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Innovative therapeutic strategies for cervical cancer: advances in pain management, angiogenesis inhibition, and peptide-based therapies

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Highlights:

- This review explores emerging therapeutic strategies such as cannabidiol (CBD) for cancer-related pain, offering potential alternatives to opioids with fewer side effects and improved patient outcomes.
- The review emphasizes the development of peptide-based vaccines targeting HPV oncogenes E6 and E7, presenting promising strategies for immunotherapy and cancer prevention.
- The paper identifies significant gaps in current treatments and outlines potential future research avenues for integrating peptide therapeutics and cannabinoid-based pain management in clinical practice.

Abstract: Cervical cancer remains a major global health burden, particularly in low-resource settings, with a prevalence of 11.7%. Persistent infection with high-risk Human Papillomavirus (HPV) strains is the primary cause, affecting approximately 660,000 women and resulting in nearly 350,000 deaths annually. The disease is often accompanied by complex pain patterns due to tumour progression, nerve invasion, and treatment-related effects, which conventional therapies fail to adequately address. The burden of cervical cancer is disproportionately high in low- and middle-income countries (LMICs), where limited access to preventive healthcare, early screening, and effective treatment exacerbates the challenge. Current treatment modalities, including surgery, chemotherapy, and immunotherapy, are associated with significant limitations such as systemic toxicity, long-term complications, and inadequate pain relief. Traditional pain management approaches, including opioids and adjuvant analgesics, are often insufficient and accompanied by severe side effects, necessitating the exploration of novel therapeutic strategies. Emerging treatment options, such as cannabinoid-based analgesics,

vascular endothelial growth factor (VEGF) inhibitors for angiogenesis suppression, and peptide-based drug delivery systems, offer promising alternatives for improving patient outcomes. These multimodal approaches aim to enhance therapeutic efficacy while minimizing systemic toxicity and treatment-related pain. This review explores innovative therapeutic strategies for cervical cancer management, with a focus on recent advancements in pain relief, angiogenesis inhibition, and peptide-based therapies. It synthesizes current research findings, identifies critical knowledge gaps, and outlines potential future directions to improve treatment effectiveness and overall patient quality of life.

Keywords: human papillomavirus (HPV); cervical cancer; angiogenesis; cannabidiol; cancer pain; peptide-targeted delivery; vascular endothelial growth factor (VEGF)

1. Introduction

Cervical cancer (CC) is a disease of global concern with a high prevalence among women in developing countries and the fourth most common cancer among women worldwide [1–4]. In 2020, cervical cancer accounted for an estimated 604,000 new cancer cases and 342,000 cancer-related deaths globally (WHO, 2022). The burden of cervical cancer disproportionately affects women in low-and middle-income countries (LMICs), where there is usually limited access to preventive healthcare, screening, and effective treatment options [1]. The primary cause of cervical cancer is persistent infection with high-risk strains (HPV 16 and HPV18) of the Human papillomavirus (HPV) [5]. These strains account for about 99% of cases, causing an infection of the epithelial cells of the cervix resulting in precancerous lesions and eventually cervical cancer if left untreated [5–7].

Current therapeutic approaches towards cervical cancer include surgery, radiotherapy, immunotherapy and chemotherapy. For early-stage disease, surgical interventions or radiotherapy are often employed, while more advanced stages require multi-modal therapies, including concurrent chemoradiation [8]. Despite the effectiveness of these standard treatments, cervical cancer management faces several challenges. Notable amongst them is high recurrence rates particularly in cases of locally advanced or metastatic disease, where treatment options are limited, and prognosis is poor [9]. Cervical cancer often leads to complex and multifaceted pain, including neuropathic and nociceptive pain, arising from various etiological factors, including non-oncologic origins, treatment-related side effects, tumour progression, and invasion into adjacent anatomical structures [10].

Current pain management strategies in cervical cancer primarily involve opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), which, although effective, are associated with several side effects, risk of dependency, and diminishing efficacy over time in the case of some opioids [11,12]. Furthermore, several patients experience a range of adverse effects from chemotherapy and radiotherapy, including gastrointestinal disturbances, myelosuppression, radiation-induced fibrosis and pain, all of which significantly impact the quality of life and overall prognosis [6,8].

The limitations highlighted above prompt the need for innovative therapeutic approaches that address both tumour progression and pain management to improve patients' quality of life. Recently, several therapeutic techniques such as immunotherapy, molecular targets, targeted delivery for existing drugs as well as use of alternative therapeutics have emerged to aid improve treatment outcomes and ultimately improve the quality of patients [13,14]. Cannabinoids particularly cannabidiol (CBD), which is derived from the *Cannabis sativa* plant have shown promise as an alternative treatment for cancer-related pain, offering

analgesic benefits without the high dependency risk associated with opioids [15]. Cannabinoids act on receptors involved in pain perception and inflammation, such as the TRPV1 and CB2 receptors, which may provide targeted relief from neuropathic and inflammatory pain commonly experienced by cervical cancer patients [16].

Importantly, angiogenesis, the formation of new blood vessels in growing tumours, has been found to play a pivotal role in cervical cancer progression. Several angiogenic targets have been identified as mediators with vascular endothelial growth factor (VEGF) being key among them, promoting tumour vascularisation and contributing to metastasis and poor prognosis [17]. Anti-angiogenic therapies, particularly those targeting VEGF and its receptors, have emerged as promising options for inhibiting tumour growth and progression. Drugs such as bevacizumab, a monoclonal antibody that targets VEGF-A, have demonstrated efficacy in extending progression-free and overall survival in advanced cervical cancer, although challenges such as resistance development and adverse side effects remain significant concerns [18].

Another novel approach in addition to cannabinoids and anti-angiogenic medicines is peptide-based therapeutics in the management of cervical cancer. Short protein peptides and self-assembling proteins offer a novel strategy that may enhance targeted delivery and efficacy in the treatment of cervical cancer [19]. Peptides have distinct benefits in drug administration and cancer immunotherapy owing to their selectivity, stability, and low toxicity [19,20]. In cervical cancer, peptides are being investigated for multiple functions, including targeted delivery systems for cancer cells and peptide-based vaccines that elicit immune responses against HPV oncoproteins such E6 and E7 [21,22]. Furthermore, peptide-functionalised nanoparticles have demonstrated efficacy in augmenting drug delivery and retention within tumour cells, minimizing systemic toxicity, and enhancing therapeutic results [19,24].

Given the complex nature of the management of cervical cancer especially in low-resource areas, these emerging therapies may offer improved treatment outcomes and enhance patients' quality of life. Accordingly, this review seeks to provide a thorough discussion on the contemporary research on cannabinoid-based pain management, VEGF-targeted anti-angiogenic medicines, and peptide-based treatments for cervical cancer management. Furthermore, the potential of these therapies to remodel cervical cancer management is delineated, with a highlight on the possible gaps that can be explored.

2. Pain management in cervical cancer

Pain is a common symptom in cancer patients, affecting 70% to 90% of individuals either as a direct consequence of the malignancy or due to the therapeutic interventions used to treat it [23]. In cervical cancer patients, the prevalence of pain is reported to be 64% in advanced disease and 59% in locally advanced disease [24]. Pain can arise from various etiological factors, including non-oncologic origins, treatment-related side effects, tumour progression, and invasion into adjacent anatomical structures. Zhang *et al.* [10] reported that 78% of pain experienced by cancer patients is attributable to tumour progression. Pain in cervical cancer patients arises primarily from tumour invasion into the viscera of the pelvic cavity, infiltration into nearby tissues, nervous plexuses, and peripheral nerves, and occasionally bone metastasis [25,26]. Medical procedures such as percutaneous nephrostomies, aimed at improving renal function, often cause significant discomfort and pain [27].

Treatment options such as radiation therapy (RT) and chemotherapy are also major contributors to pain. Chemotherapy, particularly with platinum-based drugs and taxanes, leads to chemotherapy-induced

peripheral neuropathy (CIPN) due to microtubule disruption, mitochondrial damage, altered ion channel activity, neuroinflammation, and myelin sheath destruction, affecting a substantial percentage of patients shortly after treatment [24,28]. Patients undergoing surgery for cervical cancer treatment may also experience postoperative pain, including neuropathic pain, which imposes severe physical and psychological problems on patients [29–32]. These factors create a complex pain profile in cervical cancer patients, encompassing nociceptive, neuropathic, and mixed pain types.

A combination of pain receptor-mediated actions, inflammatory and immune actions are responsible for the complexity of pain experienced by cervical cancer patients [33]. Immune cells infiltrating the tumour, such as neutrophils, T cells, and macrophages, secrete inflammatory mediators like cytokines that contribute to cancer pain. Additionally, cancers produce and secrete various algogenic (pain-producing) mediators that sensitise and/or activate primary afferent nociceptive neurons, leading to pain. These mediators include inflammatory cytokines, neurotrophic factors, ATP, protons, and proteases [34]. In cervical cancer patients, the perception and response to pain can be modulated by elevated levels of extracellular nucleotides, particularly ATP, within the tumour microenvironment. In this context, ATP interacts with purinergic receptors, influencing mechanisms associated with pain perception in cervical cancer [35]. In an experimental model of cancer pain, nociceptor sensitisation in response to tumour growth involved alterations in Ca^{2+} channels and TRPV1 receptors in dorsal root ganglion neurons. The chemical mediator CCL2, released from tumour cells, induced phenotypic changes in sensory neurons, contributing to mechanical hyperalgesia. TRPV1 (the capsaicin receptor) functions as a polymodal receptor that can be activated by noxious heat, protons, and a variety of endogenous and exogenous chemicals, including nerve growth factor (NGF), leading to the detection of nociceptive stimuli [10,36,37].

The diagram classifies the intricate pain circuits and triggers linked to cancer-related pain into neuropathic and nociceptive triggers. The primary source of nociceptive pain is the tumuor itself, as algogenic substances and nerve sprouting surrounding the tumuor site promote axonal sensitization, increasing nerve fibres' sensitivity to stimuli and intensifying pain perception. Conversely, neuropathic pain is caused by compression of the nerves and damage from treatment, such as neuritis and perineural invasion, which are frequently observed in cancer treatments. Peripheral sensitization, in which pain impulses are amplified at the nerve level, is a result of these circumstances. The pain can become more intense by central sensitization after transmitting through the sensory ganglia, integrated in the spinal cord. The brain finally processes the signals which results in cognitive perception of pain.

The cancer pain circuit consists of four regulatory levels (Figure 1): Axon Sensitization (Level I)—Sensitized peripheral sensory neurons (PSNs) in the tumour microenvironment (TME) send pain signals to the trigeminal ganglia, vagal ganglia, and dorsal root ganglia (DRG, VG, and TG). Sensory Ganglia Integration (Level II)—PSNs from the DRG project to the spinal cord, while those from TG and VG connect directly to the brainstem, facilitating pain signal processing. Central Sensitization (Level III)—Neuropeptides (SP, CGRP, somatostatin) and neurotransmitters (glutamate, GABA, glycine) modulate pain transmission in the spinal cord and brainstem, affecting nociceptive neurons and interneurons. Cognitive Perception (Level IV)—Spinal and supraspinal projection neurons relay pain signals to the brainstem, thalamus, and cortical regions (somatosensory, insular, cingulate, and prefrontal cortices), leading to pain perception.

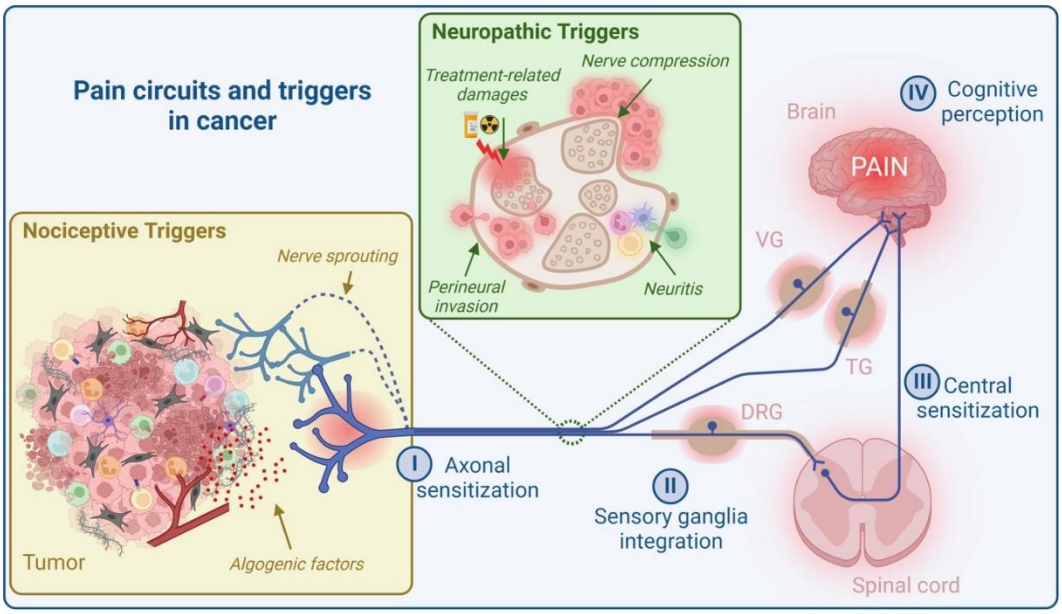

Figure 1. Cancer pain circuits and their triggers. Reprinted with permission [38]. Copyright 2024, Frontiers.

The role and expression of Transient Receptor Potential Vanilloid 1 (TPRV1) in cervical cancer are unclear as there are contradictory reports on its expression. However, a study by Han *et al.* [39] found overexpression of TPRV1 channels in cervical cancer tissue, which was associated with increased cell viability and colony formation, making it a potential prognostic maker [39]. TPRV1 has been implicated in several other cancers influencing cell proliferation, migration, invasion and pain [37,40]. In cancer pain management, TRPV1 has been targeted by antagonists to block its activity in nociception as well as the use of agonists to stimulate and desensitize them. This has been demonstrated by the administration of intrathecal resiniferatoxin, an ultrapotent capsaicin analogue to patients with intractable pain due to metastatic bone disease, such as women with cervical carcinoma metastasis to the pelvic bone [41]. Results showed ablation of TRPV1-expressing nerve endings exposed to cerebrospinal fluid, providing permanent analgesia for women with cervical cancer metastasis to the pelvic bone [41,42]. A topical patch containing Capsaicin, a natural TRPV1 agonist, was used to treat chemotherapy-induced peripheral neuropathy and post-surgical pain by reversible desensitisation of TRPV1-expressing sensory afferents, providing lasting and localised pain relief [41].

Treatment of pain in cervical cancer involves several approaches, including pharmacological and psychological approaches, to effectively manage pain and improve the quality of life of patients. Opioids, particularly morphine, have been widely used as the standard for treating pain in various cancer-related pain [43]. In cervical cancer, other analgesics such as NSAIDS have been utilised to treat specific types of pain as well as reduce the dose of opioids such as morphine and tramadol [12,14,44]. The use of opioids is, however, saddled with several drawbacks, including side effects, unavailability of oral liquid morphine in some instances, and a high tendency of dependency and abuse [11,45]. Consequently, there has been a burgeoning interest in exploring alternatives such as cannabinoids, propelled by an accumulation of evidence supporting the use of cannabis and cannabinoids for managing cancer-related pain and other symptoms [46,47].

Insights from Wiese and Wilson-Poe [51] indicate that the coadministration of cannabinoids and opioids, a strategy explored in both clinical and preclinical studies, yields synergistic analgesic effects

while mitigating opioid tolerance and other associated side effects. In another study, Nabiximol (Oro mucosal spray containing Δ^9-tetrahydrocannabinol and cannabidiol) reduced chemotherapy-induced cancer pain [49,50]. Though Δ^9-tetrahydrocannabinol (THC) has been widely used for cancer pain treatment, CBD has gained more attention lately for the same purpose due to its potential efficacy and favourable safety profile, especially as it gains legal acceptance across various regions [47]. Pain management in cervical cancer involves several approaches, usually combining different pharmacological and non-pharmacological approaches (Table 1). A personalised treatment approach involving different strategies is, however, important in achieving optimal therapy.

Table 1. Pain management strategies for the management of different types of pain in cervical cancer.

Type of Pain	Management Strategy	Common Drugs Used	Mode of Action	Potential Side Effects	References
Neuropathic Pain	Pharmacological	Opioids (Morphine, Tramadol, Buprenorphine)	Nerve signal inhibition as well as modification of pain receptor pathways.	Dizziness GIT disturbances (Nausea, vomiting) Opioid dependence	[51–53]
		Gabapentin, Pregabalin			
		Antidepressants (Amitriptyline, Duloxetine)			
		TPRV1 Agonist (Capsaicin)			
		Acupuncture	Nerve conduction and pain threshold modulation	Localised irritation.	[54–56]
		Nerve block			
	Non-Pharmacological				
Inflammatory Pain	Pharmacological	NSAIDS (Ibuprofen, diclofenac)	Inhibition of inflammatory mediators	Gastrointestinal disturbances	[53,57]
		Corticosteroids (Dexamethasone, Prednisolone)			
		Physiotherapy	Reduction in muscle tension	Minimal side effects	
	Non-Pharmacological				

Visceral Pain	Pharmacological	Opioids (Morphine, Fentanyl, Oxycodone)	Block of pain receptors in the central nervous system.	Constipation Respiratory depression	[51,53]
Palliative Care	Pharmacological	Opioids (Morphine) Adjuvant medications Antidepressants	Symptomatic pain relief.	Opioid dependence Sedation, Respiratory depression, Constipation	[58,59]
	Non-Pharmacological	Palliative radiotherapy Spiritual Emotional Freedom Technique (SEFT)			
Post-Procedure	Non-Pharmacological	Aromatherapy Reflexology Spiritual Emotional Freedom Technique (SEFT	Reduction of pain and anxiety in post-chemotherapy	Minimal side effects	[58,59]

2.1. CBD as an emerging therapeutic agent in cervical cancer pain management

Beyond conventional pain management strategies, an emerging area of interest in the treatment of cervical cancer-related symptoms is the use of Cannabidiol (CBD), a compound whose therapeutic effects are increasingly studied for its unique attributes and broad applications in cancer care [8,60,61]. The therapeutic effects of CBD have garnered heightened attention in recent times, attributed to its unique attributes of being non-psychoactive, non-intoxicating, and well-tolerated by individuals [62,63]. The precise mechanism of action for CBD remains a subject of ongoing investigation and, as of now, is not entirely understood. Initial observations indicate that CBD does not directly bind to cannabinoid receptors CB_1 and CB_2 but rather acts as an allosteric modulator, influencing the effects of agonists at these sites [64]. Molecular targets for CBD's activity include ion channels, enzymes, and several receptors, such as serotonin 1A receptor (5-HT1A), transient receptor potential vanilloid 1 (TRPV1), and G-protein coupled receptor 55 (GPR55). Additional targets encompass voltage-activated T-type calcium channels, mu and delta opioid receptors, fatty acid binding protein (FABP), type 1 equilibrative nucleoside transporter (ETN1), nuclear factor erythroid 2-related factor 2 (NRF2), adenosine and glycine receptors, and type 1 equilibrative nucleoside transporter (ETN1) [64–66].

CBD has shown potential in separate preclinical studies to prevent tumour invasion and angiogenesis, induce apoptosis as well as prevent cell proliferation in cervical cancer [8,67]. This was evidenced by a study by Lukhele and Motadi [68], where the antiproliferative and cytotoxic effects of cannabis extract as well as cannabidiol were investigated against different cervical cancer cell lines (HeLa, SiHa, and ME-180) at varying concentrations. The study employed various research methods,

including phytochemical screening, MTT assay, cell growth analysis, flow cytometry, morphology analysis, Western blot, caspase 3/7 assay, and ATP measurement assay. The findings showed that both the *Cannabis sativa* extracts and cannabidiol could stop cell proliferation in all tested cervical cancer cell lines at different concentrations. Notably, cannabidiol was found to induce apoptosis, as evidenced by an increase in subG0/G1 phase cells and apoptosis through annexin V staining. This induction of apoptosis was further confirmed by the overexpression of p53, caspase 3, and Bax proteins, along with observable morphological changes, increased activity of caspase 3/7, and reduced ATP levels [68].

These results were consistent with those of other studies which explored the effects of CBD on cancer cell viability and tumour progression. A number of mechanisms have been identified as responsible for these effects of CBD which include, CBD-mediated reactive oxygen species (ROS) production, mitochondrial dysfunction as well as caspase activation [69]. Studies indicate that CBD's ability to inhibit cancer cell viability and proliferation does not rely on direct interactions with CB1 and CB2 receptors, TRPV1, adenosine A2A receptor (A2A) or PPARγ, other studies have shown reversal of anti-proliferation effect of CBD by antagonist of CB2, TRPV1, TRPM8, COX-2, and PPARγ [70,71]. In a model with subcutaneously implanted human lung cancer cells, CBD's antitumour activity was fully reversed by a PPARγ antagonist, whereas in a mouse model of breast cancer, CBD's anti-metastatic activity was not reversed by a CB2 receptor antagonist [72,73].

CBD has also been utilised to enhance the cytotoxic effects of some anticancer drugs and therapy, leading to improved patient outcomes [74,75]. In a study by Razlog *et al.* [8], HeLa cells were exposed to varying doses of ZnPcS4 PS and CBD, with 673 nm laser irradiation at 10 J/cm2. The results revealed that the predetermined lowest dose concentrations (ICD50) of 0.125 μM ZnPcS4 PS plus 0.5 μM CBD yielded 50% cytotoxicity post-laser treatment. This combination treatment led to highly significant and favourable forms of cell death, with only 13% of cells remaining viable, 7% in early apoptosis, and 64% in late apoptosis, along with 16% necrosis. This combinative approach was able to induce primary cervical cancer cellular destruction and limit metastatic spread with minimal impact on the viability and proliferation of normal human WS1 fibroblast cells, [8]. This effect has been observed in *invitro* studies of other types of cancer. In another study, CBD was used in combination with PDT in breast cancer *in vitro* model. The results showed a dose dependent cell death in treated MCF-7 breast cancer cells [76].

CBD has also been used in combination with other cancer chemotherapeutics like doxorubicin in breast cancer and sunitinib in human renal cell carcinoma, with both studies showing inhibition of tumour growth and progression [77,78]. In the management of head and neck squamous cell carcinoma (HNSCC), CBD has been evaluated alone and in combination with cytotoxic drugs (Cisplatin, 5-Fluorouracil (5-FU), and Paclitaxel) were tested in both *in vitro* and *in vivo* experiments. The results showed significantly decreased migration, invasion, and viability of HNSCC cells, which was dose- and time-dependent when CBD was used alone. In combination with other chemotherapeutics, the efficacy of these drugs was increased by CBD [74]. Fundamentally, the expanding realm of research is progressively unravelling the potential of CBD in managing inflammation and alleviating pain in cancer, as evidenced by a growing body of studies dedicated to exploring its applications in these areas [61].

The growing interest in the use of cannabinoids for the management of cervical cancer has been largely propelled by the search for alternatives to opioids, which are the mainstay analgesic used in cancer pain management. Essentially, the notable drawbacks such as diminished effectiveness, the risk of addiction, adverse effects, and concerns regarding overdose mar the conventional use of opioids for

pain relief [79]. Although the efficacy in the management of cancer pain remains a contentious issue, several *in vitro* and *in vivo* studies have reported the potential of cannabinoids in non-cancer and cancer pain relief [80,81]. Particularly, CBD has been explored in both clinical and preclinical studies, either alone or in combination with THC, for the management of cancer-related pain. However, there are no studies specifically using CBD in cervical cancer pain despite its demonstrated analgesic, anti-inflammatory, and neuroprotective properties in various chronic pain conditions, including neuropathic and cancer pain. In a double-blind, randomised Placebo controlled study, the efficacy of a tetrahydrocannabinol: cannabidiol (THC: CBD) extract, and a THC extract were compared with placebo, in relieving pain in patients with advanced cancer. The two-week, multicentre, double-blind, randomized, placebo-controlled, parallel-group trial involved 177 patients with cancer pain who experienced inadequate analgesia despite chronic opioid dosing. They were randomized to THC: CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59). The results showed a significant improvement in favour of the THC:CBD compared with placebo, with no significant change observed in the THC group [82]. In a separate open-label extension study, the long-term safety and tolerability of the D9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray and THC spray for managing chronic pain in patients with advanced cancer. The study included 43 patients who had previously participated in a randomized controlled trial evaluating the efficacy, safety and tolerability of these cannabinoid formulations compared to placebo. The results showed THC/CBD spray was well tolerated, with no new safety concerns. Patients experienced improvements in “pain severity” and “worst pain” according to BPI-SF data, and decreases in insomnia, pain, and fatigue per EORTC QLQ-C30 data, suggesting that the benefits from the previous randomized trial were maintained with long-term use [49].

The adjuvant use of cannabinoids in managing cancer-related pain has been suggested to offer benefits without requiring increased doses of other pain-relieving medications over time. Insights from [48] indicate that the coadministration of cannabinoids and opioids, a strategy explored in both clinical and preclinical studies, yields synergistic analgesic effects while mitigating opioid tolerance and other associated side effects. In a systemic review consisting of randomised controlled trials, prospective surveys, and a case study, cannabinoids showed pain control with reduced opioid use, although most were not conclusive [83]. Moreover, the application of CBD-rich oil extract has shown promise in reducing the reliance on opioids, concurrently improving the quality of life for individuals grappling with chronic pain [47].

Blake *et al.* [84] conducted a literature review on selected clinical studies on the use of THC and CBD for the treatment of cancer pain from 1975 to 2014. In the review, five clinical trials were included, which utilised various forms of cannabis-based therapies including THC oil capsules, THC: CBD oromucosal spray (nabiximols) and THC oromucosal sprays at varying concentrations (2.7–43.2 mg/day THC and 0–40 mg/day CBD). Results showed higher doses of THC were correlated with increased pain relief in some studies, and significant pain relief was achieved in doses as low as 2.7–10.8 mg THC in combination with 2.5–10.0 mg CBD. However, there were conflicting findings on whether higher doses provided superior pain relief. Some reported side effects included drowsiness, hypotension, mental clouding, and nausea and vomiting [84].

A double-blind, multicentred, randomised, placebo-controlled trial by Lichtman *et al.* [85] showed patients with advanced cancer experiencing average pain scores between 4 and 8 on the Numerical Rating Scale (NRS), despite optimised opioid therapy, were studied. Conducted across 114 centres in

Europe and the United States, the trial randomised patients into two groups: one receiving Nabiximols (n = 199), which involved a 2-week self-titration period followed by a 3-week treatment period at the titrated dose, and the other receiving a placebo (n = 198). Results from this study showed that this Phase 3 trial did not meet the primary endpoint of superiority over placebo for per cent improvement in average pain scores. However, nabiximols showed beneficial effects on several secondary outcomes, particularly in the US patient subgroup. These findings, along with a favourable safety profile, suggest nabiximols may be useful as an adjunct therapy for advanced cancer patients with chronic pain inadequately controlled by opioids, especially for those who can tolerate lower opioid doses [85,86].

CBD presents a promise in the management of chemotherapy-induced peripheral neuropathy (CIPN) as well. Studies have demonstrated the ability of CBD to prevent the development and of CIPN as well as alleviate pain associated with chemotherapy. In a preclinical study by Ward *et al.* [90] the potential of CBD in preventing paclitaxel (PAC)-induced neuropathic pain as well as the receptor mechanisms involved were investigated. The results showed that PAC-induced mechanical sensitivity in female mice was prevented by CBD administration, which was reversed by co-administration of the 5-HT1A antagonist WAY 100635, but not by CB1 or CB2 antagonists [87]. These results suggest that CBD is protective against PAC-induced neurotoxicity mediated in part by the 5-HT1A receptor system [71,87]. This was confirmed in another study where a CBD analogue, PECS-101, demonstrated the prevention of chemotherapy-induced neuropathic pain via PPARγ receptors, further highlighting the potential of CBD derivatives in managing CIPN [88].

Some clinical trials have also indicated that oral CBD may effectively reduce CINP symptoms without significant side effects [81]. Just like most effects of CBD, the clinical efficacy of prevention of CIPN could be enhanced through the co-administration of THC. This was evidenced by a study by King *et al.* [92], where the synergy between THC and CBD in decreasing CIPN was tested in a mouse model. CBD and THC both reduced mechanical allodynia in mice treated with paclitaxel, with low ineffective doses of each showing synergy when combined [89]. Despite these promising preclinical findings, the clinical evidence supporting cannabinoids for cancer pain management remains relatively weak, highlighting the need for high-quality randomised controlled trials to assess their effectiveness and safety comprehensively. Given the high pain burden that cervical cancer patients—especially those receiving radiation therapy, chemotherapy, or palliative care—face, more research is required to determine whether CBD, either by itself or in conjunction with traditional chemo therapeutics, could reduce opioid dependence, enhance patient quality of life, and provide safer and more effective pain relief.

3. Angiogenesis and cervical cancer

3.1. Role of angiogenesis in cervical cancer progression

Angiogenesis, the formation of new blood vessels, is fundamental to tumour growth and metastasis in cervical cancer (Figure 2) [90–92]. This process is innate to most cancer cells and creates an environment favourable for the growth and metastasis of tumours [93]. Several studies confirm that the “angiogenic switch”—a shift favouring pro-angiogenic factors over anti-angiogenix ones—is essential in the progression of cervical cancer, marking the transition from early to advanced disease stages, including escalation from low-grade to high-grade cervical intraepithelial neoplasia (CIN) [94,95]. The balance of angiogenesis activators and inhibitors controls the process, which involves interactions

between cancer cells, endothelial cells, and extracellular matrix components. The intricate process of angiogenesis necessitates the coordinated action of numerous vascular components. The identification and characterisation of a wide range of signalling molecules and receptors involved in the control of angiogenesis has been confirmed to aid in the successful treatment of human cancer.

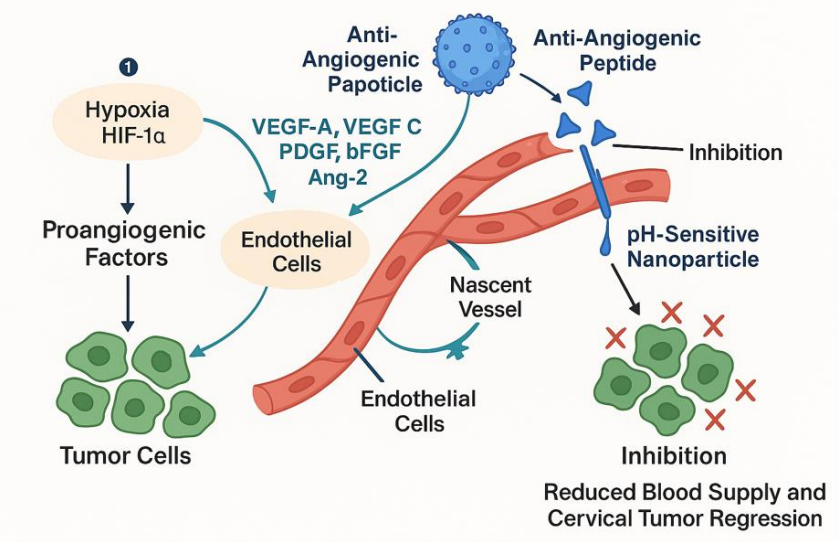

Figure 2. Tumour angiogenesis. Tumour-angiogenesis cascade in cervical cancer and its interception by a pH-responsive, anti-angiogenic-peptide nano therapy. Hypoxia within the cervical-tumour core up-regulates HIF-1α, triggering secretion of pro-angiogenic mediators—VEGF-A, VEGF-C, basic FGF, PDGF and angiopoietin-2—which recruit and activate nearby endothelial cells. Activated endothelium migrates, proliferates and forms nascent sprouts that mature into functional blood vessels, supplying nutrients to the expanding tumour mass. A nanocarrier designed to be delivered in the acidic tumour micro-environment releases an anti-angiogenic peptide that binds to endothelial receptors and blocks VEGF signalling, halting the formation of new blood vessels. The ensuing reduction in vascular supply starves the tumour, which ultimately leads to the inhibition of tumour growth.

3.2. Key angiogenic factors and their mechanisms of action in cervical cancer

Research has identified multiple pro-angiogenic factors that are crucial to the angiogenic process in cervical cancer, particularly Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (FGF2) and Transforming Growth Factor –β (TGFB). VEGF, the most extensively studied, directly promotes endothelial cell proliferation and new blood vessel formation, providing tumours with the vascular support needed for growth and survival [96–99]. Other angiogenic factors like interleukin (IL-)8, matrix metalloproteinases (MMPs), platelet-derived endothelial cell growth factor (PD-ECGF), angiopoietins, cadherins and integrins have also been implicated in cancer angiogenesis [100,101].

Integrin receptors have also been identified to play an essential role in cervical cancer progression, metastasis and ultimately the inhibition of angiogenesis. Specific integrins play various roles to achieve this; integrin α3 promotes cell migration through the c-Src/extracellular signal-regulated protein kinase cascade, enhancing angiogenesis via MMP-9 [102]. Integrin β3 has been linked to the stimulation of cancer cell proliferation, and its inhibition causes a reduction in the metastatic potential of cancer cells,

further supporting its role in metastasis [103]. Integrin αvβ3 also promotes cancer cell invasion by modulating IGF-1R signaling, and targeting it disrupt the interaction between endothelial cells and the extracellular matrix and inhibits angiogenesis [104]. Anti-integrin therapies, including monoclonal antibodies have shown promise in various cancers [105]. clinical trials have faced various challenges, and ongoing research seeks to address them, improve their pharmacological properties, and explore combination therapies in cancer management [106].

Meanwhile, few studies have identified other tumour-derived factors that are responsible for angiogenesis. Bhat *et al.* [107] assessed the angiogenic effect of exosomes isolated from cervical cancer cells on cancer progression from low-grade to high-grade cervical intraepithelial neoplasia (CIN) using human umbilical vein endothelial cells (HUVEC). The study found that exosomes from cervical cancer cells facilitated angiogenesis, promoting pro-angiogenic endothelial cell responses. HPV-positive exosomes were more angiogenic than HPV-negative ones. Exosome-treated cells showed increased migration rates and upregulated Hedgehog-GLI signalling. These effects were independent of tumour-derived VEGF-A, suggesting exosomes as potential targets for local angiogenesis [107]. In another study, the angiogenic activity of thymic stromal lymphopoietin (TSLP) secreted by cervical carcinoma cells was explored *in vitro* using human umbilical vein endothelial cells (HUVECs). The results showed that the secretion of thymic stromal lymphopoietin by both HeLa and CaSki cells was time-dependent and also stimulated angiogenesis by aiding tumour growth and activation of vascular endothelial cells [108]. In a similar *in vitro* experiment, the tumour microenvironment in cervical cancer has been found to influence the expression and function of some micro RNAs (mRNAs), promoting cell proliferation, migration and invasion. The downregulation of miR-203, miR-126 and miR-628-5p, amongst others, in cervical cancer have been established in some studies, which led to an increase in angiogenesis. Overexpression of miR-203 and miR-628-5p was found to prevent tumour growth and angiogenesis in cervical cancer by targeting VEGF [109–111].

Understanding the complex mechanisms involved in angiogenic factors and angiogenic switch in cervical cancer is crucial for therapeutic targeting in cervical cancer management. Several antiangiogenic drugs, either used alone or in combination with chemotherapy, are at different stages of clinical studies for the management of cervical cancer [6,112].

3.3. VEGF as a pro-angiogenic marker

In cancer angiogenesis, the VEGF has been identified as crucial and necessary for tumour development, progression, metastasis, and the survival of endothelial cells. Various isoforms of VEGF have been identified in cervical cancer cells, with each contributing in various ways to tumour progression and angiogenesis [113,114]. The common isoforms identified in cervical cancer include VEGF-A, VEGF-C and VEGF-D, with VEGF-A being the predominant one. VEGF-C and VEGF-D have been found to be structurally different from VEGF-A and mostly involved in lymphangiogenesis, which is the formation of lymphatic vessels. This was demonstrated in a study where elevated levels of VEGF-C in cervical cancer patients was linked to lymph node metastasis and a poor prognosis [115]. Hypoxic conditions in the tumour microenvironment have been found to influence its expression [116].

The overexpression of VEGF-A is pivotal in the cervical cancer stage and other clinicopathological parameters, which indicates its importance as a prognostic marker. Patients with high levels of VEGF have been found to have a bad prognosis of disease and a decreased survival rate [117,118]. It has been

found to work through different pathways, including stimulating the formation of endothelial cells to generate new blood vessels, thus providing essential nutrients and oxygen for tumour growth and invasion [119]. Different regulatory processes operating at multiple levels, including as transcription, mRNA stability, and translation, tightly govern the expression of VEGF. It is induced by stress signals, including hypoxia, different cytokines, growth hormones, and tumour suppressor genes like p53, which encourage the downregulation of VEGF expression [120].

Hypoxia-induced expression of VEGF plays a significant role in the angiogenesis associated with cervical cancer. Under hypoxic conditions, which are common in solid tumours due to inadequate blood supply, the expression of VEGF is upregulated, leading to several critical effects on tumour progression and vascularisation. Hypoxia-inducible factor 1-alpha (HIF-1α) is a key regulator of the cellular response to low oxygen levels. In cervical cancer, HIF-1α is stabilised under hypoxic conditions, leading to the transcriptional activation of VEGF. This process is crucial as VEGF promotes the formation of new blood vessels, supplies the tumour with necessary nutrients and oxygen, and facilitates its growth and survival [121].

Other factors like NF90 have been found to regulate the expression of HIF-1α and VEGFA in cervical cancer under hypoxic conditions. In the same study by Zhang *et al.* [121], NF90, or DRBP76, a double-stranded RNA-binding protein which is predominantly expressed in various cancers was found to be upregulated in cervical cancer cells. According to the study, NF90 was associated with the regulation of VEGF-A synthesis and release using the PI3K/Akt signalling pathway when the cells were exposed to hypoxic conditions. Silencing of NF90 was reported to suppress VEGF-A mediated angiogenesis in a human cervical cancer cell line, resulting in tumour formation *in vivo* suppression. In another study, the role of Peroxisome Proliferator-Activated Receptor-β (PPARβ) in the expression and effect of different isoforms of VEGF in cervical cancer was investigated. PPARβ was activated by the agonist L-165041, causing an increase in the expression of f VEGF121, VEGF165, and VEGF189 isoforms in HPV18-positive HeLa cells, but not in HPV-negative C-33A cells. The researchers found that VEGF expression in HPV18-positive cervical cancer cells can be increased by the PPARβ agonist L-165041 via a PPARβ-independent mechanism involving p38 MAPK-mediated stability of VEGF mRNA via the RNA-binding protein HuR [120].

The microbial environment of the vagina has also been found to influence angiogenesis mediated by VEGF. In a recent study, Peptostreptococcus anaerobius, a vaginal microbe, has been shown to influence the tumour microenvironment by promoting the polarisation of macrophages. This process enhances angiogenesis in *in vitro* studies and increases tumour migration in *in vivo* models, suggesting that this microbe may play a role in VEGF-mediated angiogenesis [119].

Increased VEGF expression in recurrent cervical cancer has been linked to radioresistance, suggesting that VEGFR-1 may play a role in the tumour's adaptive response to therapy [122]. VEGFR-3 on the other hand is mainly involved in lymphangiogenesis, plays a crucial role in the formation of lymphatic vessels and the metastatic spread of cervical cancer through lymphatic pathways. VEGF-C activates VEGFR-3, enhancing cervical cancer cell invasiveness by upregulating galectin-3, which strengthens VEGFR-3 signalling in endothelial cells. This VEGF-C/VEGFR-3 interaction is particularly important in the spread of cervical cancer to lymph nodes [116,123,124]. VEGFR-2 is the key receptor driving the pro-angiogenic effects of VEGF, playing a vital role in endothelial cell proliferation, migration, and new blood vessel formation. Studies have shown that endostar, an angiogenesis inhibitor, reduces the expression of both VEGF and VEGFR-2, underscoring the receptor's importance in cervical cancer

angiogenesis. VEGFR-2 is also crucial for tumour growth and migration, making it a significant factor in the progression of cervical cancer [96,125,126].

3.4. Targeting of VEGF as an antiangiogenetic approach in cervical cancer management

VEGF and its various receptors have served as prime therapeutic targets for the management of cervical cancer due to their pivotal role in angiogenesis and tumour metastasis (Table 2). Targeting the signalling pathway of VEGF/VEGFR-2 in cervical cancer has shown promise in both pre-clinical and clinical studies in the management of recurrent cervical cancer [125]. In clinical studies, anti-angiogenic treatment approaches using bevacizumad has been proven to show enhanced treatment outcomes in patients with advanced and metastatic disease. Bevacizumab is a recombinant monoclonal antibody that targets VEGF-A, thereby blocking the VEGFR-1 and VEGFR-2 pathways. A Phase II research indicated that single-agent bevacizumab in metastatic cervical cancer was well-tolerated, with a progression-free survival (PFS) of 3.4 months and an overall survival (OS) of 7.29 months [20]. In another report, a phase 3 randomised, controlled, open-label study examined the effects of bevacizumab, added to chemotherapy in patients with metastatic, persistent, or recurring and advanced cervical cancer. Patients were assigned randomly to one of four groups consisting of chemotherapy (cisplatin and paclitaxel or topotecan and paclitaxel) with or without bevacizumab and the outcomes of interest were overall survival and adverse reactions.

With a hazard ratio of 0.77 (95% CI 0.62 – 0.95; p = 0.007), the study demonstrated that bevacizumab added to chemotherapy significantly increased OS (16.8 months) compared to chemotherapy alone (13.3 months). According to the study's findings, bevacizumab continued to improve survival in patients with advanced cervical cancer without having a deleterious rebound impact when the medication was stopped. This finding supports the effectiveness and safety of bevacizumab as an antiangiogenesis therapy [18]. Despite these promising results of Bevacizumab use in cervical cancer, it is linked to elevated incidences of hypertension, gastrointestinal perforations, and venous thrombotic events, while its expensive cost restricts accessibility in developing nations [20]. However, in a similar way a phase II trial involving 34 patients was conducted to assess the efficacy and safety of the combination of paclitaxel, carboplatin, and bevacizumab in individuals with advanced or recurrent cervical cancer. The treatment protocol had an objective response rate of 88% and a median overall survival of 26 months. The research indicated that the combination therapy was well-tolerated, exhibiting tolerable levels of toxicity. The predominant severe adverse events were grade 3 and 4 hematologic toxicities, including neutropenia, leukopenia, anaemia, and thrombocytopenia. The median progression-free survival and overall survival were 9 months and 26 months, respectively [127].

Some tyrosine kinase inhibitors which affect multiple pathways including VEGFR'S have also been investigated for their effect on metastatic cervical cancer. These agents function by inhibiting the intracellular kinase domains of VEGFRs, therefore obstructing the signalling pathways that facilitate angiogenesis [128]. In an *in vitro* study, the efficacy of a novel tyrosine kinase inhibitor, Apatinib, was investigated alone and in combination with paclitaxel in the suppression of cervical cancer tumour cells. Apatinib was demonstrated to induce apoptosis, cause G1-phase arrest, inhibit cell proliferation, and reduce colony forming capability in cervical cancer cells. The research demonstrated that primary cancer tissues exhibiting elevated levels of VEGFR2 displayed much greater sensitivity to Apatinib. The sensitivity of cervical cancer cells in a mouse model to paclitaxel was markedly increased in with the

addition of Apatinib, resulting in enhanced suppression of tumour development, indicating that Apatinib may be an effective treatment for cervical cancer [129]. Varying degrees of efficacy have been demonstrated by agents including pazopanib, sorafenib, and brivanib in the treatment of advanced or recurring cervical cancer. In a small cohort, sorafenib in combination with radiation and cisplatin resulted in a high rate of complete response, whereas brivanib showed good efficacy in phase II research. In comparison to monotherapy, pazopanib with lapatinib produced greater results, according to a study [130].

Table 2. Agents/drugs targeting VEGFR in the management of cervical cancer.

Drug Name	Class of Drug	Mechanism of Action	Clinical Application	Common Side Effects	References
Bevacizumab	Monoclonal Antibody	Inhibit tumour angiogenesis by binding to VEGF-A hence blocking VEGFR-1 and VEGFR-2 pathways	Approved for use in combination with chemotherapy for the treatment of persistent, recurrent, or metastatic cervical cancer. Clinical trials have demonstrated improved overall survival in combination with other anticancer drugs.	Thrombolytic events Hypertension Gastrointestinal perforation	[18,20]
Apatinib	Tyrosine Kinase Inhibitor	Inhibit the intracellular kinase domains of VEGFRs, therefore obstructing the signalling pathways that facilitate angiogenesis	Explored in clinical trials for its potential benefit in advanced cervical cancer in combination with Paclitaxel. While not approved for cervical cancer, its anti-angiogenic properties have been of interest in research setting	Diarrhea, hypertension, liver function abnormalities	[129]
Pazopanib	Multiple-Tyrosine Kinase Inhibitor	Inhibits multiple tyrosine kinases, including VEGFR-1, VEGFR-2, and VEGFR-3	Explored in clinical trials for its potential benefit in advanced cervical cancer	Diarrhoea, hypertension, liver function abnormalities,	[130]
Brivanib	Tyrosine Kinase Inhibitor	Reduce tumour angiogenesis by interfering with VEGF signaling	showed good efficacy in phase II research	Hypertension Fatigue and weakness Proteinuria	[130,131]
Sorafenib	Tyrosine Kinase Inhibitor	reduces endothelial cell proliferation thereby preventing angiogenesis	Investigated in combination with radiation and cisplatin resulting in improved response	Hand-Foot Syndrome Hypertension Hypothyrodism	[130,132]

3.5. Emerging strategies for anti-VEGF therapy

Several new agents and strategies are under investigation to regulate VEGF expression in the management of cervical cancer (Table 3). Investigations are underway into gene therapy strategies designed to downregulate VEGF expression or interfere with its signalling pathways. RNA interference methods aimed at VEGF mRNA can diminish its expression and hence impede angiogenesis [115].

Table 3. Anti-angiogenic drugs employed in clinical trials for cervical cancer.

Drug	Mechanism of action	Clinical outcome	References
Bevacizumab	Monoclonal antibody targeting VEGF	Demonstrated improved overall survival when added to chemotherapy in advanced cervical cancer (GOG 240 trial)	[18]
Pazopanib	Oral tyrosine kinase inhibitor targeting VEGF receptors	preliminary data suggests in a phase II trial suggest potential benefit in prolonging PFS with low toxicity.	[133]
Endostar	Recombinant human endostatin	Inhibit VEGF expression and enhance the efficacy of chemotherapy in cervical cancer	[134]
Sunitinib	Multi-targeted tyrosine kinase inhibitor	Early-phase trials explored its use in cervical cancer, but clinical benefits are still uncertain.	[20,135]
Ang-1/Ang-2 Inhibitors	Angiopoietin inhibition	Reduced tumour growth in preclinical models	[136]

4. Peptide-based therapies

Building on the importance of angiogenesis in cervical cancer progression, recent research has shifted focus toward innovative delivery systems and therapeutic approaches, such as peptide-based therapies, which hold promise for enhancing treatment precision and efficacy [137]. These therapies employ the short chain amino acids to target and bind to specific overexpressed receptors and molecular pathways involved in cancer progression [19]. Notable amongst these targets in cervical cancer are HPV Oncoproteins, resulting in the eradication of infected cells and the prevention of malignant transformations. Peptide-based therapies also induce specific human responses by stimulating cytotoxic T lymphocytes (CTLs) to destroy cancerous cells [19,20].These therapies offer several benefits, including ease of synthesis and modification, high specificity in binding, as well as a high safety profile. They, however, may have stability concerns because of a shorter half-life, which may necessitate regular dosing [109,138]. The FDA has approved some peptide-based drugs in the management of some cancers as well as in the management of pain. Ziconotide, a synthetic peptide which works by blocking N-type voltage-sensitive calcium channels in the spinal cord, has been approved for the management of chronic pain, refractory to other treatments. Although effective, its use is limited to small number of patients due to its therapeutic window [139,140] . In the inhibition of angiogenesis, several drugs have been approved by the FDA, notable amongst them is Bevacizumab which targets VEGF. It has been marketed for the treatment of various cancers, including advanced breast, metastatic, colorectal, lung and kidney cancers with great outcomes [141]. Vorinostat, a histone deacetylase inhibitor (HDACi), which prevents angiogenesis by inhibiting the expression of HIF-1α, a critical regulator of tumour vessel formation, is also FDA approved for cutaneous T cell lymphoma [142]. Other drugs that have been used traditionally for the management of other conditions, like Azithromycin (an antibiotic) and Glipizide(an antidiabetic) have been identified as angiogenesis inhibitors in different cancer modules, preventing cancer progression and metastasis [143,144]. In the delivery of drugs, Semaglutide (Rybelsus®) and octreotide (Mycapssa®) which are FDA approved, have been formulated with permeation enhancers to improve their bioavailability in the management of type 2 diabetes and acromegaly, respectively[145]. Additionally, poly(L-lactide) (PLA) polymers, are FDA-approved for drug delivery to enhance the stability and targeting of therapeutic agents, particularly when conjugated with tumor-homing peptides to improve cancer treatment selectivity and effectiveness [146].

4.1. Types of peptide-based therapies

Peptide-based therapies stand out in multifaceted as well as targeted approaches to cancer therapy due to its biocompatibility, specificity and tunability. They involve various types including peptide alone-based therapies, peptide-based vaccines and peptide-conjugated nanomaterials, each offering specific advantages [147,148]. Innovations like anticancer peptide (ACPs) work by different mechanisms including apoptosis induction, inhibition of angiogenesis or modulation of the body's immune response to cancer progression and metastasis. These peptides can be engineered for specific binding to tumour receptors, minimising toxicity [147]. The intracellular delivery of chemotherapeutics can be further enhanced by peptide-drug conjugates (PDCs) which functions by linking peptides to chemotherapeutic agents, ensuring precise tumour targeting. Peptide receptor radionuclide therapy (PRRT) and antibody-drug conjugates (ADCs) are common examples which have demonstrated good results [149,150]. Cell-penetrating peptides (CPPs) also enable intracellular delivery of diverse therapeutic molecules, such as nucleic acids and imaging agents, primarily via endocytosis [149]. Additionally, tumour-targeting peptides (TTPs) selectively bind to tumour-specific markers, allowing for highly localized therapy with minimal impact on surrounding healthy tissue. These peptide-based strategies significantly advance cancer treatment by improving precision and reducing adverse effects [151].

Peptide self-assemblies have emerged as promising nanocarriers in cancer therapy due to their biocompatibility, biodegradability, and ability to self-organize into diverse nanostructures (e.g., nanofibers, nanospheres, nanotubes) [152,153]. These structures can be engineered for stimuli-responsive drug delivery, enabling precise delivery in tumour-specific microenvironments (e.g., low pH, high temperature) [154,155]. They have been utilized in important therapeutic applications, including drug delivery of both hydrophobic and hydrophilic agents, improving stability and bioavailability [156–158]. They are also employed in combination therapies with chemotherapeutics (e.g., doxorubicin, paclitaxel) and phototherapy through enhanced optical properties [157]. Immunotherapy, where peptide assemblies act as antigens, adjuvants, or delivery platforms, have also been explored with favourable outcomes [153,159].

These self-assembly peptides rely on non-covalent interactions (hydrogen bonding, van der Waals, ionic forces), allowing precise control over nanostructure formation [153,160]. Functional groups can be added to enable targeted delivery to tumour cells, while peptide hydrogels allow for sustained drug release, reducing dosing frequency [161].

However, key challenges remain, including: physiological stability and potential immunogenicity, scalability and cost of manufacturing peptide-based nanomedicines and the need for personalised medicine approaches, tailoring assemblies to individual patient profiles for optimized outcomes [162].

Despite these challenges, peptide-based drug delivery systems offer several advantages over inorganic metal-based systems, including higher specificity, reduced toxicity, ease of synthesis, and better biocompatibility. While metal-based systems benefit from controlled release and imaging, they face challenges related to biosafety and potential toxicity. Therefore, peptide-based systems may be more favourable for cancer therapy due to their overall safety and effectiveness [163–165].

4.2. Peptide-targeted drug delivery systems

Several methods have been employed to enhance the delivery of therapeutics, including anti-angiogenic drugs to tumour sites for cervical cancer management. Self-assembly proteins and peptides have

emerged as a promising approach to augment the efficacy of therapeutics targeting various signalling systems by promoting targeted delivery, increasing bioavailability, boosting the therapeutic index of anti-cancer agents, and minimising damage to healthy cells [166]. These peptides act by one of two main mechanisms: cell-penetrating (CPP) and tumour-homing peptides (Figure 3). While the CPP facilitates the translocation of therapeutics across cell membranes, tumour-homing peptides target overexpressed receptors on tumour cells [167]. In the management of cervical cancer, few peptide-targeted drug delivery systems are available, which include Peptide-Based Nanocarriers, Peptide-Drug Conjugates (PDCs), Peptide-Functionalised Liposomes and Peptide-Based Immunotherapy [167,168]. An antibody-drug conjugate, Tisotumab vedotin, marketed under the trade name Tivdak was approved in the United States in September 2021 for the management of cervical cancer [169].

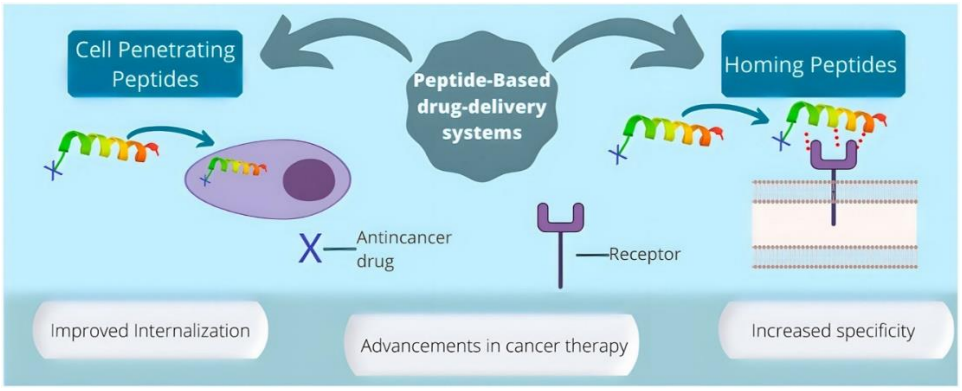

Figure 3. Image illustrating the mechanism of action of various peptides. Reprinted with permission [163]. Copyright 2022, Elsevier.

Some studies have demonstrated the use of small peptide ligands as targeting ligands to deliver therapeutics directly to the tumour site. In a recent study by W, 2020, biocompatible selenium nanoparticles were loaded with RGDFC peptide to create a tumour-targeting gene system for the delivery of siRNA in managing cervical cancer. The formulated system, RGDfC-Se@siRNA was found to have a greater uptake by the cancer cells compared to normal cells and also showed a faster siRNA release in the cancer microenvironment. Recent advancement in cancer chemotherapy has seen a surge in the use of cell-penetrating peptides (CPPs) by utilising the unique characteristics of the tumour microenvironment for targeted delivery of therapeutics [142]. Self-assembled peptides and proteins like albumin, ferritin, and virus-like particles have also been found useful in the delivery of various therapeutics such as siRNAs, mRNAs, DNA and plasmids for targeted delivery in breast and cervical cancers [169].

A tumour targeting peptide, Trans-activating transcriptional activator (TAT), have been used to improve internalization and efficacy of therapeutics in the management of cervical cancer. The TAT-modified solid lipid nanoparticles (SLNs) were developed for the co-delivery of paclitaxel and a cisplatin prodrug, resulting in high tumour accumulation with minimal toxicity as well as effective suppression of cervical cancer cell growth [170]. The use of TAT in combination therapies holds promise for enhancing drug delivery and improving cervical cancer treatment outcomes through synergistic effects. RGD peptides have also been very instrumental in delivering cancer therapeutics. They selectively target integrins like αVβ3 integrins, which are overexpressed in various cancers, enhancing the efficacy of anticancer agents [136,162]. RGD-based nanodrugs have been found to improve tumour

targeting and uptake, with radiosensitizers like RGD-SeD increasing cancer cell sensitivity to radiation, and RGD-conjugated nanoparticles enhancing drug stability, solubility, and targeted delivery [162,171]. While studies in cervical cancer are limited, the success of RGD-targeted therapies in other cancers suggests potential for improving drug and radiotherapy efficacy in cervical cancer treatment.

4.3. Peptide as anti-angiogenic agents

Anti-angiogenic peptides represent another promising avenue for cervical cancer treatment, targeting the angiogenic factors critical for tumour growth and metastasis, due to their high cancer cell penetration ability, specificity as well as low toxicity (Table 4). These anti-angiogenic peptides target pro-angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and angiopoietins, which promote neovascularization and tumour survival [136,172,173]. Other peptide-based therapies, including those derived from CXC chemokines or cyclic peptides, have also shown potential by disrupting endothelial cell interactions and inhibiting cell proliferation and migration, key steps in angiogenesis [174]. Moreover, peptides mimicking VEGF and computationally modelled peptides are advancing the field by specifically targeting angiogenic pathways, thus enhancing the design and efficacy of anti-angiogenic therapies [175]. This growing body of research suggests that anti-angiogenic peptides, either as monotherapies or in combination with traditional treatments, hold potential for enhancing therapeutic outcomes in cervical cancer.

Table 4. Specific peptides used to target cervical cancer cells.

Peptide	Function	Study	Results	Reference
CSP3	Targeting ligand	CSP3 conjugated with liposomal drug delivery loaded with doxorubicin (DOX) and microRNA 101 (miRNA) plasmids to target cervical cancer cells	Enhanced cytotoxicity against both standard and Dox-resistant cervical cancer cells (SiHa/SiHa/ADR)	[176]
Melitten	Targeting ligand	Cysteine-modified melittin-targeting peptide (CM-Target) conjugated with CKQNLAEG peptide to target squamous cell carcinima	Potent anticancer effects with fewer side effects	[177]
RGD	Functionalised prodrug	Bio responsive ruthenium prodrug functionalised with RGD (Ru-RGD) delivered to cervical cancer tumour speriods for diagnosis and *in vivo* therapy.	Selective delivery and increased accumulation of Ru prodrug into tumour cells for imaging	[22]
IHP5	Penetrating peptide	IHP5 conjugated with trichosanthin (TCS) to target cervical cancer cells (HeLa)	Increased delivery to cancer cells with enhanced inhibition of cancer cells	[178]
Endostatin-derived anti-angiogenic peptide	Therapeutic peptide	Endostatin derived peptide + DNA vaccine targeting HPV related cervical cancer in a mouse model	Significant tumour inhibition and higher lymphocyte proliferation	[19]

4.4. Nanoparticles functionalised peptides

Peptide-functionalised nanoparticles have recently been utilised to create drug delivery systems with better stability, bioavailability and targeted delivery in cervical cancer therapy. For instance,

peptide-functionalised nanoparticles and liposomes, such as those functionalised with Arg-Gly-Asp (RGD) peptides, demonstrate increased tumour specificity and enhanced intracellular retention [179]. Similarly, peptide functionalised nanoparticle systems have been utilized in the delivery of siRNA and other therapeutics in cervical cancer resulting in improved therapeutic effects [180]. Collectively, these studies suggest that functionalised peptides are effective for targeted delivery, improving bioavailability and minimising off-target effects, thus making them valuable tools in cervical cancer management. These peptides work by aiding the translocation of therapeutics across cell membranes or target specific overexpressed receptors on tumour cells, thereby reducing toxic effects to nearby healthy cells [181].

4.5. Peptide-based vaccines against HPV-induced cervical cancer

Another important application of peptides in cervical cancer management is the development of vaccines targeting the human papillomavirus (HPV), the virus mostly associated with cervical cancer. Research has demonstrated that specific portions of the HPV E7 protein can stimulate cytotoxic T lymphocytes (CTLs), immune cells, to yield encouraging results in animal models and preliminary human trials [182,183]. In other studies, innovative approaches in HPV-related cervical cancer immunotherapy using self-assembling peptides and nanofibers were highlighted. The non-immunogenic peptide Q11, was fused with the HPV-16 protein E744-62 to create the E7-Q11 vaccine, resulting in strong tumour-suppressive effects in mouse models, especially when administered intravaginally [142]. In another study, flagellar nanofibers (FNs) of varying lengths were produced from self-assembly properties of flagella. The results demonstrated that shorter FNs elicited stronger antibody responses, suggesting their potential application in cancer vaccines or adjuvants. The study also indicated the application of short FN as an adjuvant for the E6/E7 peptide of HPV-16 for intranasal delivery in a mouse model of cervical cancer, resulting in significant tumour suppression and extended longevity in the mice [184].

Table 5. Current peptide-based drug delivery systems in the management of cervical cancer.

Drug Delivery System	Example	Mechanism Of Action	Advantages	Challenges	References
Antibody-Drug Conjugates (ADCs)	Tisotumab Vedotin	Targets tissue factor (TF) overexpressed in cervical cancer cells; delivers cytotoxic MMAE upon internalization.	High specificity, targeted drug release, FDA-approved for recurrent/metastatic cervical cancer.	Expensive Ocular toxicity	[169]
Peptide-Based Nanocarriers	Melittin-Conjugated Nanoparticles	Melittin peptide disrupts cancer cell membranes; improving drug delivery and reducing systemic toxicity.	Enhanced tumour penetration	Potential enzymatic degradation and immunogenicity.	[177]
Peptide-Functionalised Liposomes	RGD-Peptide Liposomes	Peptides target integrins overexpressed in cervical cancer cells to enhance liposomal drug uptake.	Enhanced targeting, and extended circulation time.	Potential peptide degradation	[167]
Peptide-Based Immunotherapy	HPV E6/E7 Peptide Vaccine	Peptides derived from HPV oncogenes elicit immune responses to eradicate infected cells and prevent recurrence.	High specificity to HPV-related cervical cancer.	Variable response in patients.	[168]

Peptide vaccines have been found to be safer than whole viruses as they target specific viral components that elicit an immune response, hence decreasing the danger of oncogenic changes while still targeting cancer cells [185]. Table 5 show the current peptide-based drug delivery systems in the management of cervical cancer.

4.6. Challenges in peptide-based therapies

In the management of cervical cancer, peptide-based systems hold great promise; nevertheless, some drawbacks to their use call for modifications and continuous research to make it overcome such barriers (Table 5). Notable among these drawbacks is the complexity involved in large-scale production, possible immune response and immunogenicity, and clinical validation [138,186]. Peptides have also been found to have a short half life due to degradation by proteolytic enzymes, which ultimately makes such formulations highly unstable [187,188]. Most peptides have poor oral bioavailability, making the parenteral route a preferable route of administration. However, this route can be uncomfortable for some patients, reducing patient compliance. Other challenges stem from toxicity associated with some peptides having a small therapeutic window, requiring these formulations to be optimised to attain the desired therapeutic effects with limited adverse reactions[189]. The production cost of peptides is often expensive and can limit widespread use due to affordability. Notwithstanding these challenges, the regulatory landscape for peptide therapeutics is complex, with stringent requirements for process control, structural characterization, and impurity limits, making few peptide-based therapies make it from trials to clinical use. Addressing these challenges is essential for the translation of various research findings into clinical applications.

Several methods have been employed to solve these challenges, including chemical modifications like PEGylation, lipidation, and adding peptidomimetic elements to make peptides more stable and avoid rapid degradation [190]. New delivery methods, such as liposomal formulations, capsules, and subcutaneous injections, are improving peptides' efficacy and how easily they reach their target[189]. Thanks to advances in production techniques, peptides are now cheaper manufacture, as synthetic processes and combinatorial libraries have made the design and production more efficient[188]. To make peptide therapies safer, scientists are developing IDR peptides and peptidomimetics to reduce toxicity. At the same time, efforts to streamline regulatory guidelines are making it easier to develop and approve peptide-based treatments [191]. Emerging technologies like macrocyclic and stapled peptides are showing promise in blocking harmful protein interactions, opening up new treatment options. Additionally, using human organoids for disease modeling and drug screening is helping bridge the gap between preclinical research and real-world clinical applications, making peptide-based therapies even more effective [192,193].

5. Current state of formulation development of cannabinoid analgesic, VEGF inhibitors and peptide-based drugs in the management of cervical cancer

Cannabinoids, particularly THC and CBD, are being investigated for their analgesic properties in cancer pain management with results indicating cannabinoids can be effective in alleviating cancer-related pain, especially when traditional opioid therapies are insufficient or problematic [49,194]. Notably, Sativex®, an oromucosal spray containing THC and CBD, has been approved in several countries for treating cancer pain [194]. Several emerging delivery systems are being investigated to enhance the delivery and therapeutic effects of these cannabinoids, with nanotechnology being a major approach. Although research into nanomedicine for cervical cancer pain management is ongoing, there are currently no established applications using nanoparticles for direct pain relief in this context. However, nanoparticles are being explored for the targeted delivery of chemotherapeutic drugs to treat cervical cancer, which can indirectly

alleviate tumour-induced pain. Several types of nanocarriers have been used to deliver drugs both systemically and locally in the management of cervical cancer. These nanosystems enable controlled and sustained drug release, improving pain management and therapeutic consistency, while also allowing targeted delivery to tumour tissues, thereby minimizing systemic side effects. Various nanocarriers—lipid-based systems, polymeric nanoparticles, micelles, and nanoemulsions—have demonstrated improved cannabinoid delivery, reduced psychoactive effects, and enhanced anticancer activity in *in vitro* and *in vivo* models [195]. However, while preclinical results are encouraging, more translational research and clinical trials are necessary to confirm their efficacy and safety in human patients [196].

VEGF inhibition is now a key strategy for women with advanced or recurrent cervical cancer. In a phase-III GOG-0240 trial, the anti-VEGF monoclonal antibody bevacizumab showed optimal results when added to platinum-based chemotherapy, showing a prolonged median overall survival by 3.7 months and improved progression-free survival. A longer-term analysis confirmed these favourable results, however, there were some reported toxicities including gastrointestinal perforation, fistulae, thrombosis and hypertension, limiting use in some patients [197]. Other VEGFR-2 inhibitors such as apatinib are being explored as alternatives; with early trials indicating significantly longer progression-free survival (≈10 months vs 6 months for controls) and higher response rates, albeit with similar hypertension and hand-foot syndrome risks [198].

Peptide-based therapeutics are also gaining attention because they combine high tumour specificity with low systemic toxicity and relatively inexpensive synthesis. Recent examples include redox-responsive melittin conjugates that selectively kill HeLa and C33A cells while sparing normal tissue and hybrid peptides derived from the RWQWRWQWR sequence that show potent, selective cytotoxicity against cervical-cancer cell lines *in vitro* [177,199]. Despite these outcomes, peptide drugs still face challenges such as rapid *in vivo* degradation hence the need for delivery systems that maintain activity at the tumour site.

Overall, VEGF inhibitors and anticancer peptides together broaden the therapeutic arsenal for cervical cancer, however, full clinical potential will depend on strategies that mitigate adverse events, enhance *in vivo* stability, and are validated in larger trials.

5.1. Drug delivery systems in cervical cancer management

5.1.1. Cervix targeted platforms

The cervicovaginal route offers a short diffusion distance to both ecto- and endocervical lesions, and avoids first-pass metabolism, leading to continued advancement with the development of new and innovative approaches. In vaginal drug delivery, nanoparticles offer several advantages, including bioadhesion, easy penetration of the mucosa, and controlled drug release, making them especially attractive. Mucus-penetrating PLGA nanoparticles coated with low,-MW PEG has been found to achieve homogeneous distribution across the cervical epithelium and, when loaded with paclitaxel, suppress orthotopic HeLa tumours more effectively than free drug (tumour volume reduction ≈ 70 %) while sparing healthy tissue [200]. In another study, intravaginal rings fabricated from poly(ethylene-co-vinyl acetate) or medical-grade silicone was used to deliver cisplatin, 5-FU or siRNA for up to three months, providing sustained local chemotherapy and reducing systemic toxicity [201,202]. Other emerging devices include muco-adhesive nanofibre mats, bio-adhesive gels and cervical caps that concentrate therapeutics at the tumour site [202].

5.1.2. Delivery systems for VEGF inhibitors

Bevacizumab is traditionally administered successfully via the intravenous route, however, its encapsulation in nanocarriers have been confirmed to prolong exposure and enable local delivery in some studies. PEGylated multivesicular liposomes (MVLs) was found to release bevacizumab over ≥ 28 days and retain anti-angiogenic activity *in vitro* and *in vivo* [203]. In another study, PGA-liposome composites (≈ 140 nm) co-loaded with dexamethasone sustain bevacizumab release (> 10 days) and inhibit endothelial migration in the eye [203]. Organic nanoparticles (albumin, chitosan, PLGA) have likewise been engineered to stabilise bevacizumab, improve tumour penetration and reduce dosing frequency [204].

5.1.3. Delivery systems for cannabinoid analgesics

The therapeutic benefit of cannabinoids is well established, but poor aqueous solubility of THC and CBD limits oral bioavailability (< 10 %). Several methods and delivery systems have been employed to improve the solubility, notable amongst them is the use of nanotechnology. Some studies have employed different nano delivery systems to mitigate this problem with varying results. In a study to deliver CBD through nanosystems in CNS disorders, self-emulsifying lipid nano-emulsions and solid-lipid nanoparticles were found to raise bioavailability 3–4 fold and flatten Cmax [205]. In a private clinical and phase I pharmacokinetic study, an oro-buccal sub-micron spray (NanoCelle™) was found to deliver THC/CBD through the mucosa with rapid T_{max} (~15 min) and predictable exposure in the management of uncontrolled pain in advanced cancer patients [206]. In another preclinical study, Nano-channel implants provide zero-order CBD release for several months and are now entering animal pain models [207]. Exosome-based carriers are also being explored for tumour-specific cannabinoid delivery with enhanced anticancer potency [208].

5.2. Tumour microenvironment responsive delivery systems in cervical cancer management

Stimuli-responsive nanoplatforms that exploit the acidic, enzyme-rich and oxidative tumour microenvironment (TME) are rapidly reshaping cervical-cancer therapy. Acid-cleavable CCTP-SmacN7 conjugates, for example, trigger reactive-oxygen-species production, dendritic-cell maturation and cytotoxic T-cell activation while directly suppressing tumour growth in cervical cancer [209]. In another study, size-switchable, furin-responsive liposomes (PEG-cleavable Tf-CTM/L) shed their PEG shell in the TME and liberated 40-nm transferrin nanocomplexes that penetrated deeply into cervical-tumour tissue, boosting intratumoural drug levels and limiting systemic toxicity. Metal–organic frameworks have also been utilized to reformulate and deliver chemotherapeutics with enhanced effect. The is evidenced by a study involving formulation of DSF@MOF-199@FA which disintegrate under acidic pH to release Cu^{2+} and disulfiram, generating ROS and depleting glutathione to amplify apoptosis [210]. Magnetic mesoporous silica nanoparticles co-loaded with XIAP protein and miR-233 enhance radiosensitisation and markedly shrink cervical-tumour xenografts [211] , while nuclear-targeted mesoporous-silica carriers that co-deliver paclitaxel and indocyanine green enable image-guided photothermal/photodynamic–chemotherapy synergy in cervical cancer. Finally, Mn_3O_4-SiNT nanocomposites combine pH-dependent doxorubicin release with T_1 -weighted MRI contrast, permitting real-time tracking of drug deployment and yielding significant tumour regression in HeLa

models [212]. Collectively, these TME-responsive systems concentrate therapeutics at the disease site, enhance multimodal efficacy and minimise off-target toxicity, underscoring their promise for next-generation cervical-cancer management.

6. Conclusion

The reviewed studies highlight significant advancements in cervical cancer treatment through peptide-based therapeutics, specifically targeting angiogenesis and pain management—two crucial factors in enhancing patient quality of life. Peptides offer unique advantages, including high specificity, low toxicity, and ease of modification, making them valuable tools for overcoming therapeutic delivery challenges in cervical cancer. Anti-angiogenic peptides, particularly those targeting the VEGF/VEGFR pathway, show great potential in inhibiting tumour growth by disrupting vascular development. While VEGF overexpression is widely reported as a key driver of tumour angiogenesis, therapeutic strategies like bevacizumab, a monoclonal antibody targeting VEGF-A, have demonstrated clinical efficacy. However, monotherapy with bevacizumab is often accompanied by significant side effects, which can be mitigated when used in combination with chemotherapy, resulting in improved survival rates for patients with advanced cervical cancer [18].

In addition, cyclic peptides and CXC chemokine-derived peptides provide alternative mechanisms for inhibiting tumour vascularization by targeting multiple pro-angiogenic pathways. Despite their promise, these therapies are often limited by high costs, potential adverse effects (e.g., hypertension, thrombotic events), and restricted accessibility in low-resource settings [20]. Future research should focus on optimising peptide modifications and delivery systems to improve efficacy while minimising side effects and ensuring broader accessibility.

Peptide-based therapies represent a rapidly evolving frontier in cervical cancer treatment, offering novel approaches to managing both tumour progression and cancer-associated pain. Combining anti-angiogenic peptides targeting VEGF/VEGFR with innovative pain management strategies—such as TRPV1 antagonists and cannabidiol (CBD)—provides a promising alternative to opioids, reducing dependence on traditional analgesics while improving patient comfort. Additionally, peptide-functionalised delivery systems, including nanoparticles and cell-penetrating peptides (CPPs), highlight the potential of molecular design and nanotechnology in enhancing the precision and efficacy of therapeutic delivery.

Although preclinical studies have demonstrated promising outcomes, further research is essential to facilitate the clinical translation of peptide-based therapies. Future clinical trials should focus on optimizing dosage regimens, evaluating long-term safety, and assessing patient outcomes. Furthermore, the success of peptide-based treatments in cervical cancer may pave the way for broader applications in other HPV-related malignancies, ultimately improving survival rates and overall quality of life for patients worldwide.

7. Future perspectives

Innovative drug-delivery systems offer significant promise in addressing the complex pain associated with cervical cancer. Emerging technologies, such as nanotechnology-based pain relief, provide localized and efficient drug delivery while minimizing systemic side effects. Peptide-based therapies are also gaining traction, not only for their role in inhibiting angiogenesis but also for their potential in managing

cancer-related pain. By modulating nociceptor activity, peptide-based agents, such as TRPV1-targeting formulations like capsaicin-based topical treatments, offer long-lasting and localized pain relief. This marks a shift in cancer pain management, as peptide-based alternatives could reduce opioid dependence and mitigate their associated adverse effects [41]. Additionally, cannabinoid-based therapies, particularly cannabidiol (CBD), show potential in alleviating chemotherapy-induced neuropathy and pain. Studies suggest that the combination of cannabinoids and opioids may enhance analgesia while reducing opioid tolerance, highlighting a promising area for further research [15,87]. However, additional clinical trials are required to establish standardized dosing and administration protocols for CBD in cervical cancer pain management.

Advancements in cervical cancer immunotherapy also highlight the potential of peptide-based vaccines targeting HPV oncoproteins E6 and E7. For instance, E7-Q11, a self-assembled peptide vaccine, has demonstrated substantial tumour suppression in preclinical models, effectively stimulating cytotoxic T lymphocyte responses without the oncogenic risks associated with whole-virus vaccines [185]. The integration of flagellar nanofibers (FNs) as adjuvants in peptide vaccines further enhances immune responses, promoting robust antibody production and tumour inhibition in animal models [158]. Future research should explore the clinical translation of these vaccines, particularly evaluating intravaginal administration as a potentially superior delivery route for cervical cancer treatment.

Peptide-functionalised nanoparticles and cell-penetrating peptides (CPPs) also hold great promise for improving drug bioavailability and targeted therapy in cervical cancer. Studies have shown that nanoparticle-based drug delivery enhances drug retention, increases cellular uptake, and minimizes off-target effects, thereby improving therapeutic efficacy while reducing toxicity to healthy tissues [180]. Additionally, innovative applications of self-assembling peptides and proteins, such as albumin and ferritin, are being explored for RNA-based therapeutics, offering increased precision and stability in drug delivery for cancer treatment. As research advances, these novel approaches have the potential to transform cervical cancer management, paving the way for more effective, targeted, and patient-friendly therapeutic strategies.

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Authors' contribution

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Yahya Choonara; project administration, Samson Adeyemi and Yahya Choonara; funding acquisition, Yahya Choonara. All authors have read and agreed to the published version of the manuscript.

Conflicts of interests

Authors have no conflict of interest to declare.

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