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EPIGENETIC REGULATION BY CURCUMIN IN OVARIAN CANCER: A FOCUS ON miRNA NETWORKS, HISTONE MODIFICATIONS AND DNA METHYLATION

OVER KANSERİNDE KURKUMİN İLE EPİGENETİK DÜZENLEME: miRNA AĞLARI, HİSTON MODİFİKASYONLARI VE DNA METİLASYONU ÜZERİNE BİR İNCELEME

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ABSTRACT

Ovarian cancer remains a leading cause of gynaecological cancer-related deaths, driven by its late-stage diagnosis, high metastatic potential, and frequent development of chemoresistance. Current therapeutic strategies often fail to address the intricate mechanisms underlying tumour progression, necessitating innovative approaches. Curcumin, a bioactive polyphenol derived from *Curcuma longa*, has emerged as a potent epigenetic regulator with multifaceted anticancer properties. This review highlights curcumin's ability to modulate key epigenetic mechanisms such as microRNA (miRNA/miR) regulation, histone modifications, and DNA methylation, which are central to ovarian cancer pathogenesis. Curcumin selectively reprograms miRNA networks, restoring tumour-suppressive miRNAs while downregulating oncogenic miRNAs, thereby mitigating epithelial-mesenchymal transition and chemoresistance. In addition, curcumin inhibits histone deacetylase (HDACs) and EZH2-mediated histone methylation, reactivating critical tumour-suppressor genes like *BRCA1*. Through its suppression of DNA methyltransferase (DNMT) activity, curcumin reverses promoter hypermethylation, further enhancing tumour-suppressor gene expression. These synergistic epigenetic modulations disrupt oncogenic pathways, improve chemotherapy sensitivity, and restore the immune recognition of tumour cells. Despite its promise, poor bioavailability limits the clinical translation of curcumin, but advanced formulations, including nanoparticles

ÖZET

Over kanseri, geç evrede teşhis edilmesi, yüksek metastaz potansiyeli ve genellikle gelişen kemoterapi direnci nedeniyle, jinekolojik kanserlerden kaynaklanan ölümlerin başlıca nedenlerinden biri olmaya devam etmektedir. Mevcut tedavi yaklaşımları, tümör ilerlemesinin altında yatan karmaşık mekanizmaları yeterince ele alamamakta ve bu durum yenilikçi stratejilere olan ihtiyacı ortaya koymaktadır. Zerdeçalın (*Curcuma longa*) biyoaktif bir polifenolü olan kurkumin, çok yönlü anti-kanser özellikleri ile güçlü bir epigenetik düzenleyici olarak öne çıkmıştır. Bu derlemede, kurkuminin over kanseri patogenezinde önemli rol oynayan mikroRNA (miRNA/miR) düzenlemesi, histon modifikasyonları ve DNA metilasyonu gibi temel epigenetik mekanizmaları nasıl modüle ettiğine dikkat çekilmektedir. Kurkumin, tümör baskılayıcı miRNA'ları yukarı regüle ederken, onkojenik miRNA'ları aşağı regüle ederek miRNA ağlarını seçici şekilde yeniden programlamaktadır. Bu sayede, epitel-mezenkimal dönüşümü ve kemoterapi direncini azaltabilmektedir. Ayrıca, kurkumin, histon deasetilazları (HDAC'ler) ve EZH2 aracılı histon metilasyonunu inhibe ederek, *BRCA1* gibi kritik tümör baskılayıcı genlerin yeniden aktivasyonunu sağlamaktadır. DNA metiltransferaz (DNMT) aktivitesini baskılayarak, promotör hipermetilasyonunu tersine çevirmekte ve tümör baskılayıcı gen ekspresyonunu artırmaktadır. Kurkuminden kaynaklanan bu sinerjik epigenetik düzenlemeler, onkojenik yolları engellemekte, kemoterapi duyarlılığını artırmakta ve tümör hücrelerinin bağışıklık sistemi tarafından tanınmasını sağlamaktadır. Ancak,

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and liposomes, overcome this limitation. Further research is essential to optimise delivery systems, elucidate long-term epigenetic effects, and validate therapeutic efficacy through clinical trials. This review underscores curcumin's potential to enhance current ovarian cancer therapies by addressing the critical epigenetic mechanisms involved in tumour progression and resistance.

Keywords: Ovarian cancer, curcumin, epigenetics

kurkuminin terapötik potansiyeli düşük biyoyararlanımı nedeniyle sınırlıdır; bu durum, nanopartiküller ve lipozomlar gibi yenilikçi formülasyonlarla aşılmaya çalışılmaktadır. İlaç dağıtım sistemlerinin optimize edilmesi, uzun vadeli epigenetik etkilerin daha iyi anlaşılması ve klinik çalışmalarla terapötik etkinliğin doğrulanması için daha fazla araştırmaya ihtiyaç vardır. Bu derleme, kurkuminin tümör progresyonu ve direncinde rol oynayan kritik epigenetik mekanizmaları inceleyerek, over kanseri tedavisine katkı sağlama potansiyelini vurgulamaktadır.

Anahtar kelimeler: Over kanseri, kurkumin, epigenetik

INTRODUCTION

Ovarian cancer presents a multifaceted challenge to global health. Its high mortality rate, particularly due to late-stage diagnosis, necessitates a concerted effort to improve early detection strategies (1). Furthermore, the significant impact on women's reproductive health and psychological well-being demands a comprehensive approach that tackles not only the physical symptoms of the condition but also the emotional and social challenges faced by those affected (2). Continued research into the underlying biological mechanisms, coupled with the development of personalised treatment plans, is crucial to improve patient outcomes and ultimately reduce the global burden of this devastating malignancy (1).

Ovarian cancer presents significant therapeutic challenges, primarily due to chemoresistance and the propensity for metastasis (3). Chemoresistance, which refers to the capacity of cancer cells to resist the effects of chemotherapy, poses a significant barrier to attaining sustained remission and effective treatment outcomes (4). The mechanisms driving chemoresistance are intricate and multifaceted, encompassing changes in drug absorption, metabolic processes, DNA repair mechanisms, and pathways regulating programmed cell death (5). Moreover, ovarian cancer exhibits a high propensity for metastasis, spreading to distant sites such as the peritoneum, liver, and lungs (6). This metastatic spread significantly contributes to treatment failure and poor patient outcomes. The development of novel therapeutic strategies that can overcome chemoresistance and effectively target metastatic disease remains a critical area of research in ovarian cancer management.

Derived from the rhizome of *Curcuma longa* (turmeric), curcumin, a vibrant yellow pigment, has attracted considerable scientific interest for its diverse pharmacological properties, particularly its significant anti-cancer effects (7). As a polyphenol compound, curcumin exerts its anti-cancer activities through multiple mechanisms, such as inhibiting cell proliferation, inducing programmed cell death, suppressing new blood vessel formation, and modulating various signaling pathways implicated in tumorigenesis (Figure 1) (8). Curcumin effectively inhibits tumour growth through a multifaceted approach. It interacts with and regulates several key signaling pathways, including PI3K/AKT/mTOR, STAT, and NF-κB. This involves targeting key cellular processes: apoptosis (through *BCL2* and caspases), cell cycle regulation (via cyclins and CDKs), growth factor signaling (involving *VEGF* and *EGF*), and cytokine production (like interleukins) (8). Furthermore, curcumin exerts a profound impact on gene expression by influencing non-coding RNAs and modifying epigenetic mechanisms, contributing to its broad spectrum of therapeutic benefits (9). As essential regulators of gene expression, microRNAs (miRNAs/miRs) – small, non-coding RNA molecules-are crucial in influencing the behaviour and progression of cancer cells. Our 2024 study demonstrated the potential of curcumin and desmethoxycurcumin to enhance the efficacy of cisplatin in ovarian cancer treatment. Reduced *GSTP-1* and miR-133b levels in cisplatin-resistant cells may contribute to drug resistance, making them potential as therapeutic targets. Dysregulation of miRNAs, such as the observed decrease in miR-133b and its target gene *GSTP-1* in cisplatin-resistant ovarian cancer cells, contributes significantly to tumour development and progres-

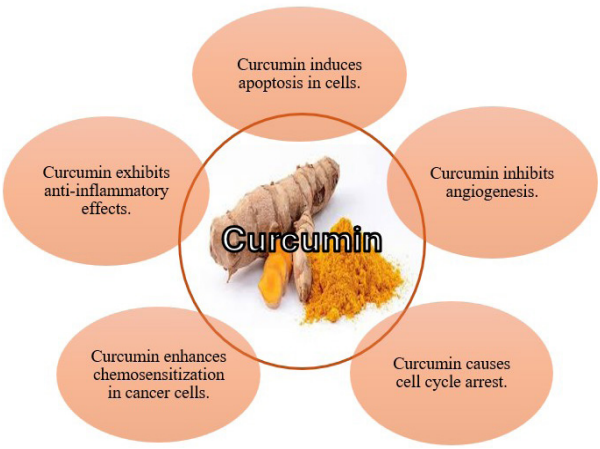

Figure 1: The figure depicts the various mechanisms through which curcumin exerts its anti-cancer effects in ovarian cancer

sion, particularly by promoting drug resistance (10). This highlights the potential of targeting miRNAs to enhance the efficacy of cancer treatments.

Curcumin's anti-cancer properties in ovarian cancer

Curcumin has emerged as a promising anti-cancer agent because of its multifaceted influence on cellular processes. Beyond its anti-oxidant and anti-inflammatory actions, curcumin demonstrates remarkable versatility in modulating gene expression. By downregulating oncogenes like *NF-κB* while simultaneously upregulating tumour suppressors such as *p53*, curcumin disrupts the delicate balance that favours tumour growth (11, 12). This intricate orchestration of gene regulation translates into a cascade of anti-cancer effects, including the inhibition of cell proliferation, induction of apoptosis, and suppression of angiogenesis, all of which are critical steps in cancer development. Furthermore, curcumin's ability to temper chronic inflammation, a significant contributor to cancer risk, underscores its potential to effectively combat the tumour microenvironment and impede disease progression (13).

Curcumin and chemosensitization

Reduction of the chemoresistance mechanisms

A significant obstacle in managing ovarian cancer is the emergence of resistance to chemotherapy. In this state, cancer cells undergo alterations that enable them to evade the cytotoxic effects of chemotherapy medications, thereby limiting the effectiveness of these treatments (14). Curcumin offers a hopeful avenue for surmounting this obstacle (12). Studies have indicated that curcumin may have the potential to improve the response of ovarian cancer cells to chemotherapy treatments by targeting and overcoming mechanisms that enable cancer cells to resist the effects of these drugs (15). Curcumin has been shown to counteract chemoresistance in ovarian cancer by inhibiting cellular efflux pumps. These transporters, including P-glycoprotein, actively pump chemotherapeutic agents out of cancer cells, thereby reducing drug efficacy. Curcumin's ability to inhibit these efflux pumps leads to increased intracellular drug accumulation, thereby enhancing the effectiveness of chemotherapy in treating ovarian cancer. Additionally, it interferes with the mechanisms that cancer cells use to repair DNA damage, making them more vulnerable to cell death. This multifaceted approach increases the potency of conventional chemotherapy, potentially resulting in better treatment outcomes in individuals with ovarian cancer (16).

Modulation of the key signaling pathways

PI3K/Akt/mTOR pathway modulation by curcumin

The PI3K/Akt/mTOR signaling pathway is crucial in controlling cellular processes such as proliferation, survival, and metabolism. However, in cancers like ovarian cancer, this pathway often exhibits aberrant activation, driven by genetic alterations such as *PIK3CA* mutations or *PTEN* loss. This aberrant activation drives tumorigenesis, promotes metastatic dissemination, and contributes to resistance to conventional therapies (17). Curcumin has emerged as a promising therapeutic agent due to its multifaceted mechanisms of action, including the modulation of the PI3K/Akt/mTOR pathway (18). Curcumin exerts its effects on this pathway through various actions. It can directly target and suppress the key components of the pathway. Furthermore, it can influence upstream regulators that control the activity of these components. Notably, curcumin can also stimulate a counteracting mechanism that helps to dampen the activity of the pathway. Furthermore, curcumin can induce autophagy, a cellular process that can contribute to tumour cell death, by inhibiting *mTORC1* activity. By targeting this critical pathway, curcumin demonstrates significant anti-proliferative and pro-apoptotic effects in ovarian cancer cells, offering a potential adjuvant therapeutic strategy for this challenging malignancy. A key mechanism underlying curcumin's anti-cancer effects in ovarian cancer involves the modulation of the PI3K/Akt/mTOR signaling pathway. The function of this pathway is indispensable for supporting essential cellular activities, such as cell growth, proliferation, and the ability of cells to survive and thrive (17).

STAT3/NF-κB/iNOS/COX-2 signaling pathway

Curcumin has been shown to effectively modulate this pathway, which is a key contributor to inflammation and tumorigenesis in ovarian cancer (18). This pathway plays a critical role in promoting cell proliferation, survival, and angiogenesis. It exerts its inhibitory effects by suppressing the activation of *STAT3* and *NF-κB*, key transcription factors that regulate the expression of downstream inflammatory mediators such as *iNOS* (inducible nitric oxide synthase) and *COX-2* (cyclooxygenase-2). By downregulating this pathway, curcumin can effectively inhibit tumour growth, induce apoptosis, and suppress tumour invasion and metastasis. This multifaceted modulation of inflammatory signaling pathways highlights the significant therapeutic potential of curcumin in ovarian cancer management (18).

The intricate interplay of signaling pathways, including *STAT3* and *NF-κB*, plays a pivotal role in orchestrating the complex cascade of events that underpin malignant transformation. The aberrant activation of *NF-κB*, a key regulator of inflammatory responses, drives the overexpression of pro-inflammatory factors such as *COX-2*, *iNOS*, cytokines (including *TNF-α*), and other inflammatory mediators, thereby fostering a pro-tumorigenic microenvironment (18, 19). Curcumin, a polyphenol derived from turmeric, has emerged as a compelling therapeutic candidate due to its ability to effectively modulate these critical signaling pathways. By inhibiting *NF-κB* activa-

tion, curcumin suppresses the expression of downstream target genes such as *p53*, *VEGF*, *Bcl-2*, *COX-2*, *iNOS*, *cyclin D1*, *TNF-α*, interleukins, and *MMP-9*, thereby exerting anti-proliferative and anti-metastatic effects (18). This inhibitory action extends to the *STAT3* pathway, further contributing to the suppression of tumour growth and metastasis. Mechanistically, curcumin inhibits the DNA-binding capacity of *NF-κB* by altering its subunit composition, while simultaneously downregulating *AP-1* transcription factors. Furthermore, in preclinical models, curcumin has been demonstrated to induce apoptosis through the activation of caspase-3, an effect closely associated with the inhibition of *NF-κB* activity and the subsequent downregulation of *COX-2* and *cyclin D1* expression (18). These findings collectively underscore the significant potential of curcumin as a therapeutic agent in various cancers by effectively targeting and disrupting the intricate network of signaling pathways that drive tumorigenesis and progression.

NF-κB/PRL-3 pathway and its impact on tumour proliferation and migration

The signaling pathway involving *NF-κB* and *PRL-3* plays a significant role in the aggressive behaviour of ovarian tumours. Curcumin can disrupt this pathway. *NF-κB*, a protein that regulates gene expression, is often abnormally active in ovarian cancers. This excessive activity stimulates the production of various genes that promote tumour growth, including the gene for *PRL-3* (20). PRL-3, an enzyme that removes phosphate groups from proteins, has been implicated in the progression of various cancers, including ovarian cancer. This enzyme has been shown to contribute to key aspects of cancer development, such as uncontrolled cell growth, metastasis, and the ability of cancer cells to penetrate and invade surrounding tissues (21). Curcumin inhibits *NF-κB* activation, leading to a subsequent downregulation of *PRL-3* expression. By targeting this critical signaling axis, curcumin may effectively suppress tumour growth and metastasis in ovarian cancer. Curcumin nanoparticles (CUR-NPs) are emerging as a novel therapeutic approach in ovarian cancer treatment. Studies have shown that CUR-NPs can effectively inhibit tumour growth and metastasis by targeting the NF-κB/PRL-3 signaling pathway. By suppressing the overactivation of *NF-κB* and consequently downregulating *PRL-3* expression, CUR-NPs demonstrate a promising strategy for developing innovative and targeted therapies for ovarian cancer (22).

Curcumin-induced ferroptosis

Ferroptosis, a regulated form of cell death driven by iron, is gaining attention as a potential therapeutic approach for ovarian cancer. It was first described in 2012 by Dixon et al., and is characterised by lipid peroxidation, iron overload, and glutathione depletion (23). Curcumin, a natural substance found in turmeric, has powerful anti-cancer effects. This includes its ability to induce ferroptosis, a cell death process that can selectively eliminate cancer cells (24). The mechanisms underlying curcumin-induced ferroptosis in ovarian cancer are likely multifaceted and may involve the disruption of cellular redox homeostasis through the depletion of glutathione and the inhibition of glutathione peroxidase 4 (*GPX4*). This results in the buildup of lipid peroxidation byproducts and reactive oxygen species, eventually causing oxidative stress and cellular death. Furthermore, curcumin may modulate iron metabolism within cancer cells, potentially increasing iron availability and worsening ferroptosis. Understanding the precise mechanisms of curcumin-induced ferroptosis in ovarian cancer is crucial for optimising its therapeutic potential and developing novel therapeutic strategies that exploit this unique form of cell death (25).

Curcumin derivative NL01 and ferroptosis induction through HCAR1/MCT1 signaling

NL01, a potent curcumin derivative, induces ferroptosis in ovarian cancer cells by targeting the HCAR1/MCT1 signaling axis (25-28). *HCAR1* (hydroxycarboxylic acid receptor 1) and *MCT1* (monocarboxylate transporter 1) are critical for cellular metabolism. By disrupting this axis, NL01 disrupts cellular metabolism, leading to iron accumulation and lipid peroxidation, ultimately triggering ferroptotic cell death (29). Furthermore, NL01 downregulates *HCAR1* and *MCT1*, activating the AMPK-SREBP1 signaling axis, leading to *GPX4* suppression and lipid peroxidation, ultimately triggering ferroptosis (30). These findings highlight NL01's potent anti-tumour activity and provide a novel therapeutic strategy for ovarian cancer by exploiting the ferroptotic pathway.

Curcumin and epigenetic regulation in ovarian cancer

Epigenetic dysregulation is a hallmark of ovarian cancer, contributing to tumour progression, metastasis, and therapeutic resistance (31). By targeting these aberrations, curcumin, a naturally derived bioactive compound, offers a promising approach to restoring the balance of gene expression. Among its mechanisms, curcumin's influence on miRNA expression, histone modifications, and DNA methylation highlights its potential to reprogram the cancer epigenome, disrupt oncogenic pathways, and enhance therapeutic efficacy (32). This section explores these epigenetic interactions, emphasising their implications for ovarian cancer management.

miRNA regulation by curcumin

miRNAs are non-coding RNA molecules that regulate gene expression post-transcriptionally, influencing various cellular processes such as proliferation, apoptosis, and metastasis (33). In ovarian cancer, the deregulation of miRNAs has been implicated in tumour progression and chemoresistance. Curcumin, a natural polyphenolic compound, has shown potential in modulating miRNA expression to exert anti-cancer effects.

Curcumin upregulates tumour-suppressive miRNAs such as miR-9, which targets the Akt/FOXO1 signaling axis, leading to increased apoptosis and reduced cell proliferation. Studies on SKOV3 ovarian cancer cells have shown that curcumin-induced expression of miR-9 inhibits the phosphorylation of *Akt* and *FOXO1*, thereby suppressing cell survival pathways and promoting caspase-3-mediated apoptosis (34). Another important miRNA modulated by curcumin is miR-199a-5p. Through its downregulation of the discoidin domain receptor 1 (*DDR1*), miR-199a-5p suppresses migration, epithelial-to-mesenchymal transition, and activation of the *NF-κB* pathway, thus impairing ovarian cancer cell invasiveness (35).

In addition, curcumin influences the circRNA-miRNA-mRNA regulatory axis. For instance, curcumin enhances the expression of *circ-PLEKHM3*, which acts as a sponge for miR-320a, an oncogenic miRNA overexpressed in ovarian cancer. By reducing miR-320a levels, curcumin restores the tumour-suppressive function of *SMG1*, a kinase involved in apoptosis and cell cycle arrest. This regulatory network underscores the ability of curcumin to modulate non-coding RNA interactions in ovarian cancer progression (36).

Moreover, curcumin affects chemoresistance by targeting extracellular vesicle-mediated miRNA transfer. In cisplatin-resistant ovarian cancer cells, curcumin inhibits the transfer of miR-214 while upregulating the lncRNA *MEG3*, reversing drug resistance and sensitising cells to chemotherapy. The modulation of these miRNAs demonstrates curcumin's potential as an adjunct to standard ovarian cancer therapies, providing a multifaceted approach to targeting tumour growth and resistance mechanisms (37). When combined with dihydroartemisinin (DHA), curcumin synergistically enhances apoptosis in SKOV3 ovarian cancer cells by modulating miR-124 expression and targeting midkine (MK), a heparin-binding growth factor implicated in tumorigenesis and poor prognosis. The co-treatment significantly upregulates miR-124, which directly binds to *MK* mRNA, leading to its degradation and a subsequent reduction in *MK* protein levels. This mechanism promotes apoptotic cell death independent of caspase-3 activation and highlights the therapeutic potential of curcumin and DHA as a combinatorial strategy for ovarian cancer. Importantly, the combination not only demonstrated efficacy in vitro but also effectively suppressed tumour growth in vivo without notable toxicity, reinforcing its clinical promise for ovarian cancer treatment (38). Notably, curcumin modulates miR-133b, an miRNA implicated in drug resistance through its regulation of *GSTP-1*. *GSTP-1*, a key enzyme in glutathione metabolism, confers cisplatin resistance in ovarian cancer cells. By downregulating *GSTP-1* expression via miR-133b, curcumin increases the sensitivity of both cisplatin-sensitive and cisplatin-resistant ovarian cancer cells to chemotherapy (10).

Through its ability to selectively target and modulate miRNA expression, curcumin reprograms the molecular landscape of ovarian cancer cells, mitigating tumour progression and resistance. This dual modulation of oncogenic and tumour-suppressive miRNAs underscores curcumin's therapeutic potential, not only as a standalone epigenetic regulator and as an adjunct to existing treatment modalities. These findings pave the way for further exploration of miRNA-focused therapeutic strategies leveraging curcumin in ovarian cancer.

Histone modifications and DNA methylation

Epigenetic alterations, including histone modifications and DNA methylation, are pivotal in regulating gene expression and chromatin structure. These processes are frequently dysregulated in ovarian cancer, leading to the aberrant silencing of tumour-suppressor genes and the activation of oncogenes (12). Curcumin, with its established role as an epigenetic modulator, exerts profound effects on both histone acetylation and DNA methylation, offering a promising therapeutic avenue for ovarian cancer.

Histone modifications

Histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, play pivotal roles in regulating chromatin structure and gene transcription. These dynamic changes determine whether chromatin adopts an open (euchromatin) or closed (heterochromatin) conformation, thereby controlling the accessibility of transcription factors to DNA. Among these modifications, histone acetylation is particularly well-studied due to its central role in maintaining transcriptional activity. Histone acetylation is catalysed by histone acetyltransferase (HATs), which add acetyl groups to lysine residues on histones, and reversed by histone deacetylase (HDACs), which remove these groups. Dysregulated HDAC activity in ovarian cancer leads to chromatin compaction and transcriptional silencing of critical tumour-suppressor genes, contributing to cancer progression, metastasis, and resistance to therapy (39, 40).

Curcumin has been shown to inhibit HDACs, which are often overexpressed in ovarian cancer, leading to the hypoacetylation of histones and the transcriptional silencing of tumour suppressor genes (9). By inhibiting HDACs, curcumin promotes the acetylation of histones H3 and H4, thereby enhancing chromatin accessibility and reactivating the silenced genes. For example, curcumin treatment increases the acetylation of histone H3 in the promoter regions of tumour suppressor genes such as *p21*, restoring their expression and inducing cell cycle arrest and apoptosis (9, 41).

In addition to its effects on acetylation, curcumin influence histone methylation. Histone methylation, particularly trimethylation at lysine residues such as H3K27me3,

is associated with transcriptional repression. Curcumin reduces the levels of H3K27me3 by downregulating the activity of histone methyltransferases (HMTs), such as *EZH2*, a key component of the polycomb repressive complex 2. This demethylation effect reactivates epigenetically silenced genes involved in tumour suppression and cell differentiation (42).

Furthermore, curcumin modulates the interplay between histone acetylation and methylation. Studies have demonstrated that curcumin alters the expression of epigenetic "writers" (HMTs), "erasers" (HDACs), and "readers" (bromodomain proteins), thereby exerting a broad impact on histone modification landscapes (43, 44). For example, the combination of curcumin with other agents, such as DNA demethylating drugs like decitabine, has been shown to synergistically alter histone and DNA methylation patterns, further enhancing tumour suppressor gene reactivation (43).

These findings underscore curcumin's potential as a therapeutic agent in ovarian cancer by reversing aberrant histone modifications, thereby restoring normal gene expression and enhancing the efficacy of existing treatments. Future studies should focus on elucidating the precise molecular mechanisms of curcumin's effects on histone-modifying enzymes and exploring its combination with other epigenetic therapies.

DNA methylation

DNA methylation, the addition of a methyl group to the fifth carbon of cytosine within CpG dinucleotides, is a crucial epigenetic mechanism that regulates gene expression without altering the DNA sequence. DNA methyltransferases (DNMTs), including *DNMT1*, *DNMT3A*, and *DNMT3B*, primarily mediate this process. Aberrant DNA methylation, characterised by hypermethylation of tumour suppressor genes and hypomethylation of oncogenes, is a hallmark of ovarian cancer and contributes to tumour progression, metastasis, and chemoresistance (43).

Curcumin modulates DNA methylation by targeting DNMTs. Studies indicate that curcumin directly inhibits DNMT activity, leading to the reactivation of silenced tumour suppressor genes such as *PTEN* and *p16INK4a*. For instance, in ovarian cancer, curcumin treatment was found to reduce CpG island hypermethylation in gene promoters, restoring normal transcriptional activity and inducing apoptosis (43, 44).

In addition to its DNMT inhibitory effects, curcumin enhances DNA demethylation through the activation of ten-eleven translocation (TET) enzymes, which convert 5-methylcytosine to 5-hydroxymethylcytosine. This dynamic regulation further contributes to the reversal of aberrant methylation marks in cancer cells (45).

Curcumin's potential to enhance the efficacy of other epigenetic therapies has garnered significant attention. When combined with DNMT inhibitors like 5-aza-2'-deoxycytidine, curcumin synergistically amplifies the re-expression of tumour suppressor genes, addressing the limitations of monotherapy such as incomplete gene reactivation and off-target toxicity. Furthermore, curcumin's inhibition of HDACs complements its suppression of DNMTs, creating a permissive chromatin environment conducive to the transcriptional activation of silenced genes. This dual modulation is particularly evident in the reactivation of *BRCA1*, which enhances DNA repair mechanisms and sensitises ovarian cancer cells to chemotherapy (44, 46).

These findings highlight curcumin's multifaceted role in regulating DNA methylation, from reactivating tumour suppressor genes to restoring the global methylation balance. Its ability to synergize with other epigenetic therapies further underscores its potential as a powerful adjunct in ovarian cancer treatment. Future research should explore the precise molecular mechanisms underpinning curcumin's epigenetic effects and assess its clinical utility in combination regimens.

Clinical implications and future directions

The ability of curcumin to modulate miRNAs, histone modifications, and DNA methylation highlights its potential as a multi-targeted epigenetic therapy for ovarian cancer. However, challenges such as curcumin's limited bioavailability and rapid metabolism hinder the translation of curcumin research into clinical settings. To overcome these limitations, advanced curcumin formulations, including nanoparticles, liposomes, and conjugates with other carriers, are being developed to enhance its stability, solubility, and targeted delivery (47, 48). These innovations improve curcumin's therapeutic efficacy in vivo.

Another promising avenue is the use of curcumin in combination therapies. Preclinical studies show that curcumin enhances the efficacy of standard chemotherapy agents, such as cisplatin and paclitaxel, by sensitising cancer cells through epigenetic reprogramming. For example, the combined use of curcumin and DNMT inhibitors has shown synergistic effects in restoring the expression of silenced tumour-suppressor genes, while its HDAC-inhibitory properties complement the actions of conventional drugs to disrupt tumour-promoting pathways (48). These combinatory approaches not only improve therapeutic outcomes but also mitigate the toxicity of high-dose chemotherapy.

Future research should also explore the long-term effects of curcumin on epigenetic regulation and its potential role in preventing relapse by maintaining tumour-suppressor gene activation. Large-scale clinical trials are needed to validate preclinical findings and establish

standardised protocols for curcumin-based therapies. By addressing these challenges and leveraging curcumin's multi-faceted epigenetic actions, this natural compound holds significant promise for improving outcomes in ovarian cancer treatment.

CONCLUSION

In conclusion, this review highlights the multifaceted role of curcumin in modulating key signaling pathways and epigenetic mechanisms implicated in ovarian cancer pathogenesis. Curcumin exhibits potent anti-proliferative, anti-metastatic, and pro-apoptotic effects in ovarian cancer cells, primarily through the inhibition of critical signaling pathways such as PI3K/Akt/mTOR, NF-κB, and STAT3. Furthermore, curcumin exerted significant epigenetic effects, including the modulation of DNA methylation, histone modifications, and miRNA expression, as evidenced by the observed downregulation of miR-133b in combination with other treatments in cisplatin-resistant ovarian cancer cells. Curcumin contributes to the reversal of chemoresistance by modulating the miRNA expression profiles. Given its favourable safety profile and promising preclinical data, curcumin holds significant potential as an adjunct therapy for ovarian cancer, either alone or in combination with conventional treatments. Future research should focus on optimising curcumin delivery systems to enhance its bioavailability and target specific tumour microenvironments. In addition, comprehensive clinical trials are warranted to evaluate the efficacy and safety of curcumin in ovarian cancer patients. By further elucidating the underlying mechanisms of curcumin's action, including its impact on miRNA expression, and conducting rigorous clinical investigations, we can pave the way for the translation of this promising natural compound into an effective therapeutic strategy for ovarian cancer.

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