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Targeting Obesity-Driven Inflammation in Cancer Progression: Therapeutic Role of Polyphenol-Rich Natural Products

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ABSTRACT

Obesity, a global epidemic, is increasingly recognized as a key risk factor for cancer development and progression. Central to this association is the state of chronic low-grade inflammation that characterizes obesity, which contributes to a pro-tumorigenic microenvironment. Adipose tissue dysfunction in obesity leads to elevated levels of inflammatory cytokines, immune cell infiltration, oxidative stress, and dysregulated adipokine secretion. These changes create a fertile ground for malignant transformation and cancer progression. Polyphenol-rich natural products, such as curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG), exhibit potent anti-inflammatory, antioxidant, and anticancer properties. Emerging evidence from in vitro studies, animal models, and clinical trials suggests that these polyphenols can modulate obesity-induced inflammation and thereby inhibit cancer initiation and metastasis. This review highlights the mechanistic link between obesity, inflammation, and cancer, and evaluates the therapeutic potential of polyphenol-rich compounds in disrupting this axis. A deeper understanding of these natural products' molecular mechanisms may pave the way for novel, safe, and effective strategies for cancer prevention and therapy, particularly in obese individuals.

Keywords: Obesity-driven inflammation; polyphenols; cancer progression; natural products; tumor microenvironment.

INTRODUCTION

Obesity has emerged as a global health crisis of alarming proportions, with current estimates from the World Health Organization (WHO) indicating that over 1.9 billion adults are overweight, and more than 650 million are classified as obese[1, 2]. This pandemic of excess adiposity is not only a leading contributor to metabolic disorders such as type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease, but is also increasingly recognized as a critical determinant in the pathogenesis of various forms of cancer[3–5]. Epidemiological studies have consistently linked obesity with an elevated risk of malignancies, including, but not limited to, breast (particularly postmenopausal), colorectal, endometrial, pancreatic, kidney, and liver cancers. As the global burden of obesity continues to rise, so too does the urgency to understand the complex biological mechanisms that connect excessive adiposity to carcinogenesis[6–8].

The obesity–cancer connection is multifactorial and involves a network of metabolic, hormonal, and inflammatory processes[7, 9–11]. Central to this relationship is the concept of chronic low-grade inflammation, a hallmark of obesity, which plays a pivotal role in promoting tumor initiation, growth, and metastasis[12, 13]. In the obese state, adipose tissue undergoes several pathological changes, including adipocyte hypertrophy, tissue hypoxia, and increased infiltration of immune cells such as macrophages, T cells, and neutrophils[14–17]. These alterations result in a dysregulated adipose microenvironment characterized by an overproduction of pro-inflammatory cytokines (e.g., TNF-α, IL-6), chemokines, and adipokines such as leptin, while levels of anti-inflammatory adiponectin are reduced. This shift towards a pro-inflammatory milieu not only disrupts metabolic homeostasis but also fosters genomic instability, angiogenesis, and epithelial-to-mesenchymal transition—hallmarks of cancer progression[18–20].

In addition to inflammation, obesity-related hormonal imbalances—particularly hyperinsulinemia and increased bioavailability of insulin-like growth factor 1 (IGF-1) can stimulate oncogenic signaling pathways, including

PI3K/Akt/mTOR and MAPK/ERK[21–23]. Furthermore, elevated circulating levels of estrogens in obese individuals, resulting from aromatase activity in adipose tissue, are linked to hormone-sensitive cancers such as breast and endometrial cancer[24]. These interrelated pathways create a permissive environment for neoplastic transformation and tumor growth, thereby making obesity a modifiable risk factor in cancer prevention and management[24].

Given the limitations and potential adverse effects of current pharmacological interventions targeting inflammation and cancer, there is increasing interest in naturally derived compounds with favorable safety profiles[8, 25]. Among these, dietary polyphenols have garnered considerable attention for their pleiotropic biological activities[26, 27]. Polyphenols are a heterogeneous group of plant-derived secondary metabolites commonly found in fruits, vegetables, whole grains, nuts, tea, coffee, wine, and spices [28]. They are broadly categorized into flavonoids, phenolic acids, lignans, and stilbenes, and have demonstrated antioxidant, anti-inflammatory, anti-obesity, and anti-carcinogenic properties in both in vitro and in vivo models[29–31].

Notable polyphenols such as curcumin (from *Curcuma longa*), resveratrol (from grapes and berries), epigallocatechin gallate (EGCG, from green tea), and quercetin (found in apples and onions) have shown efficacy in modulating key molecular pathways implicated in inflammation and cancer[31–33]. These compounds exert their effects through the inhibition of nuclear factor-kappa B (NF-κB), reduction of oxidative stress, suppression of pro-inflammatory cytokine production, and modulation of apoptotic and autophagic mechanisms[34, 35]. Furthermore, polyphenols can influence the gut microbiome, insulin sensitivity, and lipid metabolism, thereby addressing both the inflammatory and metabolic components of obesity-associated cancers[26, 31].

This review aims to comprehensively explore the intricate interplay between obesity-induced inflammation and cancer development, with a specific focus on the therapeutic potential of polyphenol-rich natural products. By examining both mechanistic insights and recent preclinical and clinical evidence, we seek to highlight the promise of dietary polyphenols as adjunctive agents in the prevention and management of obesity-driven cancers.

2. Obesity-Driven Inflammation and Cancer: An Overview

2.1 Adipose Tissue Dysfunction and Chronic Inflammation

In obesity, adipose tissue experiences significant structural and functional changes collectively referred to as adipose tissue dysfunction[16]. As adipocytes expand in size—a process known as hypertrophy—they often outpace their vascular supply, resulting in local tissue hypoxia[5, 16, 36]. Hypoxia, in turn, induces endoplasmic reticulum (ER) stress and increases the rate of adipocyte necrosis or apoptosis[12, 15]. These conditions lead to the release of damage-associated molecular patterns (DAMPs), which attract and activate immune cells, particularly macrophages, into the adipose tissue. In lean individuals, adipose tissue-resident macrophages primarily exhibit an anti-inflammatory M2-like phenotype, which supports tissue remodeling and homeostasis[37, 38]. However, during obesity, there is a pronounced phenotypic shift towards the pro-inflammatory M1-like macrophages. These M1 macrophages secrete a variety of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), creating a self-sustaining loop of chronic low-grade inflammation[37].

This inflammatory state is not confined to the adipose tissue alone. It spills over into the systemic circulation, promoting a state of "metaflammation"—metabolism-associated inflammation that affects multiple organ systems[39]. Chronic inflammation impairs insulin signaling pathways, exacerbates lipid metabolism disorders, and contributes to the development of obesity-related comorbidities such as type 2 diabetes and cardiovascular disease[39]. Importantly, this inflammatory microenvironment also lays the foundation for cancer development by fostering DNA damage, suppressing apoptosis, and enhancing cellular proliferation. Thus, adipose tissue dysfunction and chronic inflammation are not only central to metabolic dysregulation in obesity but also serve as a critical link between obesity and cancer progression[39]. Targeting the inflammatory pathways associated with dysfunctional adipose tissue offers a promising therapeutic strategy to mitigate obesity-driven pathologies, including carcinogenesis.

2.2 Inflammatory Cytokines and Tumorigenesis

In the context of obesity, the persistent release of inflammatory cytokines from both hypertrophic adipocytes and infiltrating immune cells contributes significantly to the establishment of a pro-tumorigenic environment[23, 40]. Among the most well-characterized cytokines are tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), which activate a network of signaling cascades that promote tumorigenesis. One of the key pathways activated by these cytokines is the nuclear factor-kappa B (NF-κB) pathway, a master regulator of inflammation and immune responses. NF-κB activation leads to the transcription of genes involved in cell survival, proliferation, and angiogenesis—core hallmarks of cancer[40].

In addition to NF-κB, other oncogenic signaling routes such as the signal transducer and activator of transcription 3 (STAT3) and mitogen-activated protein kinase (MAPK) pathways are similarly upregulated in the obese inflammatory milieu[41]. These pathways not only sustain the survival and uncontrolled proliferation of transformed cells but also support processes like epithelial-to-mesenchymal transition (EMT), which enables

cancer cells to invade and metastasize. The chronic presence of inflammatory cytokines also remodels the tumor microenvironment (TME) by increasing vascular permeability and recruiting additional pro-tumorigenic immune cells such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs)[41].

Moreover, inflammation disrupts the balance of adipokines secreted by adipose tissue. Leptin, which is elevated in obesity, has been shown to promote angiogenesis, cell proliferation, and survival, while adiponectin, usually reduced in obese individuals, possesses anti-inflammatory and anti-tumorigenic properties[41]. The resulting leptin-to-adiponectin imbalance skews the TME towards malignancy. Overall, the inflammatory cytokines associated with obesity not only initiate and promote tumor development but also support its progression, making them critical therapeutic targets in obesity-associated cancers[41].

2.3 Oxidative Stress and DNA Damage

Obesity is intrinsically linked with increased oxidative stress, which plays a pivotal role in promoting genomic instability and carcinogenesis[42, 43]. One of the primary sources of oxidative stress in obese individuals is mitochondrial dysfunction, particularly in inflamed and metabolically active tissues such as adipose tissue and the liver. In these tissues, excessive nutrient availability, lipotoxicity, and chronic inflammation lead to the overproduction of reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide, and hydroxyl radicals. When the endogenous antioxidant defense mechanisms—such as superoxide dismutase (SOD), glutathione peroxidase, and catalase—are overwhelmed, oxidative damage accumulates[1].

ROS can inflict direct damage on nucleic acids, leading to the formation of DNA adducts, single and double-strand breaks, and mutations in oncogenes and tumor suppressor genes[37, 44, 45]. For instance, 8-oxo-deoxyguanosine (8-oxo-dG) is a commonly used marker of oxidative DNA damage and is elevated in obesity. Such genetic insults increase the risk of initiating carcinogenesis. In addition to direct mutagenic effects, ROS also activate redox-sensitive transcription factors such as NF-κB and AP-1, which further stimulate the expression of inflammatory cytokines, growth factors, and anti-apoptotic proteins.[46]

Furthermore, oxidative stress promotes epigenetic alterations, such as DNA methylation changes and histone modifications, which can silence tumor suppressor genes and activate oncogenes[6, 47]. The chronic oxidative environment also impairs DNA repair mechanisms, further increasing the mutation load and promoting genomic instability—a hallmark of cancer. In summary, the oxidative stress associated with obesity not only serves as a driver of mutagenesis and genomic instability but also synergizes with inflammation to create a microenvironment conducive to tumor initiation and progression. Targeting oxidative stress through lifestyle interventions or antioxidant-rich therapeutics is a potential strategy for cancer prevention in obese individuals[48].

3. Polyphenol-Rich Natural Products: Classification and General Functions

Polyphenols are a diverse group of secondary plant metabolites widely recognized for their health-promoting properties, particularly in the prevention and management of chronic diseases like obesity, diabetes, cardiovascular diseases, and cancer[30, 49]. Structurally, polyphenols are classified into four major categories: **flavonoids**, **stilbenes**, **phenolic acids**, and **lignans**[50]. Flavonoids, the most abundant subclass, include compounds such as quercetin, kaempferol, catechins, and anthocyanins. Stilbenes, including the well-known resveratrol found in grapes and red wine, are less abundant but have shown potent biological activities. Phenolic acids such as ferulic acid and caffeic acid are found in whole grains and coffee, while lignans are mainly derived from seeds like flaxseed.

The therapeutic benefits of polyphenols stem from their multifaceted biological activities. They act as powerful antioxidants, neutralizing reactive oxygen species (ROS) and reducing oxidative stress—one of the major contributors to DNA damage and cancer development[32, 50]. Polyphenols also exert anti-inflammatory effects by inhibiting pro-inflammatory enzymes (e.g., COX-2), suppressing cytokine production (e.g., TNF-α, IL-6), and modulating transcription factors such as NF-κB and STAT3. Furthermore, they influence cell proliferation, apoptosis, angiogenesis, and metastasis, thereby interfering with multiple stages of carcinogenesis[51].

In the context of obesity-driven cancer, polyphenols can attenuate adipose tissue inflammation, improve insulin sensitivity, and restore adipokine balance[52]. They also modulate key oncogenic pathways such as PI3K/Akt, MAPK, and Wnt/β-catenin, thereby disrupting tumor progression. Notably, polyphenols can also affect the gut microbiota composition, contributing to systemic anti-inflammatory effects[53]. Due to their pleiotropic effects, polyphenols represent promising agents in integrative cancer prevention and therapy. However, challenges such as poor bioavailability and metabolic instability necessitate ongoing research into novel delivery systems and synergistic formulations to enhance their clinical efficacy.

4. Key Polyphenols Targeting Obesity-Driven Inflammation in Cancer

4.1 Curcumin

Curcumin is a bioactive polyphenolic compound isolated from the rhizome of *Curcuma longa* (turmeric), widely used in traditional medicine for its anti-inflammatory, antioxidant, and anticancer properties[54, 55]. Its anti-inflammatory activity primarily stems from its ability to inhibit nuclear factor-kappa B (NF-κB), a key transcription factor involved in inflammatory gene expression. Curcumin suppresses the production of pro-

inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and cyclooxygenase-2 (COX-2), which are typically elevated in obesity and associated cancers. Mechanistically, it modulates multiple oncogenic signaling pathways, including PI3K/Akt, STAT3, Wnt/β-catenin, and mTOR, thereby inhibiting tumor cell proliferation, angiogenesis, invasion, and metastasis[55].

In obesity-related cancer models, curcumin reduces macrophage infiltration into adipose tissue, inhibits adipocyte-derived inflammatory mediators, and restores metabolic balance, effectively attenuating the chronic low-grade inflammation that promotes tumorigenesis[56]. Despite its promising therapeutic potential, curcumin's clinical application is hindered by poor bioavailability due to limited absorption, rapid metabolism, and systemic elimination. To overcome this limitation, several strategies such as structural analogs, liposomal formulations, nanoparticles, and curcumin-phospholipid complexes are being developed to enhance its stability and systemic availability. Overall, curcumin represents a valuable natural compound in the chemoprevention and treatment of obesity-associated inflammation and cancers.

4.2 Resveratrol

Resveratrol is a naturally occurring stilbene polyphenol predominantly found in the skin of grapes, red wine, blueberries, and peanuts[57, 58]. It is renowned for its broad-spectrum biological activities, particularly its anti-inflammatory, antioxidant, cardioprotective, and anticancer effects. A key mechanism by which resveratrol exerts its anti-inflammatory function is through the activation of sirtuin-1 (SIRT1), a NAD^+-dependent deacetylase that inhibits NF-κB signaling, thereby reducing the transcription of inflammatory cytokines such as TNF-α, IL-1β, and IL-6. In cancer biology, resveratrol enhances apoptosis by activating p53, suppressing anti-apoptotic proteins like Bcl-2, and promoting caspase activation. It also induces cell cycle arrest at the G1/S phase and inhibits angiogenesis and metastasis[59].

In obesity models, resveratrol has been shown to improve insulin sensitivity, enhance mitochondrial function, decrease adipogenesis, and suppress chronic inflammation in adipose tissue. Its dual role in modulating both metabolic dysfunction and inflammatory pathways makes it a potent candidate for targeting obesity-driven tumorigenesis. Preclinical studies have demonstrated its anticancer efficacy in models of breast, colon, prostate, and pancreatic cancers, particularly when obesity is a contributing factor[60]. Although its bioavailability is modest, ongoing research into resveratrol analogs and delivery systems aims to optimize its therapeutic utility in managing obesity-associated inflammation and cancer progression.

4.3 Quercetin

Quercetin is a flavonoid abundant in various fruits and vegetables, including apples, onions, citrus fruits, berries, and tea. Known for its potent antioxidant and anti-inflammatory properties, quercetin acts by inhibiting key pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS)[61, 62]. It also suppresses the release of cytokines, including IL-6, IL-1β, and TNF-α by downregulating NF-κB signaling. In the context of cancer, quercetin exerts antiproliferative effects by inducing apoptosis via p53-dependent mechanisms and caspase activation, disrupting mitochondrial membrane potential, and promoting oxidative stress in tumor cells[63].

In obesity, quercetin mitigates chronic low-grade inflammation and oxidative stress by reducing macrophage infiltration into adipose tissue and decreasing levels of reactive oxygen species (ROS). It also improves metabolic parameters such as lipid profile and insulin sensitivity. In experimental cancer models, quercetin has demonstrated the ability to inhibit tumor growth, angiogenesis, and metastasis[61]. It targets hypoxia-inducible factor-1 alpha (HIF-1α) and vascular endothelial growth factor (VEGF), which are critical regulators of tumor vascularization. The combination of its anti-inflammatory, antioxidant, and anticancer properties makes quercetin a promising phytochemical in the prevention and treatment of obesity-linked cancers, although its pharmacokinetics remain a challenge requiring further formulation advancements.

4.4 Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG) is the most abundant and active catechin found in green tea, widely studied for its anti-inflammatory, antioxidant, and anticancer properties[26, 64]. EGCG exerts its anti-inflammatory effects by inhibiting several signaling pathways such as nuclear factor-kappa B (NF-κB), activator protein-1 (AP-1), and mitogen-activated protein kinases (MAPKs), which are crucial in the transcriptional regulation of pro-inflammatory mediators. It downregulates the expression of IL-6, TNF-α, and COX-2, thereby reducing systemic and tissue-level inflammation. In cancer cells, EGCG induces apoptosis, inhibits cell proliferation, and blocks angiogenesis and metastasis through mechanisms involving p53 activation, caspase cascade initiation, and downregulation of VEGF[65].

In obesity-related studies, EGCG supplementation has been associated with reduced body weight, decreased adipose tissue inflammation, and improved insulin sensitivity[26]. It inhibits adipogenesis and enhances fat oxidation, which collectively help mitigate the pro-inflammatory state that predisposes obese individuals to cancer. Furthermore, EGCG has been reported to enhance the efficacy of conventional chemotherapy drugs while simultaneously reducing chemoresistance, making it a promising adjuvant in cancer therapy[65]. Although its bioavailability is limited, advancements in nanoencapsulation and EGCG-based drug formulations

are being developed to improve systemic delivery. EGCG stands out as a multifaceted natural compound in managing obesity-driven cancer progression.

5. Molecular Mechanisms of Polyphenols in Modulating Obesity-Linked Cancer Inflammation

5.1 Inhibition of Pro-inflammatory Signaling Pathways: Polyphenols exhibit potent anti-inflammatory effects by targeting key signaling pathways involved in obesity-driven inflammation and cancer development[31, 50]. Specifically, they inhibit the activation of nuclear factor-kappa B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and mitogen-activated protein kinase (MAPK) pathways. These signaling cascades are typically upregulated in the context of chronic inflammation, leading to increased transcription of genes encoding pro-inflammatory cytokines, chemokines, and cell adhesion molecules. By suppressing these pathways, polyphenols reduce the production of inflammatory mediators, thereby attenuating both local and systemic inflammation and creating a less favorable environment for tumor initiation and progression[26, 66].

5.2 Suppression of Macrophage Polarization and Immune Cell Infiltration: Polyphenols such as curcumin, resveratrol, and quercetin modulate the immune microenvironment by interfering with macrophage polarization and immune cell recruitment[6, 52]. In obesity and cancer, macrophages often shift from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype, contributing to chronic inflammation and tumorigenesis. Polyphenols help reverse this polarization, promoting a more anti-inflammatory state. Additionally, they inhibit the secretion of chemotactic factors that drive immune cell infiltration into adipose and tumor tissues[67]. By dampening immune cell recruitment and maintaining macrophages in a less inflammatory state, polyphenols help curb the inflammatory milieu that supports tumor growth and immune evasion.

5.3 Regulation of Adipokines: Polyphenols influence the secretion of adipokines—hormones produced by adipose tissue that regulate metabolism and inflammation. In obesity, there is an imbalance characterized by elevated pro-inflammatory adipokines like leptin and reduced anti-inflammatory ones like adiponectin[49, 67]. Polyphenols restore this balance by upregulating adiponectin and downregulating leptin levels. This rebalancing helps to reduce systemic inflammation and inhibits proliferative signaling, particularly in hormone-sensitive cancers such as breast and endometrial cancers[68]. The modulation of adipokine levels by polyphenols not only improves metabolic health but also reduces the risk of tumor progression, making them promising agents in integrative cancer therapies.

5.4 Epigenetic Modulation: Polyphenols possess epigenetic regulatory properties that influence gene expression without altering the DNA sequence. Compounds like epigallocatechin gallate (EGCG), curcumin, and genistein can modulate DNA methylation patterns, histone acetylation, and the expression of microRNAs[33, 68]. These epigenetic changes can reprogram both adipose-derived and cancerous cells, shifting them toward less aggressive or more differentiated phenotypes. For instance, polyphenols can restore the expression of tumor suppressor genes silenced by hypermethylation or inhibit oncogenes activated by histone modifications. By reshaping the epigenetic landscape, polyphenols contribute to the suppression of inflammation and tumor progression, offering a complementary strategy in obesity-related cancer prevention and therapy[51].

6. Challenges and Future Perspectives

Despite the growing body of preclinical evidence supporting the anticancer and anti-inflammatory effects of polyphenol-rich natural products, their translation into clinical practice faces significant hurdles. One of the foremost challenges is the inherently low bioavailability of many polyphenols. These compounds often exhibit poor gastrointestinal absorption, are rapidly metabolized in the liver, and are quickly eliminated from systemic circulation, thereby limiting their therapeutic concentrations in target tissues. Additionally, standardization remains a critical issue, as the concentration and composition of polyphenols can vary significantly between plant sources, cultivation conditions, and preparation methods, leading to inconsistent efficacy.

Another barrier is the lack of robust, large-scale clinical trials evaluating the long-term safety and effectiveness of polyphenol-based interventions in human populations, particularly among obese individuals with cancer. Most existing studies are small-scale, lack appropriate controls, and often have short durations, limiting their generalizability and clinical relevance. Without rigorous, placebo-controlled trials, it remains challenging to establish definitive conclusions about their therapeutic utility. Moreover, the variability in individual metabolic responses to polyphenols, influenced by genetics and gut microbiota, complicates efforts to predict outcomes and recommend standardized dosages.

To overcome these challenges, future research should prioritize the development of advanced delivery systems such as nanoparticles, micelles, or liposomes to improve polyphenol stability, absorption, and tissue targeting. Investigating synergistic combinations of polyphenols with conventional chemotherapeutic agents could enhance treatment outcomes while potentially reducing side effects. Importantly, personalized nutrition strategies that consider genetic, metabolic, and microbiome profiles may optimize the benefits of polyphenol interventions. Finally, well-designed clinical trials with adequate sample sizes, long-term follow-up, and standardized polyphenol formulations are essential to validate efficacy, establish therapeutic windows, and promote clinical integration of these promising natural compounds in obesity-associated cancer therapy.

7. CONCLUSION

The convergence of obesity, inflammation, and cancer represents a major challenge in modern medicine. Polyphenol-rich natural products offer a promising avenue for disrupting this pathogenic axis. Through their multi-targeted actions on inflammatory pathways, oxidative stress, adipokine balance, and tumor signaling, polyphenols such as curcumin, resveratrol, quercetin, and EGCG hold potential as safe, adjunctive therapies in cancer management, particularly for obese individuals. While current evidence is encouraging, translational hurdles must be overcome through innovative formulation strategies and rigorous clinical research to fully harness their therapeutic benefits.

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