabolic dysregulation underpinning many cancers, particularly those linked to obesity[40]. Moreover, the structural diversity and unique modes of action of marine compounds offer opportunities for the development of new pharmacophores that can overcome resistance mechanisms often encountered in conventional therapy.

In sum, marine ecosystems provide a treasure trove of compounds with the potential to target both lipid metabolism and cancer progression. Agents like fucoxanthin, halichondrin B, didemnin B, and marine polyphenols not only suppress tumor growth but also modulate the metabolic environment that fosters cancer development in obese individuals. Their ability to regulate adipokine signaling further underscores their relevance in obesity-associated cancer therapy. Continued exploration of these marine bioresources, supported by advances in biotechnology, synthetic biology, and drug delivery systems, will be essential in harnessing their full therapeutic potential.

4. Mechanisms of Action: Molecular Pathway Crosstalk

Marine compounds are emerging as powerful agents capable of modulating multiple biological pathways simultaneously, which is particularly advantageous in complex conditions such as metabolic disorders and cancer[41]. These compounds often exert their dual effects by targeting interconnected signaling networks that regulate both lipid metabolism and tumor progression. By influencing these key molecular pathways, marine-derived substances offer promising therapeutic potential for managing the dual burden of metabolic diseases—such as obesity and dyslipidemia—and cancer. Below is an in-depth exploration of some critical signaling pathways modulated by marine natural products[41].

AMP-activated Protein Kinase (AMPK) Activation: AMPK functions as a master regulator of cellular energy homeostasis, acting as a metabolic sensor that maintains energy balance by switching on catabolic processes like lipid oxidation and turning off anabolic processes such as lipogenesis. Activation of AMPK is thus a desirable therapeutic target for treating metabolic syndromes and obesity-related disorders[42]. Marine carotenoids like fucoxanthin and astaxanthin have been shown to activate AMPK effectively. Fucoxanthin, found abundantly in brown seaweed, enhances AMPK activity, which promotes the breakdown of fatty acids and reduces lipid accumulation in tissues[43]. At the same time, astaxanthin, a potent antioxidant pigment from microalgae and seafood, stimulates AMPK signaling to suppress the synthesis of new fats. Intriguingly, these same compounds also inhibit the mechanistic target of rapamycin (mTOR) pathway, a downstream target of AMPK known for driving tumor growth and proliferation[43]. By concurrently promoting lipid catabolism and inhibiting tumorigenic signaling, these marine compounds provide a dual benefit in controlling metabolic imbalances and cancer progression.

Inhibition of NF-κB Signaling: Chronic inflammation is a well-established driver of both metabolic diseases and cancer. The nuclear factor-kappa B (NF-κB) pathway is a central regulator of inflammatory responses, controlling the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules[44]. Persistent activation of NF-κB fosters a microenvironment that supports tumor initiation, growth, and metastasis, while also exacerbating insulin resistance and lipid abnormalities in obesity. Several marine-derived compounds demonstrate the ability to inhibit NF-κB signaling effectively[44]. By blocking this pathway, these substances reduce the levels of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β). This attenuation of chronic inflammation can slow cancer progression and improve metabolic health, highlighting the anti-inflammatory potential of marine bioactives as part of integrated therapeutic strategies.

Modulation of the PI3K/Akt/mTOR Pathway: The phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling cascade is pivotal in regulating cell growth, survival, metabolism, and lipid biosynthesis[45]. Aberrant activation of this pathway is frequently observed in various cancers and metabolic disorders, making it a prime target for drug development. Marine-derived peptides and terpenoids have shown promising modulatory effects on this pathway[45]. These compounds can downregulate PI3K/Akt signaling, leading to decreased lipogenesis and suppressed cancer cell survival. By inhibiting mTOR, they prevent tumor cell proliferation and angiogenesis while also restoring metabolic balance. The ability of marine natural products to simultaneously target PI3K/Akt/mTOR signaling makes them uniquely suited to address the metabolic and proliferative abnormalities that characterize obesity-related cancers[45].

Epigenetic Regulation: Beyond direct effects on signaling pathways, some marine alkaloids influence gene expression through epigenetic mechanisms[46]. Epigenetic regulation involves reversible modifications to DNA or histone proteins that alter chromatin structure and gene accessibility without changing the DNA sequence itself. These modifications include histone acetylation, methylation, and regulation by microRNAs

(miRNAs), all of which play essential roles in adipogenesis and tumorigenesis[46]. Marine alkaloids have been found to modulate histone modification enzymes, such as histone deacetylases (HDACs), thereby influencing the expression of genes involved in fat cell differentiation and cancer progression[46]. Additionally, these compounds can regulate miRNAs that target transcripts linked to lipid metabolism and cell proliferation. By fine-tuning epigenetic landscapes, marine natural products offer an innovative approach to controlling gene networks underlying metabolic disease and cancer, expanding the scope of their therapeutic potential.

The pleiotropic effects of marine natural products on these interconnected signaling networks underscore their considerable therapeutic advantage[47]. Their capacity to simultaneously regulate lipid metabolism and inhibit tumorigenic pathways offers a multifaceted approach to managing the complex interplay between metabolic disease and cancer. As research advances, marine-derived compounds hold promise not only as single agents but also as part of combinatorial therapies designed to tackle the dual challenges of obesity-related metabolic disorders and cancer[47]. Harnessing these natural products could pave the way for novel interventions that are both effective and have reduced side effects compared to conventional therapies.

5. Challenges and Translational Perspectives

Despite their immense therapeutic potential, several critical challenges hinder the successful clinical translation of marine-derived compounds, particularly in the context of treating obesity-associated cancers[48]. These challenges encompass pharmacokinetic limitations, toxicity concerns, insufficient clinical data, and sustainability issues. Addressing these obstacles is crucial for unlocking the full potential of marine bioactives as viable therapeutic agents[48].

One major limitation lies in the **bioavailability and stability** of marine-derived compounds. Many of these molecules exhibit poor oral bioavailability due to low solubility, rapid metabolism, or instability in the gastrointestinal tract[49]. This limits their systemic absorption and therapeutic efficacy. Moreover, some compounds degrade quickly in physiological conditions, reducing their biological activity before reaching target tissues. To overcome these limitations, researchers are exploring advanced drug delivery systems[49]. Nanotechnology-based approaches such as liposomes, solid lipid nanoparticles, and polymeric micelles have shown promise in enhancing the pharmacokinetics of marine compounds. These systems can protect unstable compounds from degradation, improve cellular uptake, and allow for controlled release, ultimately increasing therapeutic concentrations at tumor sites while minimizing systemic toxicity[50].

Toxicity and selectivity also pose significant hurdles. While many marine compounds demonstrate strong anticancer and lipid-modulating properties, their high potency may lead to off-target effects and systemic toxicity, particularly in non-cancerous tissues[51]. These adverse effects could be especially problematic in obese cancer patients who already suffer from multiple comorbidities. To address this, structural modification through medicinal chemistry can help reduce toxicity by refining the molecule's interaction with non-target proteins. Additionally, targeted delivery systems such as antibody-drug conjugates or ligand-directed nanoparticles can enhance tumor selectivity by exploiting overexpressed receptors on cancer cells, thus sparing healthy tissue and improving safety profiles[50].

Another significant challenge is the **lack of clinical trials**. Although preclinical studies using cell lines and animal models have demonstrated the efficacy of several marine-derived compounds, there remains a paucity of rigorous clinical investigations, especially in obese cancer patient populations[52]. The complex interplay between obesity, inflammation, lipid metabolism, and cancer progression demands well-designed, stratified clinical trials that account for metabolic variability among patients. These studies are critical to assess not only the therapeutic efficacy of marine compounds but also their safety, optimal dosing, and long-term outcomes in real-world clinical settings[52].

Moreover, the **sustainable sourcing** of marine compounds is an ecological and ethical concern. Many bioactive compounds are derived from rare marine organisms such as sponges, tunicates, or algae, whose overharvesting can threaten marine biodiversity. To circumvent this issue, scientists are turning to synthetic biology, microbial fermentation, and total chemical synthesis to produce these compounds in a more sustainable and scalable manner, reducing the environmental impact and ensuring a consistent supply for research and clinical use[53].

Future research must adopt a **multi-omics approach** integrating transcriptomics, lipidomics, proteomics, and metabolomics to comprehensively map the interactions between marine compounds and biological systems. Such an approach can identify biomarkers of response, elucidate mechanisms of action, and guide the development of personalized therapeutic strategies[53]. This systems-level understanding is essential for optimizing marine compound applications in precision oncology, particularly for metabolically complex diseases such as obesity-associated cancers.

CONCLUSION

Marine-derived compounds offer a novel and promising avenue in addressing the dual pathophysiology of lipid dysregulation and tumor progression in obesity-associated cancers. By targeting shared molecular pathways involved in lipid metabolism and oncogenesis, these bioactives can potentially overcome the limitations of current monotherapies. Integrating marine pharmacology with systems biology and advanced drug delivery platforms could pave the way for next-generation therapeutics in oncology and metabolic disorders.

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