



Insights into the Therapeutic Potential of Combining Ivermectin and Ascorbic Acid Against HPV-Induced Cervical Cancer: A Mini Review

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Abstract

Cervical cancer remains a global health challenge, particularly in developing countries. Current treatment strategies include radiation, chemotherapy, immunotherapy, surgical removal, or a combination thereof. However, these approaches are associated with challenges such as tumor recurrence, drug resistance, and toxicity. Moreover, such treatments are often inaccessible in resource-limited regions, underscoring the need for alternative therapeutic approaches. A promising cancer treatment is currently considered to be one that targets both the bulk of tumor cells and cancer stem cells (CSCs). In this review, we critically examine the rationale for combining ivermectin and ascorbic acid. We discuss the molecular targets of both agents in relation to human papillomavirus (HPV)-induced molecular changes in the cervix. The review explores the complementarity of ivermectin and ascorbic acid in targeting HPV-driven cancer hallmarks, metabolic reprogramming, and CSCs. Furthermore, we examine the challenges associated with the use of ivermectin and ascorbic acid in cervical cancer treatment. We hypothesize that this combination could be explored as a postoperative adjuvant therapy to prevent recurrence, pending preclinical and clinical validation.

Keywords: Cervical Cancer, HPV, Ivermectin, Ascorbic Acid, Cancer Stem Cells, Combination Treatment

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Introduction

Cancer remains a major global health threat, characterized by extensive heterogeneity and a remarkable capacity for adaptation, which often limits the effectiveness of both standard and precision-based therapies.¹ Cervical cancer is the fourth most common malignancy and a leading cause of cancer-related mortality among women worldwide.² It is primarily caused by infection with high-risk human papillomavirus (HPV) strains, particularly types 16 and 18, whose E6 and E7 proteins drive carcinogenesis.³ The burden of cervical cancer is disproportionately concentrated in developing countries, especially in sub-Saharan Africa and Asia. In sub-Saharan Africa, more than 85% of cases are reported, and cervical cancer-related mortality can reach 87%.^{2,4} Survival rates following diagnosis in this region are as low as 35%.²

Despite notable advances in cancer care, tumor recurrence and treatment resistance remain major barriers. Recent studies have identified cancer stem cells (CSCs) as

key contributors to these challenges, making them an attractive target for more effective therapeutic strategies.⁵ In clinical settings, however, major obstacles include tumor recurrence due to undetected tumor growth and the emergence of drug resistance. Standard treatment modalities, radiotherapy, chemotherapy, surgery, and combination regimens, remain the cornerstone of cancer care. Although these approaches are effective in many cases, therapeutic resistance remains a substantial hurdle.^{6,7} Targeted therapies have advanced considerably, yet chemotherapy remains the most widely used treatment; approximately 90% of chemotherapy failures are attributed to drug resistance, particularly during invasion and metastasis.⁷ This resistance arises from both genetic and non-genetic mechanisms that enable cancer cells to evade treatment and survive intensive interventions.^{7,8} A promising therapeutic strategy currently involves combining agents that target the bulk of tumor cells and CSCs.⁶ In addition, rational combination approaches

targeting cancer metabolism and CSCs have been proposed.⁷

Although several reviews have addressed CSC targeting, bulk tumor targeting, and drug repurposing as alternatives in targeted cancer therapy, the novelty of this review lies in its critical examination of cervical cancer and the potential of two drugs, ivermectin and ascorbic acid, as a rational combination for cervical cancer treatment. This work evaluates key targets of both drugs based on findings from primary studies and presents a rationale for combining and investigating them in cervical cancer treatment. Given the disproportionate burden of cervical cancer management in developing countries, this approach may offer an alternative therapeutic strategy for cervical cancer in low- and middle-income countries (LMICs).

HPV-Induced Molecular Changes in Cervical Carcinogenesis

The high-risk HPV strains, particularly HPV 16 and 18, express the E6 and E7 oncoproteins, which are essential for cervical carcinogenesis. As part of the viral life cycle, these oncoproteins promote several hallmarks of cancer, including uncontrolled cell proliferation, angiogenesis, evasion of apoptosis, metastasis, telomerase activation, invasion, and evasion of growth suppressors.⁹ Multiple studies have shown that cervical cancer cells undergo cell death when E6 and E7

activity is lost, confirming the essential role of E6 and E7 in maintaining HPV-associated cancer.¹⁰ These proteins promote malignant progression by modulating multiple cancer-associated molecular pathways. Figure 1 summarizes the major cancer hallmarks induced by the HPV E6 and E7 oncoproteins and their associated molecular targets.

Overcoming Programmed Cell Death

proteins that operate through the extrinsic and intrinsic apoptotic pathways.¹¹ The E6 and E7 proteins interfere with these signaling pathways to facilitate sustained cancer cell growth. E6 inhibits apoptosis through both p53-dependent and p53-independent mechanisms.¹² E6 can also act independently of p53 by interfering with TNF-mediated extrinsic apoptosis through its PDZ domain, which binds TNFR1 and disrupts its interaction with TRADD.¹³ E6 can disrupt the apoptotic cascade by targeting multiple factors, including caspase-8 and Fas-associated death domain protein (FADD), ultimately leading to their ubiquitination. Another notable function of E6 is activation of the survivin promoter, which similarly inhibits apoptosis.¹³ TALEN-mediated editing of HPV E7 induced necrosis in cell lines and demonstrated superior therapeutic efficacy.¹⁴

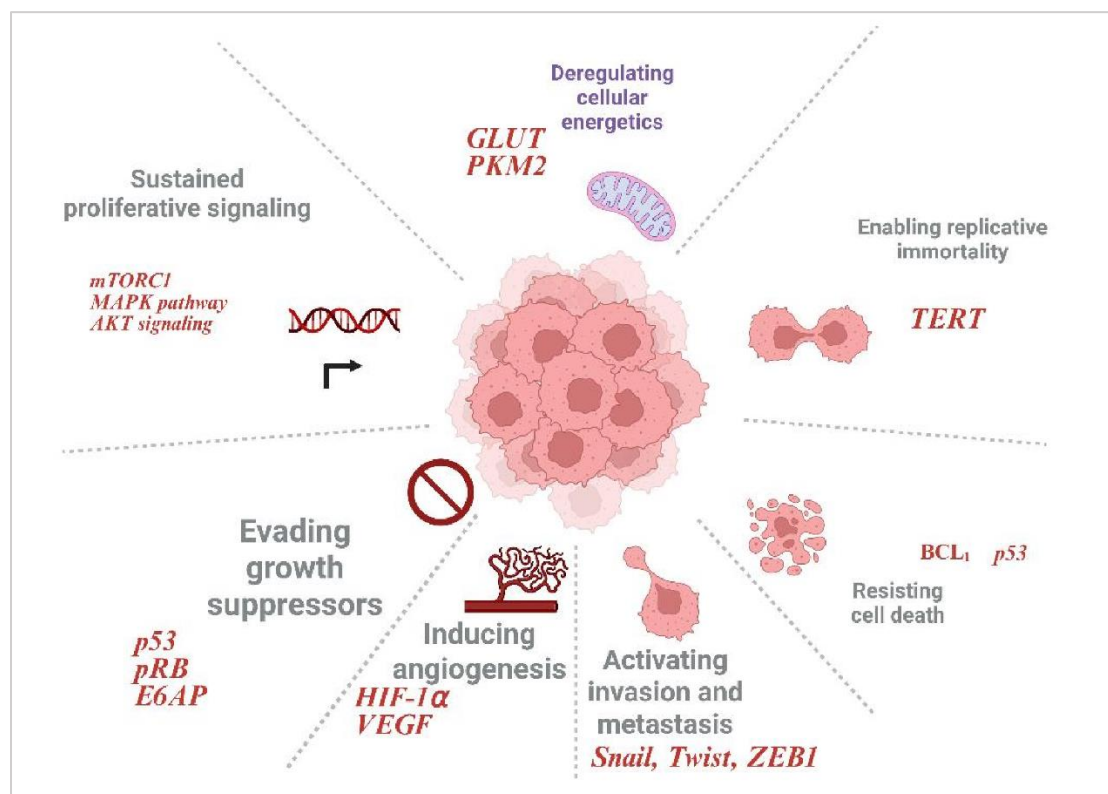


Figure 1. Schematic Illustration of Major Cancer Hallmarks Driven by Persistent Human Papillomavirus (HPV) Infection through the Coordinated Activity of the Viral Oncoproteins E6 and E7. E6 promotes p53 degradation and suppresses intrinsic and extrinsic apoptotic signaling, enabling evasion of programmed cell death. E6 and E7 inactivate key growth suppressors, E6 targeting p53 and E7 targeting pRB, leading to loss of cell-cycle control and sustained proliferative signaling via MAPK, AKT, and mTOR pathways. HPV oncoproteins also stimulate epithelial–mesenchymal transition, enhancing cellular invasion and metastasis. Angiogenesis is promoted by increased HIF-1 α and VEGF expression, facilitating tumor vascularization. In addition, constitutive telomerase (hTERT) activation establishes replicative immortality. Collectively, these molecular alterations drive malignant transformation and progression of cervical cancer.⁶ This figure was created using the BioRender tool, free version available at: <https://www.biorender.com>

HPV-Induced Inactivation of Growth Suppressors

HPV infection and expression of the viral oncoproteins enable cancer cells to inactivate growth suppressors. E6 targets the critical growth suppressor p53, whereas E7 primarily targets retinoblastoma protein (pRb). E6-mediated inhibition of p53 enables multiple cellular alterations that promote carcinogenesis through unregulated cell proliferation by bypassing critical cell-cycle checkpoints.^{10,15} Under cellular stress, including oxidative damage, p53 initiates transcription of genes required for cell-cycle arrest or programmed cell death. Murine double minute 2 (MDM2), an E3 ubiquitin ligase, maintains p53 at low levels in healthy cells. Therefore, E6-mediated disruption of p53 is essential for maintaining continuous cellular proliferation in cervical cancer.¹⁶ Ubiquitination of p53 by the E6 oncoprotein is mediated by E6-associated protein (E6AP). HPV E6 binds to the conserved domain of E6AP, forming a heterotrimer and initiating p53 degradation via ubiquitination.¹⁵ This enables cells to divide uncontrollably, bypassing the checkpoints that normally safeguard them. *In*

vivo studies have shown that interaction with E6AP is necessary for tumorigenesis in different tumor types.¹⁵

Similarly, the E7 oncoprotein inhibits pRb, enabling cell-cycle progression and promoting unregulated cell growth. The interaction between pRb and E2F transcription factors is a crucial regulatory point in the G1-to-S phase transition. If cells are not ready for S phase, pRb remains bound to E2F, preventing transcription of genes required for S phase.^{1,17} In HPV-infected cells, E7 ubiquitinates pRb, releasing E2F factors that promote transcription of cyclin A, cyclin E, and p16INK4A (a CDK4/6 inhibitor). This drives premature entry into S phase.¹⁷ HPV E7 induces p16INK4A expression by degrading pRb and activating KDM6B, an epigenetic regulator. HPV-infected cells express both oncoproteins, which sustains oncogenic signaling. The abnormal growth signal caused by E7-mediated pRb degradation could be corrected by p53; however, p53 is also blocked by E6.¹⁸ This state enables cells to bypass critical growth checkpoints and divide uncontrollably, as shown in Figure 2.

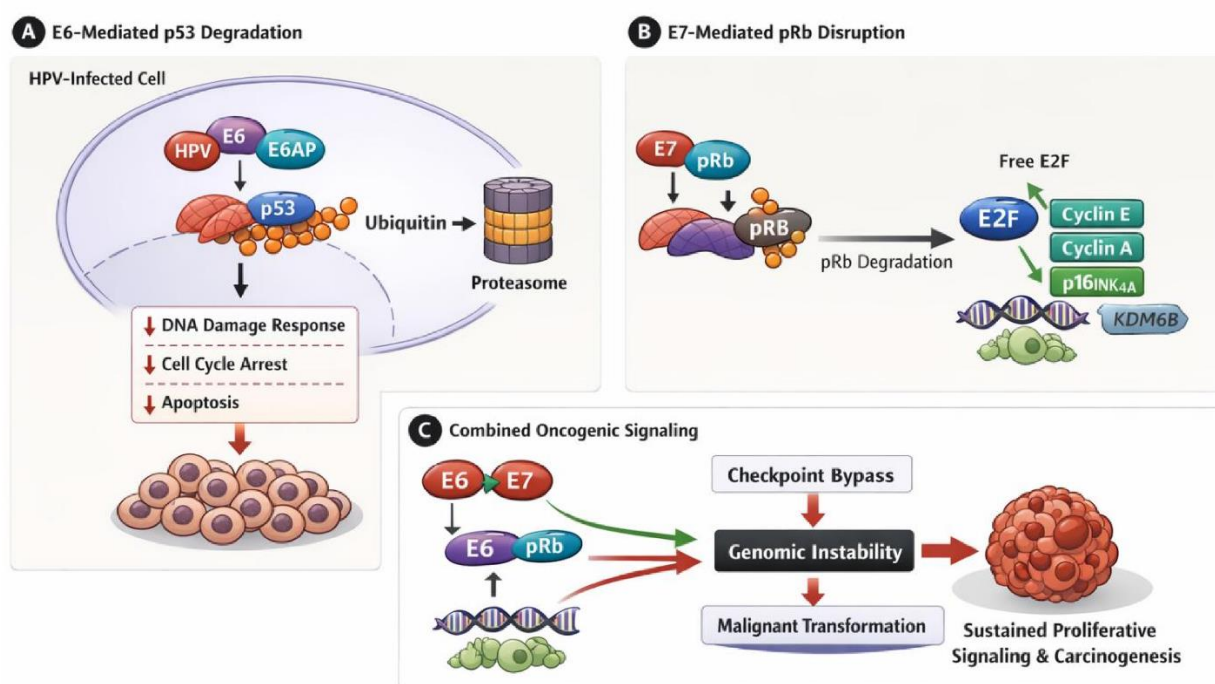


Figure 2. HPV-mediated Inactivation of Cellular Growth Suppressors by the E6 and E7 Oncoproteins. The figure illustrates the coordinated mechanisms through which human papillomavirus (HPV) disrupts key tumor-suppressive pathways to promote malignant transformation. **(A)** Ubiquitin-mediated proteasomal degradation of p53 by the E6–E6AP complex. **(B)** Degradation of retinoblastoma protein (pRb) and subsequent release of E2F transcription factors, leading to expression of cyclin A, cyclin E, and p16INK4A. **(C)** Coordinated inhibitory effects of E6 and E7 on major cell-cycle checkpoints, resulting in functional inactivation of growth suppressors.^{10,15,17} This figure was created using GPT-5.6 Luna and manually edited by the authors.

Cell Invasion and Metastasis

The invasion and spread of cervical cancer cells to other tissues are facilitated by the epithelial-to-mesenchymal transition (EMT), which is mediated by E6 and E7. Kim et al.¹⁹ used the epithelial MDCK cell line as an *in vitro* model to show that spindle-shaped mesenchymal cells can ectopically express E6/E7, resulting in the formation of

cobblestone-shaped epithelial cells. E6 and E7 oncoproteins can increase cellular migratory and invasive potential by activating EMT-inducing transcription factors such as ZEB1, Twist, Slug, and ZEB2.²⁰ This study found that, in response to E6 and E7, the epithelial marker E-cadherin decreased, whereas the mesenchymal markers N-cadherin, fibronectin, and vimentin increased.¹⁹

Sustained Cell Proliferation

Various mechanisms contribute to the dysregulation of cancer signaling pathways, thereby sustaining uncontrolled cellular proliferation.¹³ The MAPK pathway is stimulated by E6, as indicated by immunohistochemical analysis of organotypic raft cultures.^{21,22} Moreover, Yeo-Teh et al.²³ showed that E6 and E7 significantly influence the mTOR pathway, which governs cellular proliferation. Unlike normal cells, E7-expressing cells continue to proliferate despite nutrient deprivation, ultimately undergoing caspase-independent cell death. However, this is prevented in the presence of E6, which activates mTORC1 signaling and leads to enhanced protein synthesis even in the absence of growth factors. E6 can activate mTORC1 via the upstream kinases PDK1 and mTORC2, even without sufficient nutritional cues.²⁴ Subsequently, growth factor receptors initiate a cascade involving AKT and mTORC1 through interactions with adaptor proteins such as GRB2 and SHC.^{13,25}

Angiogenesis

Vascularization is critical for tumor cells, enabling them to obtain nutrients and oxygen from adjacent tissues through angiogenesis. Altered expression of p53 and pRb due to E6 and E7 activity is associated with modulators of angiogenesis. A study by Zhang et al. (2020) showed that interference with E6/E7 and miR-377 inhibited angiogenesis in cervical cancer models. The study also found that this inhibition was related to expression of the lysophosphatidic acid receptor 2 (LPAR2) gene, which is known to promote endothelial cell proliferation, thereby accelerating angiogenesis and cervical cancer development.²⁶ Vascular endothelial growth factor (VEGF) is an established promoter of angiogenesis and is regulated by p53 through HIF-1 α . Inhibition of p53 by the E6 protein results in VEGF activation and enhanced tumor vascularization.²⁷ Regulation of VEGF by E6 may occur through activation of the Sp1 transcription factor, independent of p53. Another study²⁸ found that VEGF expression is linked to angiogenesis in clinical samples and, synergistically with Ang-2, plays a key role in tumor vasculature.

Establishing Immortal Replication

During mitosis, telomere repeats reach a critical threshold that signals advanced replicative age, leading to replicative senescence. Emerging cancer cells bypass this checkpoint when TP53 and RB are lost. However, subsequent telomere loss initiates a second proliferative barrier known as crisis. During this crisis, cells experience severe chromosomal instability (CIN) and cell death, frequently accompanied by autophagy.⁹ The E6 and E7 oncoproteins are capable of establishing replicative immortality in HPV-infected cervical malignancies through constitutive expression of hTERT, the catalytic subunit of telomerase.^{12,29} In addition to c-Myc,

Sp1, and NFX1, E6 can activate the hTERT promoter via the cellular ubiquitin ligase E6AP, and one study found that E6 induced hTERT promoter acetylation and telomerase activity.³⁰

HPV-Induced Molecular Changes in Cervical Cancer Metabolism

A critical prerequisite for extensive cellular proliferation is the provision of adequate energy and essential biomolecules for cell growth, division, proliferation, and survival. Normal cells that are non-proliferative or temporarily proliferative within their tissue microenvironment often rely on mitochondrial oxidative phosphorylation or, in some cases, glycolysis to generate energy from glucose metabolism.⁹ Metabolic reprogramming facilitates continuous cell proliferation, enables cells to evade growth suppressors, enhances cellular immortality, and increases cell invasion. Altered metabolism allows tumors to obtain nutrients efficiently, synthesize essential molecules, and endure adverse environments. Increased expression of glucose transporter 1 (GLUT1) enhances glucose uptake, facilitating the Warburg effect, while the pentose phosphate pathway (PPP) contributes to ribose synthesis for nucleotide biosynthesis, thereby promoting cellular proliferation.³¹

Glucose uptake into cancer cells is mediated by glucose transporters (GLUTs), which have several isoforms. p53 regulates glycolysis by targeting GLUT1 and GLUT4.^{32,33} It inhibits glucose uptake by promoting transcription of glycolytic inhibitor proteins, thereby preventing GLUT1 translocation to the plasma membrane. Degradation of p53 by E6 therefore elevates GLUT1 expression, indicating enhanced glucose uptake.³³ Downstream effects of p53 through the TP53-induced glycolysis and apoptosis regulator (TIGAR) protein involve regulation of phosphofructokinase-1 (PFK-1), a rate-limiting enzyme in glycolysis, whose enhanced activity increases glycolytic flux.³⁴

The HPV E7 oncoprotein facilitates acetylation of pyruvate kinase M2 (PKM2), which catalyzes the conversion of phosphoenolpyruvate (PEP) to pyruvate while producing ATP. Because PKM2 can exist in tetrameric or dimeric forms, E7 promotes a dimeric conformation with reduced substrate affinity, leading to PEP accumulation. Consequently, glycolytic intermediates are redirected into alternative metabolic pathways, facilitating tumor cell proliferation.³⁵ A study by Pappa et al. (2021) demonstrated metabolic programming in the cancer cell models SiHa and HeLa. In that study, HPV-positive cells exhibited metabolic reprogramming and the Warburg effect as a result of E6 protein expression.³⁶ Studies have shown that inhibition of O-GlcNAcylation reduces tumorigenesis in cervical cancer cells.³⁷ O-GlcNAcylation is associated with cell proliferation, progression, and metastasis under nutrient deprivation or increased cellular stress.³⁸ These findings demonstrate that

targeting metabolic alterations in cancer provides an alternative approach to cervical cancer treatment. As suggested by Tan et al. (2025), targeting cancer metabolism is a promising strategy for cancer elimination.⁷

HPV-Induced Molecular Changes Enhancing Cervical Cancer Stemness

A subpopulation of tumor cells has been reported to possess self-renewal and differentiation capacity and is responsible for tumor development, metastasis, drug resistance, and recurrence.^{1,5–7,39} In HPV-associated malignancies, cancer stem cells (CSCs) are pivotal in driving development and drug resistance.^{39,40} HPV oncoproteins promote the development and protection of CSCs by impairing tumor suppressor pathways, specifically p53 and pRb, resulting in increased levels of stem cell-associated transcription factors such as SRY-box 2 (SOX2), NANOG, and OCT3/4. Reactivation of OCT4 expression, a key gene in maintaining cancer cell stemness, has been demonstrated. For instance, both oncoproteins enhance OCT4 expression, but E7 reduces expression of methyl-CpG-binding domain protein 2 (MBD2) and elevates TET1 expression, thereby disrupting methylation at the OCT4 promoter.^{40,41} Further interaction between E7 and OCT4 enhances stemness features and facilitates cellular plasticity. OCT4 expression is also enhanced by E6 via inhibition of p53 transcription.⁴²

CSCs depend on a meticulously organized signaling network that preserves their stem-cell-like characteristics and allows rapid adaptation to therapeutic and micro-environmental stresses. The flexibility of CSCs is fundamentally linked to the convergence of various signaling pathways, including Notch, Hedgehog, and PI3K/AKT/mTOR, which are associated with metabolic reprogramming, lineage specification, and self-renewal.⁴³ Signal transducer and activator of transcription 3 (STAT3) is reported to be regulated by the JAK–STAT, Hedgehog, Notch, and PI3K/AKT/mTOR pathways and is associated with CSCs.⁴⁴ A study by Wang et al. (2017) performed immunohistochemical analysis and found that OCT4, STAT3, NANOG, and SOX2 were expressed in chronic cervicitis and cervical cancer tissues. They also found that these genes were expressed in cells negative for cervical cancer, indicating the presence of undetectable cervical CSCs.⁴⁵ Targeting CSCs helps prevent drug resistance and recurrence of cervical cancer after treatment.

Repurposed Drug Combinations for Cervical Cancer

Drug repurposing, or repositioning, involves identifying novel applications for approved and commercially available pharmaceuticals. This approach significantly reduces costs and research duration relative to conventional drug discovery and development, given that the medicine's safety profile, pharmacokinetics, and tolerability have already been

evaluated. Multiple studies have indicated the potential for repurposing cardiovascular medications in cancer treatment. Examples include antimalarials, statins, beta-blockers, aspirin, cardiac glycosides, and antiparasitic drugs. For cervical cancer, several drugs have been studied as repurposing agents, including ivermectin, ascorbic acid, levosimendan, narciclasine, betamethasone, and methylprednisolone.^{46–48} Here, we propose the combination of ivermectin and ascorbic acid as a potential treatment for cervical cancer. Based on the HPV-induced molecular mechanisms that propagate cervical cancer cells to acquire cancer hallmarks, reprogram energy metabolism, and maintain stemness, this combination could target these characteristics. Currently, a rational combination of drugs that target cancer cells, their metabolism, and CSCs has been suggested as an alternative approach to cancer treatment.^{6,7}

Molecular Targets of Ivermectin in Cell Death and Energy Metabolism

Ivermectin is the most successful medicine within the avermectin family and received FDA approval for human use in 1978.⁴⁹ Studies have shown antiproliferative activity of ivermectin in cervical cancer cell models. One study found that ivermectin induced apoptosis and cell cycle arrest in cervical cancer HeLa cells.⁵⁰ In the same study, Zhang et al. (2019) found that ivermectin induced collapse of mitochondrial membrane potential and induced apoptosis in a caspase-dependent manner.⁵⁰ This suggests that ivermectin causes cell death through the mitochondrial pathway. Similar studies show antitumor effects of ivermectin on cancer cells, but raise issues regarding attainment of clinical concentrations. Qabbus et al. (2022) showed that ivermectin's anticancer effects on HeLa cells were mediated by aggregate formation. They argued that the activity of ivermectin reported should match *in vivo* concentrations.⁴⁷ Such findings necessitate strategies for reducing ivermectin concentration, which can be achieved through drug combinations. Combinations with micronutrients that possess anticancer activity have been suggested.^{6,49}

Ivermectin has been shown to interfere with glucose metabolism in other cancer types. In a study involving network pharmacology and proteomic analysis, ivermectin was found to induce cell cycle arrest and apoptosis via targeting glycolysis.⁵¹ In this work, an association was found between oxidative phosphorylation, glycolysis, and the existence of both Warburg and reverse Warburg effects in epithelial ovarian carcinoma (EOC).⁵¹ The ability of ivermectin to target metabolic changes also present in cervical cancer makes it a strong candidate for repurposing. However, direct evidence for ivermectin in cervical cancer is extremely limited; thus, application of ivermectin's mechanisms drawn from other cancer types to HPV-induced cervical cancer remains speculative. Table 1 summarizes the

Table 1. Summary of Mechanisms by Which Ivermectin Induces Cell Death in Cancer Cells

Cancer type	Study model	Treatment (Single or combination)	Cell death mechanisms	Relevance to cervical cancer	Refs
Cervical Cancer	<i>In vitro</i> (HeLa cells)	Single (Ivermectin)	Cell cycle arrest at G1/S phase Apoptosis via mitochondrial pathway Target genes/proteins: Cyclin D1, Bax, Bcl-2, Caspase-9, Caspase-3.	Direct	Zhang P, et al. 2019 ⁵⁰
Cervical Cancer	<i>In vitro</i> (HeLa)	Single (Ivermectin)	Apoptosis with formation of ivermectin precipitates in culture media;	Direct	Qabbus M, et al. 2022 ⁴⁷
Pancreatic Cancer	<i>In vitro</i> (MIA PaCa-2 and PANC-1 cells); <i>In vivo</i> (Xenograft mouse model using MIA PaCa-2 cells)	Combination (Ivermectin + Gemcitabine)	Induces apoptosis via mitochondrial dysfunction death. Cell cycle arrest mTOR/STAT-3 signaling. Inhibited glycolysis and oxidative phosphorylation	Indirect	Lee DE, et al. 2022 ⁵²
Colorectal Cancer	<i>In vitro</i> (SW480 and SW1116 cells)	Single (Ivermectin)	Apoptosis through the mitochondrial pathway Upregulated Bax and cleaved PARP, downregulated Bcl-2, increased caspase-3/7 activity; induces S phase arrest. Target genes/proteins: Bax, Bcl-2, PARP, Caspase-3/7.	Indirect	Zhou S, et al. 2021 ⁵³
Epithelial Ovarian Carcinoma (EOC)	<i>In vitro</i> (EOC cell lines); Human tissues (8 EOC and 11 control ovary tissues for proteomics)	Single (Ivermectin)	Targets glucose metabolism Cell cycle arrest, apoptosis mediated by targeting glycolysis. Anti-Warburg and reverse Warburg effects.	Indirect	Li N, et al. 2020 ⁵¹
Ovarian Cancer	<i>In vitro</i> (TOV-21G cells)	Single (Ivermectin)	Proteomic profiling reveals alterations in signaling pathways, including cancer pathogenesis, replication, RNA metabolism, translational machinery, and cell-cycle proteins.	Indirect	Li N, et al. 2020 ⁵¹

mechanisms by which ivermectin induces cell death in different cancer cell types.

Molecular Targets of Ascorbic Acid in Cell Death and Energy Metabolism

Although HPV infection is transient in most women, it persists in 10–20% of infected individuals, resulting in persistent infection that can ultimately lead to cervical cancer.¹⁸ Human cross-sectional studies suggest that ascorbate may protect against cervical cancer.^{54,55} These findings indicate that a diet rich in ascorbate may reduce the risk of HPV and influence the course of persistent HPV infection. Several studies have demonstrated the anticancer activity of ascorbic acid in various cancer models. A recent study showed that high-dose ascorbic acid exerts activity against endometrial cancer in a PTEN/AKT/mTOR-dependent manner.⁵⁶ This pathway serves as a salvage pathway in HPV E6/E7-induced cervical cancer and plays a role in the maintenance of cancer stem cells (CSCs).⁴⁴ Interestingly, when combined with a conventional chemotherapeutic agent, ascorbic acid demonstrated improved activity compared with either drug alone.⁵⁶ Wu et al. (2022) similarly reported reactive oxygen species (ROS)-mediated cell death induced by high-dose ascorbate in HeLa cells, along with cell-cycle arrest. The same study also reported that high-dose ascorbate affected hypoxia-inducible factor 1 alpha (HIF-1 α) and angiogenic proteins, which promote tumor progression and poor prognosis.⁴⁸ These findings highlight the potential of drug combinations for effective cancer elimination and treatment.

The capacity of ascorbic acid to target CSCs has emerged as an area of increasing research interest. Studies have

shown that ascorbic acid can target CSC-like cells by generating ROS, effectively eliminating them in hepatocellular carcinoma (HCC) cell lines; combination treatment with a chemotherapeutic agent has been suggested for postoperative treatment.⁵⁷ Ascorbic acid can also eliminate the CSC population in liver cancer independently of CSC gene expression (e.g., NANOG, ALDH1A1, and SOX2), warranting further investigation into the mechanisms of ascorbic acid-induced death in CSCs.⁵⁸

HPV-induced metabolic reprogramming is a hallmark associated with cervical cancer. Tumor cells predominantly utilize glycolysis for energy generation, resulting in upregulation of GLUT1 and sodium-dependent vitamin C transporter 2 (SVCT2).⁵⁹ This facilitates glucose uptake and also increases intracellular concentrations of vitamin C or its oxidized form, dehydroascorbic acid (DHA). Within cells, DHA competes with glucose for uptake via GLUT1 and is rapidly converted to ascorbate, depleting NADPH stores and inducing oxidative stress. This leads to depletion of intracellular glutathione, a ROS scavenger, thereby inhibiting GAPDH, an essential glycolytic enzyme. Consequently, glycolysis is impaired, causing an energy crisis and cell death.⁵⁹ Recent studies have shown that ascorbic acid interferes with glucose metabolism in pancreatic cancer cells.⁶⁰ Table 2 summarizes the molecular mechanisms by which ascorbic acid targets cancer and CSCs.

Taken together, both ivermectin and ascorbic acid are potential agents that could target sustained proliferation in HPV-induced cervical cancer. Figure 3 illustrates the key targets of these two compounds and their predicted synergistic effects.

Table 2. Molecular Mechanisms of Ascorbic Acid in Targeting Cancer and Cancer Stem Cells

Cancer type	Model / Cell	Cell death / Targeting CSC	Molecular targets	Refs
Endometrial cancer	<i>In vitro</i> (KLE and Hec-1B cells) and <i>in vivo</i> (mice)	Induced cell death; prevented invasion	PTEN/AKT/mTOR pathway; VEGFR; ROS	Shen et al., 2025 ⁵⁶
Cervical cancer	<i>In vitro</i> (HeLa)	ROS-mediated cell death; cell cycle arrest	ROS; HIF-1 α ; angiogenic proteins	Wu et al., 2020 ⁴⁸
Hepatocellular carcinoma (HCC)	<i>In vitro</i> (cell line Li-7)	Elimination of CSC-like cells via ROS	ROS	Seyama et al., 2024 ⁵⁷
Liver cancer	Huh7 and Hep3B	Elimination of CSC population; reduced CSC viability	CD44; CD133; NANOG; ALDH1A1; SOX2	Wan et al., 2021 ⁵⁸
Pancreatic cancer	Cell lines: SU.86.86, HPAC, Hs 700T, PANC-1, HPAF-II, BxPC-3, and Hs 766T) Patient-derived cells (PR11-077T and PR11-043T)	Interference with glucose metabolism: GLUT1 SVCT-2 GAPDH	Glucose metabolism pathways (not further specified)	Jang et al., 2025 ⁶⁰

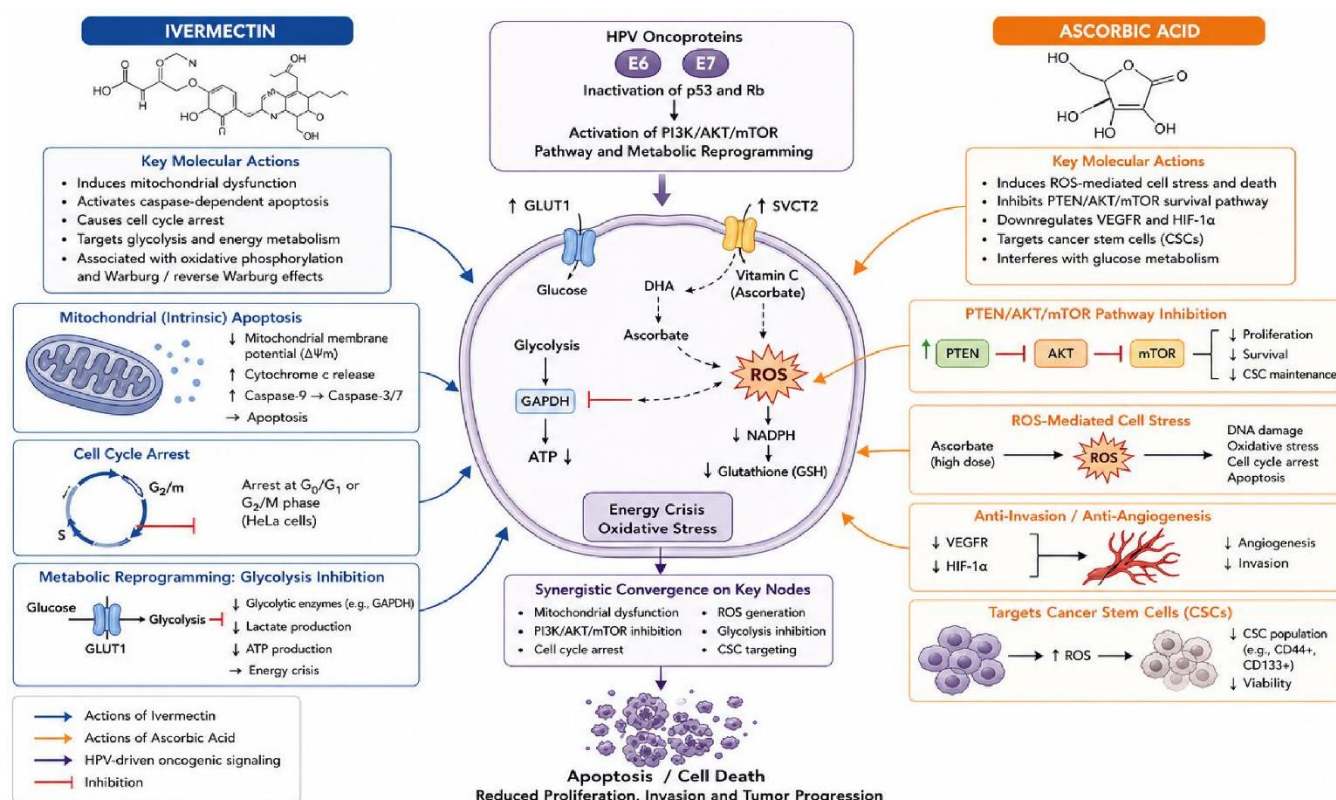


Figure 1. Schematic Illustration of the Predicted Synergistic Molecular Nodes Targeted by Ivermectin and Ascorbic Acid in HPV-induced Cervical Cancer. HPV oncoproteins E6 and E7 inactivate p53 and pRb, activating the PI3K/AKT/mTOR pathway and driving metabolic reprogramming characterized by increased GLUT1-mediated glucose uptake and SVCT2-mediated ascorbate uptake. Ivermectin (blue) induces mitochondrial dysfunction, leading to cytochrome c release, caspase activation, and apoptosis, and causes cell-cycle arrest at G₀/G₁ or G₂/M. It also inhibits glycolysis by downregulating glycolytic enzymes such as GAPDH, reducing ATP production and contributing to an energy crisis. High-dose ascorbic acid (orange) enters cells via SVCT2, while dehydroascorbic acid (DHA) enters via GLUT1 and is rapidly converted to ascorbate, generating reactive oxygen species (ROS) that cause oxidative stress, DNA damage, and cell-cycle arrest. Ascorbic acid also inhibits the PTEN/AKT/mTOR survival pathway, downregulates VEGFR and HIF-1 α to suppress angiogenesis and invasion, and targets cancer stem cells (CSCs) via ROS-mediated elimination. Both agents converge on complementary and overlapping nodes that may underlie synergistic effects. Dashed arrows indicate metabolic interconversions or indirect effects.⁶¹ This figure was designed using Claude Sonnet 5 and manually edited by the authors.

Conclusions and Future Directions

Drug repurposing has become an area of increasing research interest in oncology. Ivermectin, often described as a “wonder drug,” has emerged as a promising agent for repurposing in cancer treatment owing to its capacity to inhibit cell growth, induce apoptosis, trigger cell-cycle arrest, induce reactive oxygen species (ROS), inhibit glycolysis, and cause mitochondrial dysfunction. Ascorbic

acid has also demonstrated anticancer activity, particularly at millimolar concentrations, and has been shown to cause cell death through ROS-mediated pathways and to target cancer stem cells. It has also been found to interfere with glucose metabolism. Thus, the two drugs share overlapping targets, including the induction of oxidative stress, cell-cycle arrest, and interference with glucose metabolism. The apoptosis-inducing capacity of ivermectin and the CSC-targeting

ability of ascorbic acid represent a combination that could potentially eliminate both the bulk of tumor cells and CSCs responsible for tumor recurrence. Accordingly, combination with ascorbic acid has been proposed as an approach to eliminate CSCs and prevent recurrence in patients.⁶²

Although drug repurposing is a rapid and promising approach in drug development for cervical cancer, challenges in clinical application have emerged for both ivermectin and ascorbic acid. Preclinical studies have demonstrated that ivermectin may exert activity at doses that are not clinically attainable, and the interpretation of several preclinical studies should therefore be approached with caution.⁴⁷ Research on the application of ivermectin in oncology remains confined to preclinical studies using cell cultures and animal models. A recent study demonstrated in vitro dose-dependent synergy between ivermectin and ascorbic acid in cervical cancer HeLa cells, with synergy observed at doses above the IC₅₀ concentration.⁶³ This study provides preliminary insights into the potential use of the combination for cervical cancer treatment, as the combination lowered the dose of ivermectin to a clinically attainable threshold (5.2 μ M) with a favorable dose reduction index.^{63,64}

Currently, no clinical trials involving human subjects with cervical cancer have been conducted; therefore, it is impossible to evaluate the safety and efficacy of ivermectin or to make informed assumptions regarding its superiority to the existing standard of care. Despite the existence of numerous other cancer treatment modalities, the absence of robust evidence prohibits any ethical endorsement of ivermectin for cervical cancer. The safety and efficacy of ivermectin in cervical cancer remain uncertain and unsubstantiated. This review hypothesizes that drug combinations can reduce ivermectin concentrations while enhancing activity through synergistic interactions. The proposed combination with ascorbic acid may enhance the activity of ivermectin, although confirmatory clinical studies are required. Conversely, high-dose ascorbic acid is limited by challenges of instability and bioavailability in systemic and intratumoral compartments.⁵⁹ These challenges may be overcome through appropriate formulations, including nanoformulations. Moreover, because studies have shown that ascorbic acid activity occurs at higher doses, novel combination therapies are needed to reduce the required doses.⁶⁵

A critical consideration for drug combinations is the expected safety profile following potential drug interactions in patients. Ivermectin has broad therapeutic application in mammals because it does not readily cross the blood–brain barrier (BBB) and because an active P-glycoprotein efflux pump in cells limits its intracellular accumulation, contributing to its safety.⁶⁶ The oral bioavailability of ivermectin depends on dietary intake (increased bioavailability with a high-fat diet) and dosage form.⁶⁷ Although human studies have

demonstrated tolerance to ivermectin, clinical observations report side effects such as ataxia, seizures, coma, or even death. These side effects are reportedly associated with individual factors such as impaired BBB function, misuse of veterinary formulations, or genetic mutations in efflux pumps.⁶⁶ Interestingly, vitamin C was found to provide protective effects against ivermectin-induced effects in both adult and juvenile mice by improving kidney function and metabolism in animals.⁶⁸ Co-administration of ivermectin and ascorbic acid has been recommended, especially in adults, as no adverse interactions between the two drugs have been reported.⁶⁷ However, this remains speculative because of a lack of clinical data demonstrating co-administration of the two drugs in oncology settings.

Therefore, we hypothesize that a combination of ivermectin and high-dose ascorbic acid could serve as a potential therapeutic strategy for cervical cancer. Recently, combination therapy with ascorbic acid has been proposed because of its believed capacity to eradicate the CSC population.⁶⁹ This review has shown that ivermectin can induce apoptotic cell death and target cancer energy metabolism, causing an energy crisis in cancer cells that leads to cell death. High-dose ascorbic acid has been presented in this review for its ability to cause ROS-induced cell death, target tumor metabolism, and target CSCs. Such a combination is therefore potentially effective in targeting cancer cells and CSCs, an approach considered promising for preventing tumor recurrence. However, only ascorbic acid has shown anti-CSC activity (and only in liver cancer models), and the combination hypothesis for CSCs remains untested. Moreover, because these drugs are repurposed, their safety profiles are known, and they may cause fewer serious side effects in normal cells than conventional chemotherapy. If proven effective, the low cost and wide availability of both drugs could make this combination particularly attractive for low-resource settings. Thus, given the potential to prevent tumor recurrence by targeting CSCs, we hypothesize that combination treatment with ivermectin and ascorbic acid could be used as postoperative care for patients who have undergone surgical removal of a cancerous growth. However, key translational challenges include drug dosing, delivery, toxicity, and lack of clinical trial data. Future studies should determine the efficient delivery route, toxicity profile of the combination, and effective combination dosages for clinical use. Moreover, nanoformulations for ascorbic acid in cancer treatment and associated synergies have been proposed.⁷⁰ Therefore, these insights into the use of ivermectin and ascorbic acid for cervical cancer provide a basis for further research into their application in cervical cancer treatment and potential clinical translation.

Authors' Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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