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Synergistic Effects of Natural Products with Metformin in the Treatment of Obesity-Associated Endometrial Cancer: A Mini Review

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ABSTRACT

Endometrial cancer (EC) is one of the most common gynecological malignancies worldwide, with obesity recognized as a major risk factor contributing to its incidence and progression. Metformin, a widely used antidiabetic drug, has shown promising anticancer effects in obesity-associated EC through modulation of metabolic and signaling pathways. Concurrently, various natural products derived from plants and dietary sources exhibit antineoplastic properties, including modulation of oxidative stress, inflammation, and epigenetic regulation. Emerging evidence suggests that combining metformin with natural products may exert synergistic therapeutic effects against obesity-associated EC by targeting multiple pathways simultaneously. This review comprehensively summarizes the molecular mechanisms underlying obesity-associated EC, the anticancer mechanisms of metformin and natural products, and the current preclinical and clinical evidence supporting their synergistic use. We also discuss challenges and future directions for developing combination therapies harnessing metformin and natural bioactive compounds to improve EC treatment outcomes and reduce obesity-related cancer burden.

Keywords: Endometrial cancer, obesity, metformin, natural products, synergistic therapy

INTRODUCTION

Endometrial cancer (EC) is one of the most common gynecological malignancies worldwide and represents a significant health burden among women[1–3]. It primarily arises from the lining of the uterus, the endometrium, and its incidence has been steadily rising, particularly in developed countries[3]. The increasing prevalence of EC correlates strongly with global trends in obesity, a major modifiable risk factor implicated in the disease's etiology and progression[4–6]. Obesity affects more than 650 million adults globally and is characterized by excessive accumulation of adipose tissue that disrupts normal metabolic homeostasis. This excess adiposity triggers a complex network of biological changes, including hormonal imbalances, chronic systemic inflammation, and metabolic dysregulation, which collectively promote carcinogenesis in the endometrium[7–9].

The pathophysiological link between obesity and EC is multifaceted. Adipose tissue acts as an active endocrine organ, secreting hormones, adipokines, and inflammatory mediators. Among these, the conversion of androgens to estrogens via the enzyme aromatase in adipose tissue is pivotal in increasing circulating estrogen levels in obese women, especially postmenopausal women who lack ovarian estrogen production[10–12]. Elevated estrogen without the counterbalance of progesterone (unopposed estrogen) stimulates excessive proliferation of endometrial cells, thereby enhancing the risk of hyperplasia and malignant transformation[13]. Simultaneously, obesity induces insulin resistance—a hallmark of metabolic syndrome resulting in hyperinsulinemia and increased bioavailability of insulin-like growth factors (IGFs). These growth factors act as mitogens that promote cell proliferation and inhibit apoptosis, further supporting tumor growth[14].

Beyond hormonal and growth factor changes, obesity also creates a chronic inflammatory milieu. The excessive adipose tissue secretes pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and leptin, which contribute to a tumor-permissive microenvironment by activating various oncogenic signaling pathways and suppressing anti-tumor immune responses[15]. Additionally, obesity-associated oxidative stress leads to increased generation of reactive oxygen species (ROS), which cause DNA damage and genomic instability, critical drivers of cancer initiation and progression. Epigenetic modifications—such as DNA methylation, histone acetylation, and microRNA expression are also influenced by metabolic disturbances in obesity, resulting in altered gene expression profiles that favor oncogenesis[15, 16].

Given the complex biological underpinnings of obesity-associated EC, effective therapeutic strategies must address multiple pathological mechanisms simultaneously. Metformin, a biguanide-class oral antihyperglycemic agent primarily used to treat type 2 diabetes mellitus (T2DM), has gained attention for its potential anti-cancer properties[17]. Metformin improves insulin sensitivity and lowers circulating insulin levels, thus counteracting hyperinsulinemia-driven tumor promotion. Mechanistically, metformin activates AMP-activated protein kinase (AMPK), a cellular energy sensor, which in turn inhibits mammalian target of rapamycin (mTOR) signaling, an important regulator of cell growth and proliferation[17]. Clinical and preclinical studies have reported that metformin can reduce tumor growth, enhance apoptosis, and improve survival outcomes in various cancers, including EC.

In parallel, natural products derived from plants such as polyphenols (e.g., resveratrol, epigallocatechin gallate), flavonoids (e.g., quercetin, genistein), and alkaloids (e.g., berberine) have demonstrated promising anticancer effects[18, 19]. These compounds exhibit multifaceted biological activities, including antioxidative, anti-inflammatory, pro-apoptotic, and epigenetic modulatory effects. For instance, many natural products inhibit key signaling pathways implicated in cancer progression, modulate the tumor microenvironment, and reverse aberrant epigenetic marks. Importantly, natural products tend to have low toxicity profiles, making them attractive candidates for adjunctive therapy[20–22].

Combining metformin with natural products holds significant therapeutic promise in obesity-associated EC. This combinatorial approach targets the disease's multifactorial nature by simultaneously modulating metabolic, inflammatory, hormonal, and epigenetic pathways. Synergistic effects may enhance antitumor efficacy, reduce drug resistance, and minimize adverse effects compared to conventional chemotherapies. Moreover, integrating natural products could support cancer prevention strategies in high-risk obese populations by attenuating underlying pathogenic mechanisms. Therefore, understanding the interplay between metformin and natural compounds and their mechanistic roles in EC is crucial to developing novel, effective, and safe treatment modalities tailored for obesity-driven endometrial carcinogenesis.

2. Obesity and Endometrial Cancer: Pathophysiological Link

Obesity is recognized as one of the strongest risk factors for endometrial cancer (EC), significantly influencing both its incidence and prognosis[23]. The relationship between obesity and EC is complex and multifactorial, involving an intricate interplay of hormonal imbalances, metabolic disturbances, chronic inflammation, oxidative stress, and epigenetic alterations. Each of these factors contributes to an environment conducive to malignant transformation and tumor progression in the endometrium[24].

Hormonal Imbalance: One of the central mechanisms by which obesity increases EC risk is through hormonal dysregulation. Adipose tissue is an active endocrine organ that expresses aromatase, the enzyme responsible for converting androgens—primarily androstenedione and testosterone into estrogens (estrone and estradiol)[25]. In obese individuals, increased adiposity leads to enhanced peripheral aromatization, resulting in elevated circulating estrogen levels, particularly in postmenopausal women. Unlike premenopausal women, who produce estrogens mainly from the ovaries and have balanced progesterone secretion, postmenopausal women rely on adipose tissue for estrogen production and often lack sufficient progesterone[26, 27]. This state of unopposed estrogen stimulates the proliferation of the endometrial lining without the counter-regulatory effects of progesterone, promoting endometrial hyperplasia, a precursor lesion to EC[28]. Moreover, estrogen promotes the expression of growth factors and anti-apoptotic proteins, which further facilitates tumorigenesis.

Insulin Resistance and Hyperinsulinemia: Obesity is frequently accompanied by insulin resistance, a condition in which peripheral tissues become less responsive to insulin, leading to compensatory hyperinsulinemia [29]. High insulin levels have mitogenic and anti-apoptotic effects on various tissues, including the endometrium[30]. Insulin directly stimulates endometrial cell proliferation and also increases the bioavailability of insulin-like growth factor-1 (IGF-1) by reducing levels of IGF-binding proteins. IGF-1 binds to its receptor on endometrial cells, activating intracellular pathways such as PI3K/Akt and MAPK, which promote cell growth and survival. Thus, insulin and IGF-1 signaling create a proliferative and anti-apoptotic environment that encourages malignant transformation[30].

Chronic Inflammation: Adipose tissue, especially visceral fat, is a rich source of pro-inflammatory cytokines and adipokines[15, 26]. In obesity, adipocytes and infiltrating immune cells such as macrophages secrete increased levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), leptin, and other inflammatory mediators. These cytokines activate transcription factors like NF-κB and STAT3 in endometrial cells, which drive the expression of genes involved in proliferation, angiogenesis, and immune evasion[7, 12, 31]. Chronic low-grade inflammation contributes to DNA damage, supports tumor cell survival, and promotes the development of a tumor-friendly microenvironment. Additionally, obesity-associated inflammation impairs the function of immune cells, reducing their ability to detect and eliminate malignant cells.

Oxidative Stress: Obesity is associated with elevated levels of reactive oxygen species (ROS), which are chemically reactive molecules containing oxygen[4, 32, 33]. The imbalance between ROS production and antioxidant defenses leads to oxidative stress, which can damage DNA, proteins, and lipids. DNA damage induced by ROS includes mutations, strand breaks, and chromosomal instability, all of which are hallmarks of cancer development. Oxidative stress also promotes activation of oncogenic signaling pathways and inhibits tumor suppressor functions, further facilitating carcinogenesis[34–36]. The persistent oxidative environment in obese individuals contributes to genomic instability in endometrial tissue, accelerating the progression from hyperplasia to malignancy.

Epigenetic Alterations: Emerging evidence indicates that obesity induces significant epigenetic changes that contribute to EC pathogenesis[37]. Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation control gene expression without altering the DNA sequence. Metabolic stress associated with obesity, including hyperinsulinemia and chronic inflammation, alters these epigenetic marks, leading to the silencing of tumor suppressor genes and activation of oncogenes. For instance, hypermethylation of promoter regions in key regulatory genes can prevent their transcription, disrupting cell cycle control and apoptosis[37–39]. Additionally, obesity-driven changes in histone acetylation patterns can affect chromatin structure and gene accessibility, further influencing tumor behavior. These epigenetic modifications are reversible and thus represent promising therapeutic targets.

In sum, obesity promotes endometrial carcinogenesis through a constellation of interrelated mechanisms: hormonal imbalances favoring unopposed estrogen action, insulin resistance and hyperinsulinemia enhancing proliferative signaling, chronic inflammation creating a tumor-promoting microenvironment, oxidative stress causing DNA damage, and epigenetic dysregulation affecting gene expression. These factors collectively contribute to the increased incidence and poorer prognosis of EC observed in obese women. Understanding these pathophysiological links not only sheds light on the etiology of obesity-associated EC but also highlights potential therapeutic targets for intervention and prevention.

3. Metformin in Obesity-Associated Endometrial Cancer

Metformin, a widely used antidiabetic drug, has garnered significant attention for its potential anticancer effects, particularly in obesity-associated endometrial cancer (EC). Obesity promotes a metabolic and hormonal milieu that fosters EC progression, and metformin's multifaceted mechanisms counteract these cancer-promoting processes[17, 40, 41].

One of the primary anticancer actions of metformin involves activation of AMP-activated protein kinase (AMPK), a critical cellular energy sensor. Activation of AMPK leads to inhibition of the mammalian target of rapamycin (mTOR) pathway, a key driver of protein synthesis, cell growth, and proliferation[17, 41]. By dampening mTOR signaling, metformin effectively reduces tumor cell proliferation and promotes energy stress-induced apoptosis in cancer cells. This mechanism is particularly relevant in obesity-associated EC, where mTOR is often hyperactivated due to excess nutrient and growth factor signaling.

In addition to AMPK activation, metformin improves systemic insulin sensitivity, leading to reduced circulating insulin and insulin-like growth factor-1 (IGF-1) levels. Since insulin and IGF-1 can directly stimulate cancer cell growth through their respective receptors, lowering their availability interrupts these proliferative signals. This insulin/IGF-1 pathway modulation by metformin is crucial in obese patients, where hyperinsulinemia frequently fuels tumor progression[40, 42, 43]. Moreover, metformin has been shown to selectively target cancer stem-like cells (CSCs) within EC tumors. CSCs contribute to tumor initiation, metastasis, and resistance to conventional therapies. By inhibiting CSC self-renewal and survival, metformin may enhance treatment efficacy and reduce recurrence rates[44]. Metformin also exhibits anti-inflammatory effects by reducing pro-inflammatory cytokines such as TNF-α and IL-6, thereby modulating the tumor microenvironment. Chronic inflammation is a hallmark of obesity and a key factor in EC pathogenesis[44].

Emerging evidence indicates that metformin can influence epigenetic modifications, including DNA methylation and histone acetylation. These epigenetic changes may reverse obesity-induced dysregulation of gene expression patterns that favor tumor growth[45]. Clinical studies support these mechanistic insights, showing that metformin use in obese EC patients is associated with improved overall survival, reduced tumor cell proliferation markers, and enhanced responses to chemotherapy[46]. Thus, metformin holds promise as a valuable adjuvant therapy in managing obesity-associated endometrial cancer[46].

4. Natural Products with Potential Synergy with Metformin

Several natural compounds exhibit anticancer properties through mechanisms that complement metformin's actions, making them promising candidates for combined therapy in obesity-associated endometrial cancer[47]. These compounds often target signaling pathways, metabolic regulators, and epigenetic modifications that are dysregulated in cancer cells. By working synergistically with metformin, which primarily activates AMPK and inhibits mTOR signaling, natural products can enhance apoptosis, reduce inflammation, improve insulin sensitivity, and suppress tumor progression[48]. Their multi-targeted effects may also help overcome resistance mechanisms and improve overall treatment efficacy. The following natural compounds have been extensively studied for their potential to augment metformin's anticancer benefits.

4.1 Curcumin: Curcumin is a bioactive polyphenol extracted from turmeric (Curcuma longa) known for its potent anti-inflammatory and anticancer properties[49, 50]. It inhibits NF-κB signaling, a critical pathway involved in chronic inflammation and cancer progression, thereby reducing the production of pro-inflammatory cytokines. Curcumin also suppresses angiogenesis by downregulating vascular endothelial growth factor

(VEGF) and modulates epigenetic regulators, including DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), which influence gene expression in cancer cells[50, 51]. Importantly, curcumin sensitizes endometrial cancer cells to apoptosis and has been shown to enhance the antiproliferative effects of metformin by targeting complementary molecular pathways. Its multi-faceted actions make curcumin a valuable natural product to explore in combination with metformin for improved therapeutic outcomes in obesity-associated endometrial cancer.

4.2 Resveratrol: Resveratrol, a polyphenolic compound found predominantly in grapes, berries, and red wine, exerts anticancer effects by activating key metabolic and longevity pathways such as SIRT1 and AMPK[52–54]. Activation of these pathways promotes apoptosis and inhibits mTOR signaling, which is often hyperactive in cancer cells. Resveratrol improves insulin sensitivity and reduces oxidative stress, addressing metabolic disturbances common in obesity that can drive tumor growth[55, 56]. Its ability to target multiple signaling cascades and metabolic processes suggests it could potentiate the anticancer efficacy of metformin, which also activates AMPK and inhibits mTOR. By simultaneously modulating cellular energy metabolism and stress responses, resveratrol may enhance metformin's therapeutic benefits in obesity-associated endometrial cancer.

4.3 Epigallocatechin-3-gallate (EGCG): EGCG is the major catechin present in green tea, widely recognized for its antioxidant, anti-inflammatory, and antiangiogenic properties[57]. It exerts anticancer effects by inhibiting critical oncogenic signaling pathways such as PI3K/AKT and MAPK, which regulate cell proliferation, survival, and metastasis. These pathways often interact with the AMPK/mTOR axis targeted by metformin[57]. EGCG's ability to suppress tumor angiogenesis limits nutrient supply to the tumor, further enhancing growth inhibition. Additionally, EGCG reduces oxidative stress and inflammation, factors that promote cancer progression in obesity[58, 59]. When combined with metformin, EGCG's complementary targeting of overlapping and distinct molecular pathways may result in improved tumor suppression and metabolic regulation.

4.4 Quercetin: Quercetin is a flavonoid abundant in various fruits, vegetables, and grains, known for its capacity to induce cell cycle arrest and apoptosis in cancer cells[60–62]. It modulates important regulators of cell death and survival, including tumor suppressor p53, anti-apoptotic protein Bcl-2, and caspase activation pathways [63]. Quercetin also enhances insulin sensitivity and alleviates obesity-related systemic inflammation, both of which are critical in reducing cancer risk and progression linked to metabolic dysfunction[62, 64]. Its multifaceted mechanisms, targeting both cancer cell intrinsic pathways and systemic metabolic disturbances, align well with metformin's mode of action. This synergy could improve therapeutic responses in obesity-associated endometrial cancer by promoting tumor cell death while ameliorating metabolic risk factors.

6. Challenges and Future Directions

Bioavailability: One of the foremost challenges limiting the clinical utility of many natural products is their poor bioavailability. Despite demonstrated therapeutic potential in vitro or in animal models, these compounds often face issues such as low solubility, poor absorption in the gastrointestinal tract, rapid metabolism, and quick systemic clearance when administered orally. These pharmacokinetic barriers significantly reduce the effective concentration of active compounds reaching target tissues, diminishing their efficacy in clinical settings. To address this, advanced drug delivery systems such as nanoparticle-based carriers have garnered significant interest. Nanoparticles can enhance the solubility, stability, and absorption of natural products, protect them from enzymatic degradation, and enable controlled or targeted release. For example, encapsulating curcumin or resveratrol in lipid or polymeric nanoparticles has shown promise in improving their bioavailability and therapeutic effects. Additionally, such delivery platforms may also reduce toxicity and improve patient compliance. However, translating these nanotechnologies from bench to bedside requires overcoming challenges related to large-scale production, safety profiling, and regulatory approval. Continued interdisciplinary research integrating nanotechnology, pharmacology, and natural product chemistry is crucial to overcoming bioavailability hurdles and fully harnessing the potential of natural compounds in combination therapies such as with metformin.

Standardization: A critical barrier to the reproducibility and clinical translation of natural products is the lack of standardization in their preparation and dosing. Natural compounds are typically extracted from plant or microbial sources, and their chemical composition can vary widely depending on factors such as species, geographic origin, harvesting time, extraction methods, and storage conditions. This variability leads to inconsistencies in the concentration and profile of bioactive ingredients between batches, complicating the interpretation of experimental results and clinical outcomes. Without standardized formulations, comparing findings across studies or replicating effects becomes difficult, hindering regulatory approval and clinical acceptance. Additionally, the dosing of natural products is often empirically determined, lacking clear pharmacokinetic or pharmacodynamic guidance, which may lead to suboptimal efficacy or safety concerns. Developing rigorous protocols for the cultivation, harvesting, extraction, and quality control of natural products is essential. Analytical techniques like high-performance liquid chromatography (HPLC), mass spectrometry, and nuclear magnetic resonance (NMR) spectroscopy play vital roles in fingerprinting and quantifying active constituents. Establishing pharmacopeial standards and ensuring batch-to-batch consistency will improve reliability, facilitate mechanistic studies, and build clinician and patient confidence in natural product-based adjunct therapies alongside drugs like metformin.

Mechanistic Understanding: Despite promising preclinical data supporting the synergistic anticancer effects of metformin combined with natural products, the precise molecular mechanisms underlying these interactions remain incompletely understood. Both metformin and many natural compounds exert multifaceted actions on cellular metabolism, signaling pathways, epigenetic regulation, and the tumor microenvironment, often involving overlapping or complementary targets. For example, metformin activates AMP-activated protein kinase (AMPK) and inhibits mTOR signaling, while natural polyphenols like curcumin modulate NF-κB, STAT3, and epigenetic enzymes such as DNMTs and HDACs. Understanding how these pathways intersect, potentiate, or counter-regulate each other is essential to rationally design combination regimens, optimize dosing schedules, and minimize adverse effects. Comprehensive mechanistic studies employing systems biology, omics technologies (transcriptomics, proteomics, metabolomics), and advanced molecular modeling can reveal key nodes of synergy and resistance. Additionally, elucidating the impact on cancer stem cells, immune modulation, and metabolic reprogramming will clarify how these combinations may improve outcomes in obesity-associated endometrial cancer and other malignancies. Greater mechanistic insight will also enable identification of biomarkers predictive of response and facilitate personalized therapeutic strategies. Therefore, intensified multidisciplinary research integrating molecular biology, pharmacology, and computational modeling is critical for translating natural product-metformin combinations into effective clinical interventions.

Personalized Therapy: The heterogeneity of cancer biology and patient metabolic profiles presents both a challenge and an opportunity for optimizing the use of metformin combined with natural products. Personalized therapy aims to tailor treatment regimens based on individual patient characteristics such as genetic mutations, metabolic status, epigenetic landscape, and tumor microenvironment. In obesity-associated endometrial cancer, patients may exhibit variable degrees of insulin resistance, inflammation, hormone receptor expression, and molecular subtypes, which can influence their response to metformin and natural compounds. Stratifying patients using genomic, metabolomic, and immunologic profiling can help identify subgroups more likely to benefit from synergistic interventions. For instance, patients with hyperinsulinemia or high mTOR pathway activity may respond particularly well to metformin's metabolic effects, while those with epigenetic alterations might benefit more from polyphenol-based HDAC or DNMT inhibitors. Integration of liquid biopsy, imaging biomarkers, and artificial intelligence-driven predictive models will enhance precision medicine approaches. Additionally, personalized regimens can optimize dosing to balance efficacy and toxicity, reduce unnecessary treatments, and improve adherence. Ultimately, developing clinically feasible diagnostic tools and validated biomarkers to guide the use of metformin-natural product combinations will be essential to advance personalized oncologic care and improve outcomes for patients with obesity-driven cancers.

Large-Scale Clinical Trials: While preclinical studies and early-phase clinical trials have shown promising anticancer effects of metformin and natural product combinations, robust evidence from large-scale, randomized controlled trials (RCTs) is indispensable to confirm their safety, efficacy, and clinical utility. Many current studies are limited by small sample sizes, heterogeneous patient populations, varying formulations, and short follow-up durations. Well-designed multicenter RCTs with adequate statistical power are necessary to evaluate clinical endpoints such as progression-free survival, overall survival, quality of life, and biomarker response in obesity-associated endometrial cancer and other malignancies. Standardized protocols for dosing, administration routes, and patient stratification must be implemented to ensure reproducibility and comparability. Regulatory agencies require rigorous clinical evidence to support the approval of new combination therapies and incorporation into treatment guidelines. Moreover, large trials can uncover potential adverse effects, drug interactions, and long-term safety profiles. Collaboration between academic institutions, industry, and funding agencies is essential to support these resource-intensive studies. Inclusion of diverse populations will also ensure generalizability of results across different ethnicities and metabolic conditions. Ultimately, translating the promise of natural product-metformin synergy into clinical practice depends on generating high-quality evidence through comprehensive clinical trials to inform evidence-based guidelines and improve patient care.

6. CONCLUSION

The combination of metformin with natural products represents a promising strategy to target the multifaceted mechanisms driving obesity-associated endometrial cancer. By simultaneously modulating metabolic, inflammatory, and epigenetic pathways, these combinations may improve therapeutic efficacy and patient outcomes. Future research and clinical validation are critical to translate these synergistic approaches into standard clinical practice.

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