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Phytochemical-Based Therapeutic Targeting of Notch and Related Signaling Pathways in Cervical Cancer: A Narrative Review

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Abstract: Natural products have long served as a vital reservoir of bioactive compounds in drug discovery, particularly in the field of oncology. In cervical cancer, where dysregulation of developmental and survival signaling pathways contributes to tumor progression, therapeutic resistance, and poor clinical outcomes, naturally derived compounds are increasingly being investigated as complementary and alternative targeted interventions. Among the critical molecular pathways influenced by natural products are those governing programmed cell death, including apoptosis and autophagy, as well as embryonic developmental signaling cascades such as the Notch, Wnt, and Hedgehog pathways. Aberrant activation of the Notch signaling pathway has been directly implicated in the proliferation of cervical cancer cells, epithelial–mesenchymal transition, and cancer stemness. This narrative review summarises and synthesizes recent preclinical and translational evidence on phytochemicals and other natural compounds targeting the Notch signaling pathway in cervical cancer. Particular emphasis is placed on their molecular mechanisms of Notch modulation, crosstalk with parallel oncogenic pathways, and their effects on tumor growth, invasion, and therapeutic sensitivity in cervical cancer models. Despite the historical and emerging promise of natural compounds, major limitations remain, including limited bioavailability, insufficient target selectivity, and a heavy reliance on *in vitro* and animal studies. Furthermore, a substantial translational gap persists between promising laboratory findings and clinical application, as only a small number of phytochemicals have progressed to well-designed clinical trials in cervical cancer. By critically analyzing current evidence and existing challenges, this review aims to provide a comprehensive, clinically relevant perspective on the potential of Notch-targeting phytochemicals to support the rational development of multi-targeted, translationally feasible therapeutic strategies for cervical cancer.

Keywords: cervical cancer; Notch signaling pathway; natural products.

1. Introduction

Cervical cancer is a malignant neoplasm arising from the cervix uteri and remains a major public health challenge worldwide, despite being largely preventable through effective vaccination and screening strategies [1]. According to the International Agency for Research on Cancer (IARC), cervical cancer continues to rank among the leading causes of cancer incidence and mortality in women globally, with a disproportionate burden in low- and middle-

income countries [2]. Persistent inequalities in access to human papillomavirus (HPV) vaccination, organized screening programs, and timely clinical management continue to hinder global disease control. For the purpose of this mechanistic review, it is important to emphasize that cervical cancer remains a clinically significant disease primarily because a substantial proportion of patients still present with locally advanced or recurrent disease, for which therapeutic outcomes remain suboptimal [3]. Cervical cancer is a multifactorial disease, with persistent infection by high-risk HPV types recognized as the principal etiological driver. However, HPV infection alone is insufficient to induce malignant transformation, and disease progression is strongly influenced by host, behavioral, and microenvironmental factors, including immune dysregulation, co-infections, hormonal exposure, smoking, and alterations in the vaginal microbiome [4].

From a clinical perspective, the current standard-of-care management of cervical cancer is stage-dependent and includes surgery for early-stage disease, concurrent chemoradiotherapy for locally advanced tumors, and systemic chemotherapy with or without targeted agents (such as anti-angiogenic therapy) or immune checkpoint inhibitors for recurrent or metastatic disease [5]. Despite these multimodal strategies, treatment resistance, therapy-related toxicity, and limited survival benefits in advanced disease remain major challenges [6]. These clinical limitations highlight an unmet need for novel molecularly targeted and biologically rational therapeutic approaches that can complement existing treatment modalities and improve long-term outcomes [7].

Natural products represent an important source of anticancer drug leads, and phytochemicals have been widely investigated for their ability to modulate multiple oncogenic pathways simultaneously [8]. Among the signaling networks implicated in cervical carcinogenesis, the Notch pathway plays a central regulatory role in cell fate determination, proliferation, epithelial–mesenchymal transition, cancer stem cell maintenance, and therapeutic resistance. Increasing experimental evidence indicates that dysregulated Notch signaling contributes directly to cervical cancer progression and poor treatment response [9]. However, despite the growing number of studies reporting Notch-modulating effects of phytochemicals, a coherent and critical synthesis of their molecular mechanisms, pathway crosstalk, and translational relevance in cervical cancer is currently lacking [10]. Therefore, the specific knowledge gap addressed by this review is the absence of an integrated, pathway-focused evaluation of natural compounds and phytochemicals targeting Notch signaling in cervical cancer, including their mechanistic actions, interactions with parallel oncogenic pathways, and their potential to enhance therapeutic efficacy [11].

2. Methodology

A systematic back-to-back literature search has been conducted on the Notch signaling pathway specifically pertaining to cervical cancer. This includes 3 separate database searches using PubMed, Scopus, and Web of Science, focusing on papers that use natural products (e.g., phytochemicals) for the treatment of cervical cancer and/or are somewhat relevant to Notch signaling and cervical cancer. Searches were limited to those published between 2022 and 2025 by using a combination of controlled vocabulary and free text, as well as using the appropriate combination of Boolean operators for those terms associated with cervical cancer (or carcinoma) and Notch signaling/pathway/receptors/ligands, along with additional terms that related to therapy, including anticancer, treatment, chemoresistance, and radioresistance. Studies included in the review had to use either cervical cancer models (cell lines, animals, or

patient-derived tissue specimens) and evaluate components of the Notch signaling pathway, and evaluate the biological and/or therapeutic effects of phytochemicals and/or natural products; the articles reviewed were limited to those published in English that were peer-reviewed. Excluded from the review were studies that focused on malignancies other than cervical cancer, were lacking mechanistic or pathway-level evidence, or were published as abstracts/conference proceedings/editorials/commentaries. Titles and abstracts were screened prior to full-text assessment, and data were extracted on compound type, experimental model, targeted Notch components, downstream molecular effects, pathway crosstalk, and reported therapeutic or sensitizing outcomes. To reduce selection bias, multiple databases and predefined eligibility criteria were applied; however, potential publication bias and heterogeneity in experimental design, compound purity, and dosing could not be fully eliminated. Owing to the diversity of study designs and outcome measures, evidence was synthesized using a narrative and mechanistic integration approach rather than quantitative meta-analysis. Publication bias and heterogeneity in experimental design, compound purity, and dosing could not be fully eliminated. Owing to the diversity of study designs and outcome measures, evidence was synthesized using a narrative and mechanistic integration approach rather than quantitative meta-analysis.

3. Notch: Fundamental Concepts and Underlying Mechanisms

The Notch signaling pathway is a highly conserved cell–cell communication system that regulates fundamental processes, including proliferation, survival, and differentiation [12]. Although both canonical and non-canonical Notch signaling are frequently deregulated in cancer, their functional relevance in cervical cancer appears highly context-dependent. In normal cervical epithelium and in early premalignant lesions, Notch activity has been associated with epithelial differentiation and growth control, supporting a predominantly tumor-suppressive role. In contrast, during malignant progression, particularly in high-grade cervical intraepithelial neoplasia and invasive carcinoma, Notch signaling is commonly reprogrammed to an oncogenic function, largely driven by persistent human papillomavirus (HPV) infection. Mechanistically, activation of Notch receptors by their ligands leads to proteolytic release of the Notch intracellular domain (NICD), which regulates gene expression through either canonical CSL-dependent transcriptional complexes or alternative, non-canonical intracellular effectors [13–17].

Importantly, in cervical cancer, this pathway is not uniformly oncogenic. Instead, the dual behavior of Notch reflects disease stage and cellular context. Experimental and clinical observations indicate that HPV oncoproteins E6 and E7 reshape Notch signaling outputs, shifting the pathway from differentiation-associated programs towards transcriptional networks that promote proliferation, stem-like properties, and resistance to apoptosis. In parallel, non-canonical Notch signaling has been shown to activate oncogenic pathways such as PI3K/Akt in HPV-positive cervical cancer cells, bypassing classical CSL-mediated regulation and further reinforcing tumor-promoting activity [18]. These findings suggest that while canonical Notch signaling may restrain early epithelial transformation, both canonical and non-canonical branches can be co-opted at later stages to support tumor progression. Collectively, this stage-dependent and context-specific switch from tumor suppression to oncogenic signaling underscores the complexity of Notch deregulation in cervical carcinoma and highlights the need for stratified therapeutic approaches [19]. Rather than uniformly suppressing Notch activity, future interventions should consider tumor stage, HPV status, and

patterns of pathway activation when targeting Notch signaling within the broader network of genetic, epigenetic, and immune-related alterations that drive cervical cancer development and progression (Figure 1).

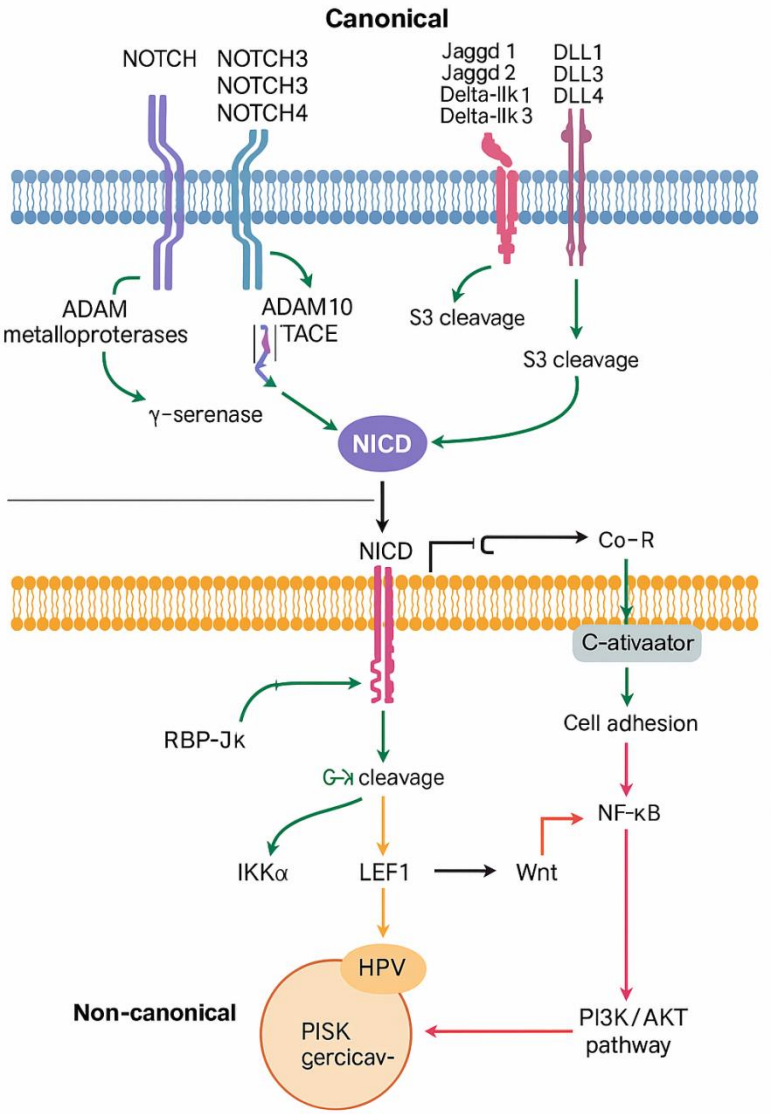

Figure 1. Graphical illustration of the molecular events in the Notch pathway.

Notch receptor is initially synthesized as a single polypeptide precursor, which undergoes proteolytic processing in the trans-Golgi network by Furin-like convertases, resulting in the first cleavage event (S1). This cleavage yields a heterodimeric receptor complex, comprising a non-covalently associated extracellular and transmembrane-intracellular subunit. The mature receptor, in its heterodimeric form, is directed to the plasma membrane, where it becomes competent to interact with ligands presented on the surface of adjacent cells. Upon ligand binding, typically with members of the Delta-like or Jagged family on neighboring cells, the receptor undergoes a second cleavage (S2) within its extracellular juxtamembrane domain [20]. This event is catalyzed by the metalloprotease TACE, also known as ADAM17. Subsequent to cleavage, the extracellular portion of Notch is trans-endocytosed into the adjacent ligand-presenting cell. This ligand-induced endocytosis is regulated by E3 ubiquitin ligases, such as Neuralized and Mindbomb, which ubiquitinate the ligand and promote endocytic internalization. Following S2 cleavage, the receptor undergoes a third proteolytic event (S3) within its transmembrane domain, mediated by the γ-secretase complex

[21]. This multi-subunit protease complex consists of presenilin (PS), nicastrin, anterior pharynx-defective 1 (APH-1), and presenilin enhancer 2 (PEN-2). The S3 cleavage liberates the Notch intracellular domain (NICD), which subsequently translocates into the nucleus [22]. This interaction displaces co-repressor complexes (CoR) and facilitates the recruitment of co-activators (CoA), such as Mastermind-like (MAML) proteins. The resulting transcriptional activation complex initiates the induction of Notch-regulated gene expression, thereby modulating cellular processes such as differentiation, proliferation, and apoptosis [23].

4. Pathway-specific Targets of Notch Signaling in Cervical Cancer Advancement

A key viral oncoprotein, E6, interferes with epithelial homeostasis and initiates deregulation of the differentiation program through direct modulation of host regulatory pathways, including the Notch signaling cascade, which governs stem cell maintenance, lineage commitment, and terminal differentiation [24]. In cervical keratinocytes and cervical cancer–derived models, HPV16 E6 suppresses NOTCH1 transcription primarily through proteasomal degradation of p53, a known positive regulator of NOTCH1 expression, thereby attenuating Notch-driven differentiation programs at early stages of infection. This E6–p53–NOTCH1 regulatory axis has been directly demonstrated in HPV-positive cervical epithelial models. In that loss, of p53 activity results in reduced NOTCH1 expression, impaired squamous differentiation, and prolonged maintenance of a proliferative basal-like state [25]. In parallel, HPV16 E7 functionally cooperates with E6 by deregulating the Rb/E2F pathway, thereby indirectly reshaping Notch pathway output by sustaining cell-cycle progression and preventing differentiation signals normally reinforced by Notch activation [26]. Cervical cancer–specific studies further indicate that E7 expression alters the transcriptional responsiveness of Notch target genes, including HES1 and HEY1, thereby uncoupling Notch receptor activation from its canonical differentiation-promoting transcriptional program [27]. Importantly, this viral suppression of Notch activity appears to be stage dependent in cervical carcinogenesis. While E6/E7-mediated repression of NOTCH1 facilitates early persistence of HPV-infected basal cells and blocks terminal differentiation, reactivation or functional repurposing of Notch signaling has been observed in advanced cervical lesions and carcinomas, where NOTCH1 and JAG1 are frequently upregulated and contribute to tumor cell survival, migration, and EMT [28]. This dual behavior supports a cervical cancer–specific model in which HPV oncoproteins initially antagonize Notch-driven differentiation, but later permit or even exploit Notch signaling to promote malignant progression [29].

Dysregulation of these developmental signaling pathways-through genetic mutations, copy number alterations, or epigenetic modifications-leads to the erosion of barriers against dedifferentiation, facilitating the emergence of cancer stem-like cells (CSCs) [30]. These CSCs contribute to intratumoral heterogeneity, tumor progression, chemoresistance, and metastatic dissemination [31]. The Notch signaling pathway, which plays context-dependent roles in various epithelial malignancies, has been implicated in both tumor-suppressive and oncogenic functions during cervical cancer development [32,33]. While Notch activity is essential for promoting differentiation during early stages of cervical epithelial transformation, it may later cooperate with oncogenic stimuli to promote malignant progression [34]. In primary human keratinocytes expressing HPV16 E6 and E7 oncoproteins, activated NOTCH1 enhances cellular transformation, indicating a pro-oncogenic role under specific genetic contexts [35]. Clinical and transcriptomic studies further support the involvement of the Notch pathway in cervical carcinogenesis. Elevated expression levels of NOTCH1 and its ligand JAG1 have been

associated with advanced tumor stage and poor clinical outcome in cervical cancer cohorts [36]. In addition, the DARS-AS1/miR-628-5p/JAG1 regulatory axis has been shown to promote cervical cancer cell proliferation by directly activating Notch signaling [37], providing cervical cancer–specific evidence that viral–host reprogramming of upstream regulators converges on Notch pathway activation. Functionally, Notch signaling enables resistance to anoikis, fosters cellular migration, and triggers epithelial–mesenchymal transition (EMT), particularly when HPV E6/E7 oncoproteins are co-expressed with AKT pathway activation [38]. Data from The Cancer Genome Atlas revealed that approximately 15% of primary cervical squamous cell carcinomas harbor loss-of-function alterations in FBXW7, a negative regulator of NICD degradation, thereby favoring sustained Notch activation [39]. Collectively, these cervical cancer–specific molecular studies support a model in which HPV16 E6 and E7 initially suppress differentiation-associated Notch activity to promote viral persistence and basal cell expansion, whereas subsequent genetic and epigenetic alterations-such as FBXW7 loss and JAG1 upregulation-enable reactivation and functional rewiring of Notch signaling to drive invasion, EMT, and tumor progression [40-46].

5. Integration of Notch Signaling with Other Oncogenic Cascades

In human malignancies, the Notch signaling pathway exhibits context-dependent functionality, acting either as a tumor suppressor or an oncogenic driver, depending on the tissue type, cellular microenvironment, and disease stage. Upon activation, the Notch signaling cascade induces the transcription of multiple downstream effector molecules that mediate bidirectional intercellular communication among tumor cells, stromal fibroblasts, and endothelial cells, thereby shaping the tumor microenvironment (TME) and influencing tumor dynamics [47]. In cervical cancer, available evidence indicates that aberrant activation of Notch signaling-particularly Notch1 and Notch3-contributes to tumor growth, invasion, angiogenesis, and maintenance of stem-like phenotypes in commonly used cervical cancer models, including HPV-positive and HPV-negative cell lines and xenograft systems. However, compared with breast, colorectal, and glioma models, mechanistic studies dissecting Notch-centered signaling crosstalk in cervical cancer remain limited in number and depth. Given its central regulatory role, Notch signaling is known to intersect and crosstalk with several other oncogenic and developmental signaling pathways, amplifying or modulating their biological outcomes [48]. In addition, Notch signaling interfaces with inflammatory and survival pathways, notably nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and the PI3K/Akt/mTOR axis, forming a complex signaling network with widespread implications for tumor biology [49].

In the context of cervical cancer, functional interactions between Notch and the NF-κB and PI3K/Akt pathways have been reported to regulate cell survival, migration, and therapy response. Nevertheless, most of the detailed molecular circuitry describing how NICD directly cooperates with NF-κB subunits or PI3K/Akt downstream effectors has been derived predominantly from non-gynecological tumor models. Consequently, the precise molecular nodes of Notch–NF-κB and Notch–PI3K/Akt crosstalk in cervical carcinoma remain incompletely characterized and are often inferred from other cancer types rather than directly demonstrated in cervical tumor tissues. The molecular crosstalk between Notch and these pathways governs critical oncogenic processes, including cell proliferation, epithelial–mesenchymal transition (EMT), migration, invasion, angiogenesis, metastatic dissemination, and cancer stem cell (CSC) self-renewal. These multifaceted interactions underscore the

therapeutic potential of targeting Notch signaling, either alone or in combination with other pathway-specific inhibitors, as a rational strategy in anticancer drug development [50]. Importantly, while these biological consequences are well established across multiple tumor entities, direct experimental validation linking Notch-driven crosstalk to EMT, CSC maintenance, and metastatic competence in cervical cancer remains comparatively scarce and largely restricted to in vitro systems, limiting firm conclusions regarding in vivo relevance. From a developmental biology perspective, Notch signaling is intimately involved in embryogenesis, where it operates synergistically with other evolutionarily conserved pathways, including Wnt and Hedgehog, to orchestrate organogenesis and tissue patterning. The integration of Notch with Wnt and Hedgehog signaling governs key processes such as stem cell maintenance, cell fate determination, and differentiation, which are often dysregulated in oncogenesis [51].

In cervical cancer, aberrant activation of Wnt/β-catenin and Hedgehog signaling has been independently associated with tumor progression and resistance to therapy; however, direct mechanistic studies demonstrating coordinated or reciprocal regulation between Notch and these developmental pathways in cervical tumors remain limited. Most available evidence for Notch–Wnt and Notch–Hedgehog cooperation is extrapolated from gastrointestinal, neural, and breast cancer models. Importantly, these signaling axes are frequently co-opted during tumorigenesis, where aberrant activation leads to dysplastic transformation, tumor heterogeneity, and therapy resistance. Understanding the intricate molecular interdependencies and context-specific functional outcomes of Notch crosstalk with other oncogenic pathways offers promising avenues for targeted therapeutic intervention [52]. Taken together, although Notch-centered signaling crosstalk with NF-κB, PI3K/Akt/mTOR, Wnt, and Hedgehog pathways is well documented in diverse malignancies, its functional relevance in cervical cancer has not yet been comprehensively validated and remains an important knowledge gap. Dedicated studies employing cervical cancer patient-derived samples, three-dimensional culture systems, and in vivo models are required to define whether the crosstalk mechanisms described in other tumor types are conserved in cervical carcinoma.

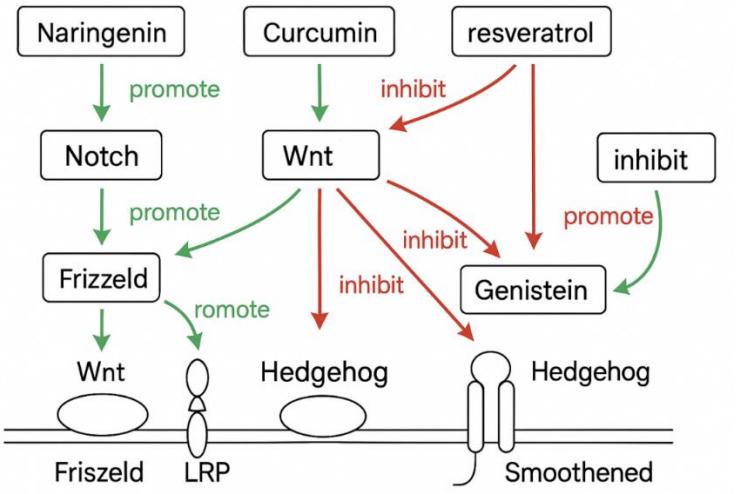

Figure 2. An illustrative schematic representation demonstrates how phytochemicals may modulate the crosstalk between the signaling pathways of Wnt/Hedgehog and Notch. Within the figure, the term "promote" denotes the potential of specific phytochemicals to upregulate the expression or enhance the activity of target proteins within these pathways. Conversely, the term "inhibit" indicates the ability of these compounds to downregulate protein expression or suppress the functional activity of the respective signaling components.

Specifically, this review focuses on how phytochemicals may modulate Notch-centered signaling networks in cervical cancer, while critically distinguishing between mechanisms demonstrated directly in cervical tumor models and those extrapolated from other malignancies. By dissecting these context-dependent interactions, we highlight the translational potential and current limitations of phytochemical-based strategies to attenuate tumor progression and overcome therapeutic resistance in cervical cancer, as illustrated in Figure 2.

5.1. Wnt signaling pathway.

The Wnt signaling pathway is a pivotal developmental cascade that regulates essential biological processes, including cellular proliferation, differentiation, epithelial–mesenchymal interactions, and the maintenance of tissue homeostasis, particularly during embryonic development [53]. It is broadly classified into two major branches: the canonical Wnt/β-catenin pathway and non-canonical pathways, such as the Wnt/Ca^{2+} axis, which modulates intracellular calcium signaling and cytoskeletal organization [54]. Dysregulated Wnt activity is strongly associated with tumorigenesis across diverse malignancies, making it an important therapeutic target in cancer research [55]. Increasing evidence also highlights a close functional crosstalk between the Wnt and Notch signaling pathways. For example, overexpression of Notch ligands has been shown to counteract Wnt1-mediated transformation in human mammary epithelial cells, underscoring a regulatory interplay between these pathways during tumor development [56]. In addition, ESC-3, a recently identified cytotoxic compound, exerts anticancer activity by concurrently inhibiting Notch and Wnt/β-catenin signaling, thereby promoting apoptosis and suppressing tumor growth in ovarian cancer xenograft models [57], while emodin, a natural anthraquinone derivative, suppresses Wnt activity by downregulating active β-catenin in glioma stem cells, impairing their self-renewal and oncogenic capacity [58]. Mechanistically, β-catenin has been implicated in the activation of the Notch pathway through transcriptional upregulation of the Notch ligand Jagged1 [59]. Consistently, Bruceine D, a quassinoid isolated from Brucea javanica (L.) Merr. inhibits Jagged1 expression, an effect that is enhanced by β-catenin silencing and reversed by β-catenin overexpression, whereas Jagged1 knockdown does not alter β-catenin levels, indicating a unidirectional regulatory axis from β-catenin to Jagged1 [60]. Aberrant activation of Wnt signaling promotes nuclear accumulation of β-catenin, where it functions as a co-transcription factor to induce oncogene expression and drive tumor progression [61]. In this context, several natural compounds, including resveratrol, 8,12-dimethoxysanguinarine, and emodin, have demonstrated the capacity to inhibit Notch activity, while resveratrol in particular suppresses ovarian cancer cell proliferation by concomitantly downregulating β-catenin and Hes1, reflecting dual inhibition of both Wnt and Notch signaling components. Collectively, these findings highlight β-catenin as a central molecular nexus mediating Wnt–Notch crosstalk and support its therapeutic potential for disrupting interconnected oncogenic signaling networks in cancer [62].

5.2. Hedgehog signaling pathway.

The Hedgehog (Hh) signaling pathway is a pivotal developmental cascade that governs key biological processes, including embryogenesis, tissue patterning, epithelial-mesenchymal polarity, regeneration, and tumorigenesis [63]. The core components of the Hh pathway include Hedgehog ligands (Sonic, Indian, and Desert Hedgehog); Patched (PTCH1/PTCH2), a 12-

transmembrane receptor that functions as a negative regulator; Smoothened (SMO), a G-protein-coupled receptor-like signal transducer; and cytoplasmic mediators, which play a key role in gonadal development [64]. Emerging evidence has revealed intricate crosstalk between the Hedgehog and Notch signaling pathways, in which Notch regulates components of Hh signaling. Specifically, Notch downstream effectors, including Hes1 and CSL (CBF1/RBP-Jκ/Suppressor of Hairless/Lag-1), modulate the nuclear translocation and transcriptional activity of Gli proteins, thereby impacting Hh-mediated oncogenic processes. The fungal metabolite physciosporin, derived from Phomopsis granulata, significantly downregulated Gli, Hes1, and CSL transcriptional activity in human colon CSC221 cancer stem cells, and suppressed spheroid formation in cells overexpressing Gli1/2 or DeltaEN1, a truncated active form of Notch1. However, this suppressive effect was not observed when both Gli1/2 and DeltaEN1 were co-overexpressed, suggesting that physciosporin targets the oncogenic synergy between the Sonic Hedgehog and Notch pathways to reduce cancer stemness [65].

Additionally, NUMB, an endocytic adaptor protein and well-established negative regulator of Notch, binds directly to the Notch intracellular domain (NICD) to prevent transcriptional activation of downstream target genes. NUMB also inhibits Hedgehog signaling by targeting Gli1 for proteasomal degradation via the E3 ubiquitin ligase Itch, underscoring its dual role in both pathways [66]. Interestingly, quercetin, a flavonoid with anticancer properties, reduces tumor progression by inhibiting NUMB activation and Hedgehog pathway signaling, indicating its therapeutic relevance and highlighting NUMB as a potential biomarker for cancer. Conversely, Hedgehog signaling has been shown to regulate the Notch pathway, particularly by modulating NICD and Hes1 expression. For instance, Hedgehog activation induces Hes1 transcription in Hep2 cells, a human epithelial carcinoma line; however, this induction is attenuated by epigallocatechin gallate (EGCG), a polyphenolic compound that acts as a NICD inhibitor [67]. This suggests that Hedgehog-mediated upregulation of Hes1 may occur through NICD stabilization or enhancement of NICD nuclear activity. Furthermore, cordycepin (3′-deoxyadenosine), a nucleoside analog known for its anti-inflammatory, antioxidant, and antitumor effects, has been shown to downregulate Gli transcriptional activity, resulting in decreased expression of Notch1, Notch3, Jagged1, and Hes1 in MDA-MB-231 triple-negative breast cancer cells. Notably, Gli knockout abrogated the effects of cordycepin on apoptosis, epithelial-mesenchymal transition (EMT), and Notch signaling, indicating that cordycepin-mediated suppression of Notch is Gli-dependent [68].

Moreover, studies have reported that the Notch ligand Jagged2 can be transcriptionally induced by Hedgehog signaling during tumorigenesis. In support of this, the Hedgehog pathway inhibitor cyclopamine has been shown to suppress the expression of Notch1–3, Jagged2, and Delta-like ligand 1 (DLL1) in odontogenic keratocytes, highlighting the role of Hh signaling in modulating the Notch axis during carcinogenesis [69]. In conclusion, the post-translational modification and nuclear translocation of Gli transcription factors, as well as the ubiquitination and degradation of regulatory proteins such as NUMB, are key mechanisms underpinning the bidirectional crosstalk between the Hedgehog and Notch signaling pathways. Targeting these molecular interactions may provide promising therapeutic strategies for malignancies characterized by aberrant activity in both pathways [70].

6. Natural Compounds Targeting Notch in Cancer

Accumulating evidence demonstrates that naturally occurring compounds exhibit significant anticancer potential. Bioactive compounds exert significant anticancer effects by

modulating the Notch signaling cascade. These effects are mediated via inhibition of Notch receptor activation, suppression of γ-secretase complex activity, disruption of the Notch transcriptional activation complex, and downregulation of Notch downstream target genes. Compared with other compounds, cucurbitacins and oleandrin consistently exhibit nanomolar activity, ranking among the most potent natural inhibitors of Notch-associated tumor phenotypes. In contrast, polyphenols such as EGCG, resveratrol, and curcumin generally act in the micromolar range, indicating lower intrinsic potency but broader multi-target activity and superior safety profiles, which may be advantageous for long-term or combinatorial therapeutic strategies.

6.1. Plant-derived phytochemicals influence Notch signaling regulation.

6.1.1. Gamma-secretase inhibitors.

The γ-secretase complex, composed of presenilin proteins (PSEN1/PSEN2), nicastrin (NCSTN), anterior pharynx-defective 1 (APH-1), and presenilin enhancer 2 (PEN-2), plays a central role in mediating the proteolytic processing of Notch receptors, ultimately releasing the Notch intracellular domain (NICD). Pharmacological blockade of γ-secretase has been shown to exert strong antitumor effects across multiple cancer types, including colorectal, lung, ovarian cancers, and melanoma. However, clinical applications of GSIs have been significantly hampered due to dose-limiting toxicities-primarily gastrointestinal complications, dermatological reactions, and severe diarrhea-limiting their therapeutic utility in targeting Notch signaling. In colon cancer models, Cucurbitacin B and Cucurbitacin I suppress NICD formation and cell viability at nanomolar concentrations (approximately 20–100 nM), indicating substantially higher potency than most dietary polyphenols, which typically require micromolar concentrations to achieve comparable inhibition of Notch pathway activity.

Consequently, alternative approaches for γ-secretase modulation are being actively explored. Natural compounds such as Cucurbitacin B and Cucurbitacin I have been shown to downregulate the expression of Notch receptors and ligands, inhibit γ-secretase enzymatic activity, and suppress NICD generation. These effects culminate in the repression of Notch1 signaling and its downstream gene expression, thereby attenuating tumor progression in colon cancer models [71]. Notably, combining quercetin with γ-secretase inhibitors or ionizing radiation has been shown to potentiate anticancer efficacy, suggesting that quercetin may serve as an adjuvant to mitigate the adverse effects associated with GSIs and enhance their therapeutic index [72].

6.1.2. Inhibitors of the Notch transcriptional activation complex.

The interaction between the Notch intracellular domain (NICD) and CSL (CBF1/Suppressor of Hairless/Lag-1) serves as a central regulatory event in the activation of downstream gene transcription within the canonical Notch signaling pathway. This NICD–CSL complex facilitates the displacement of transcriptional co-repressors and the subsequent recruitment of co-activators, such as members of the Mastermind-like (MAML) protein family, ultimately promoting the transcription of Notch target genes implicated in tumorigenesis. Several phytochemicals have demonstrated the capacity to interfere with this transcriptional activation machinery, exerting antitumor effects by disrupting the NICD–CSL complex, suppressing co-activator function, or enhancing co-repressor recruitment. For example, silybin,

a flavonolignan derived from Silybum marianum, suppresses Notch signaling by promoting apoptosis and reducing NICD activity in hepatocellular carcinoma cells [73].

In carcinoid tumors, it inhibits ASCL1, a proneural transcription factor associated with Notch signaling [74]. Furthermore, in glioma cells, resveratrol enhances the recruitment of the transcriptional co-repressor HDAC1, thereby further attenuating Notch-mediated gene expression. Collectively, these findings emphasise the therapeutic relevance of disrupting NICD–CSL–co-activator complexes and promoting co-repressor-mediated transcriptional repression as a strategic approach to inhibit aberrant Notch signaling in cancer.

6.1.3. Notch downstream target genes inhibitors.

The terminal phase of canonical Notch signaling involves the transcriptional activation of downstream target genes, predominantly those belonging to the Hairy and Enhancer of Split (Hes) and Hes-related with YRPW motif (Hey) gene families, which function as basic helix-loop-helix (bHLH) transcriptional repressors. Among these, Hes1 has been extensively characterized for its oncogenic role, in which its upregulation reinforces Notch signaling, promoting cellular proliferation and suppressing apoptosis. A growing body of evidence highlights the therapeutic potential of natural compounds in modulating the expression of Notch downstream effectors. Notably, oleandrin and cowanin have been reported to suppress Hes1 and Hes5 expression significantly, thereby impeding the progression of T-cell acute lymphoblastic leukemia (T-ALL) [75]. This suggests that targeted inhibition of Hes/Hey gene families by bioactive phytochemicals may represent a promising strategy in the development of Notch-targeted anticancer therapies.

6.2. Natural phytochemicals were shown to downregulate Notch pathway activation.

The Notch signaling pathway is initiated upon interaction between the extracellular domain of Notch receptors (Notch1–Notch4) and their corresponding ligands-Delta-like (DLL1, DLL3, DLL4) and Jagged (Jagged1, Jagged2)-which are typically expressed on adjacent signal-sending cells [76]. This ligand-receptor interaction activates a proteolytic cascade, ultimately releasing the Notch intracellular domain (NICD), which translocates to the nucleus and modulates transcription of downstream target genes. Notch signaling plays a pivotal role in determining cell fate, proliferation, differentiation, and apoptosis in both physiological and pathological contexts, including cancer (Table 1) [77].

6.2.1. EGCG.

EGCG, the predominant catechin in green tea, has demonstrated inhibitory effects on Notch signaling by downregulating Notch receptor expression in various malignancies. Specifically, EGCG suppresses Notch1 expression in oral squamous cell carcinoma, colorectal cancer, and chemoresistant models and Notch2 in ovarian cancer [78]. In a murine tongue cancer model, EGCG attenuated Notch1 activation, resulting in enhanced apoptosis and reduced cellular proliferation. Furthermore, EGCG has been shown to downregulate cleaved Notch1 in 5-fluorouracil (5-FU)-resistant colorectal cancer cells, indicating its potential to reverse chemoresistance by modulating Notch pathway components. However, current literature lacks evidence for EGCG's regulatory effects on Notch ligands. In oral squamous cell carcinoma and colorectal cancer cell models, EGCG reduces Notch1 and cleaved Notch1

levels at concentrations of approximately 20–60 μM, which coincide with its growth-inhibitory and pro-apoptotic activity.

6.2.2. Resveratrol.

Resveratrol, a polyphenolic stilbene found in grapes, berries, and peanuts, exhibits antitumor properties through multiple molecular mechanisms. It inhibits cell cycle progression, induces apoptosis and differentiation, and suppresses autophagy and metastasis [79]. Resveratrol downregulates the expression of several Notch receptors (Notch1, Notch2, Notch4) and ligands (DLL1, DLL4, Jagged1), thereby attenuating Notch pathway activation in diverse tumor models. However, Notch signaling appears dispensable for resveratrol-induced differentiation and apoptosis in certain medulloblastoma subtypes. Resveratrol-mediated suppression of Notch receptors and ligands is typically observed at 30–100 μM *in vitro***,** consistent with its reported IC_{50} values for cell viability and differentiation responses in glioma, colorectal, and medulloblastoma models. Notably, combinatory regimens combining resveratrol with γ-secretase inhibitors (GSIs) exhibit enhanced efficacy in suppressing autophagy, underscoring their synergistic potential in targeted therapy.

6.2.3. Curcumin.

Curcumin (diferuloylmethane), a bioactive compound from Curcuma longa, exerts antitumor effects through multifaceted mechanisms, including suppression of Notch signaling. It significantly downregulates Notch1, Notch3, and Jagged1, thereby inhibiting cell self-renewal, migration, and invasion, and inducing DNA damage-mediated apoptosis [80]. Curcumin also modulates microRNA expression, upregulating tumor-suppressive miR-222-3p and miR-34a, and downregulating oncogenic miR-27a. Curcumin-induced downregulation of Notch1/Notch3 and Jagged1, as well as inhibition of γ-secretase activity, is commonly detected at 10–30 μM, which corresponds to its reported IC_{50} range for growth inhibition in osteosarcoma and colorectal cancer cells. Moreover, it inhibits the activity of the γ-secretase complex. In osteosarcoma cells, Notch1 overexpression abrogated curcumin's inhibitory effects, indicating the centrality of Notch1 in its mechanism of action. Interestingly, in prostate cancer cells (DU145), curcumin did not alter Notch1 expression but impaired NICD's DNA-binding activity, suggesting a transcriptional interference mechanism [81].

6.2.4. Silybin.

Silybin (silibinin), a flavonolignan from *Silybum marianum* (milk thistle), is well known for its anti-inflammatory and hepatoprotective effects. It suppresses NICD activity and downregulates Jagged1 expression, thereby impeding Notch activation in hepatocellular carcinoma. The attenuation of its anticancer activity by recombinant Jagged1 reinforces the significance of ligand-targeting in therapy. The therapeutic potency of silybin is enhanced when combined with Notch inhibitors such as DAPT or Notch1 siRNA, underscoring its potential as an adjuvant in Notch-targeted strategies.

Overall, available quantitative data demonstrate that natural Notch-modulating compounds span a wide potency range, from low nanomolar (cucurbitacins, oleandrin) to mid micromolar (EGCG, curcumin, resveratrol, and silybin). This highlights a clear trade-off between potency and modulation of pleiotropic signaling, and supports the strategic use of lower-potency phytochemicals primarily as sensitizers or combinatorial agents rather than as

standalone Notch inhibitors. Aberrant Notch signaling is implicated in various hematologic neoplasms such as chronic lymphocytic leukemia (CLL), T-cell acute lymphoblastic leukemia (T-ALL), and non-Hodgkin lymphomas [82]. In lymphopoiesis, Notch1 is essential for T-cell lineage commitment, and its aberrant activation in CLL renders it a viable therapeutic target. Notably, suppression of Notch1/2 sensitizes CLL cells to chemotherapeutic agents like fludarabine and venetoclax. However, in T-ALL, Notch1 mutations often occur later in clonal evolution, potentially reducing the efficacy of Notch1-targeted therapies. Additional natural compounds have demonstrated efficacy in modulating Notch signaling by suppressing receptor and ligand activity. These include emodin, carvacrol, withaferin A, and quercetin [83]. These phytochemicals suppress Notch pathway activation, thereby reducing cellular aggressiveness and enhancing therapeutic response across various tumor types (Table 1).

Table 1. Natural compounds targeting the Notch signaling pathway in cancer.

Phytochemical	Chemical class	Notch-related mechanism / molecular targets	Other relevant anticancer actions/crosstalk	Notes/evidence (cancer types/comments)	Evidence level	References
Curcumin	Polyphenol (diarylheptanoid)	↓ Notch 1 receptor, ↓ Jagged 1 ligand, ↓ γ-secretase components → ↓ NICD-1 and downstream transcription	Suppresses MMP-2/MMP-9, reduces proliferation, synergizes with chemotherapy, modulates NF-κB, and induces apoptosis	Broad evidence across cancer types	Cell line + animal model	[84]
Epigallocatechin-3-gallate (EGCG)	Polyphenol (catechin)	↓ Notch 1 (and in some reports Notch 2), ↓ NICD, ↓ downstream targets (e.g., Hes1)	Induces apoptosis, reduces CSC phenotype, inhibits angiogenesis and EMT, suppresses VEGF and MMPs	Neuroblastoma, head and neck, colon, and tongue carcinoma models	Cell line	[85]
Resveratrol	Stilbene	Downregulates Notch receptors and ligands, reduces NICD and downstream activation; possible epigenetic modulation	Cell-cycle arrest, apoptosis; STAT3 and Wnt crosstalk	Various cancers; some cervical cancer reports	Cell line	[86]
Genistein	Isoflavone	Suppresses Notch 1 protein expression and downstream signaling	Cell-cycle modulation, apoptosis, and possible anti-angiogenic effects	Breast, colon, neuroblastoma, and other models; limited cervical cancer data	Cell line	[87]
Quercetin	Flavonoid	Downregulates Notch receptors, ligands, γ-secretase complex, and NICD	Antioxidant, anti-inflammatory, apoptosis induction, therapy sensitization	Colon CSCs and other tumor models; limited cervical cancer data	Cell line	[88]
Silibinin (Silybin)	Flavonolignan	Inhibits NICD-mediated transcription; reduces N1ICD and RBP-Jκ activity	Induces apoptosis, inhibits proliferation, and affects ERK/AKT signaling	Hepatocellular carcinoma models	Cell line	[89]
Baicalein	Flavonoid (flavone)	↓ Notch 1, Hes 1, and Hes 5; reduced proliferation; apoptosis induction	Possible involvement of the GSK-3β pathway	Cervical cancer-specific models	Cell line (cervical cancer)	[90]
Cucurbitacin B / I	Triterpenoid	Downregulation of Notch receptors, ligands, γ-secretase components, and Hes 1; reduced sphere/colony formation	Induces apoptosis, inhibits proliferation, suppresses CSC-like traits	Mainly colon cancer and tumor sphere models	Cell line	[91]

Phytochemical	Chemical class	Notch-related mechanism / molecular targets	Other relevant anticancer actions/crosstalk	Notes/evidence (cancer types/comments)	Evidence level	References
Diallyl trisulfide (DATS)	Organosulfur compound	↓ Notch 1 and Jagged 1 expression; reduced Notch activation	Antiproliferative, pro-apoptotic, anti-inflammatory	Prostate and other *in vitro* models	Cell line	[92]
Berberine	Alkaloid	Interferes with Notch activity and downstream gene expression	Antiproliferative, pro-apoptotic, anti-inflammatory	Colon cancer and leukemia models	Cell line	[93]
Xanthohumol	Prenylated chalcone (polyphenol)	↓ Notch 1, Hes 1, and survivin expression	Induces apoptosis, suppresses proliferation	Pancreatic cancer cell models	Cell line	[94]
Carvacrol	Monoterpenoid phenol	↓ Notch 1 receptor and Jagged 1 ligand in PC-3 cells	Pro-apoptotic, anti-inflammatory, anti-invasive	Prostate cancer *in vitro* model	Cell line	[95]
Withaferin A	Withanolide (steroidal lactone / terpenoid-derived)	Inhibits Notch 1 signaling; suppresses Akt, NF-κB and Bcl-2	JNK activation, mTOR inhibition, antiproliferative	Colon cancer cell models	Cell line	[96]
Wogonin	Flavonoid (flavone)	Suppresses Notch receptors and downstream activation	Anti-inflammatory, pro-apoptotic, therapy sensitization	Mostly non-cervical cancer models	Cell line	[97]
Cucurbitacin E	Triterpenoid	Downregulates Notch receptors, ligands, γ-secretase, and Hes 1; reduced sphere formation	Induces apoptosis, inhibits proliferation, suppresses CSC maintenance	Mainly colon and other cancer cell models	Cell line	[98]
Sanguinarine	Alkaloid	Potential Notch inhibitor (review-based)	Anticancer, anti-inflammatory, pro-apoptotic	General cancer cell models	Cell line	[99]
Glycyrrhizin	Triterpene glycoside (saponin)	Suggested Notch modulation in reviews	Anti-inflammatory, antioxidant, anticancer	Correlative or in-silico evidence	In silico / review only	[100]
Ellagic acid	Polyphenol (tannin)	Reported downregulation of Notch components	Antioxidant, anti-inflammatory, pro-apoptotic	Mostly non-cervical cancer cell studies	Cell line	[101]

7. Comparison of Different Notch-targeting Approaches in Cervical Cancer

In the context of HPV-driven cervical carcinoma, the comparative strategies summarized in Table 2 illustrate that therapeutic targeting of the Notch pathway is not biologically equivalent across intervention levels and is likely to yield substantially different clinical consequences. Receptor- and ligand-directed antibodies offer relatively high molecular specificity; however, their activity is intrinsically constrained by receptor and ligand redundancy within cervical tumors and by the coexistence of both tumor-intrinsic and microenvironment-driven Notch signaling. In particular, ligand-directed approaches, while conceptually attractive for modulating tumor–stroma and angiogenic interactions, remain limited by well-documented vascular liabilities and by compensatory activation of alternative ligands, which is especially problematic in highly adaptive HPV-driven tumor ecosystems. By contrast, γ-secretase inhibitors broadly suppress Notch activation, thereby circumventing receptor-ligand redundancy. Nevertheless, their limited clinical success to date, together with dose-limiting gastrointestinal and endocrine toxicities and pharmacokinetic instability, argue against their unselected application in cervical cancer. Importantly, because HPV oncoproteins primarily reprogrammed downstream transcriptional outputs of Notch rather than merely increasing receptor activation, upstream pathway blockade alone may be insufficient to reverse the oncogenic transcriptional state established by E6 and E7 [102].

The transcriptional-complex–targeting strategy outlined in Table 2 represents a mechanistically distinct and potentially more rational approach for cervical cancer, as it directly interferes with the nuclear NICD–CSL–Mastermind transcriptional machinery that integrates HPV-mediated pathway rewiring. Conceptually, this level of intervention may allow suppression of oncogenic Notch outputs while avoiding broader inhibition of γ-secretase substrates that contribute to systemic toxicity. However, this theoretical precision is counterbalanced by practical challenges, including the delivery of peptide or small-molecule disruptors to the nucleus, uncertainty about off-target transcriptional perturbations, and the likelihood of epigenetic or protein–protein interaction–based resistance mechanisms. Collectively, the comparison in Table 2 therefore supports the view that no single Notch-targeting modality is universally suitable for cervical carcinoma. Instead, the translational value of each strategy depends on its ability to selectively suppress HPV-driven Notch transcriptional dependency while minimizing compensatory signaling and systemic toxicity. This reinforces the need for biomarker-guided patient stratification and supports prioritizing transcription-level and combination-based approaches as future directions for integrating Notch-directed therapies into personalized treatment strategies for cervical cancer [103].

Table 2. Comparative analysis of Notch-targeting strategies: receptor antibodies vs. ligand antibodies vs. γ-secretase inhibitors vs. transcriptional-complex targeting.

Feature / Consideration	Receptor antibodies	Ligand antibodies	γ-Secretase inhibitors	Transcriptional-complex inhibitors
Specificity	High (paralog-selective)	Moderate (ligand-specific)	Low (pan-Notch, broad)	Potentially high (NICD-complex specific)
Mechanistic breadth	Blocks certain receptor isoforms	Blocks ligand-driven paracrine signaling	Blocks all receptor cleavage → broad NICD suppression	Blocks transcriptional output downstream of NICD
Representative toxicities	Receptor-specific physiologic effects	Cardiovascular/vascular toxicity (DLL4)	GI, fatigue, ovarian dysfunction, potential off-target substrate effects	Dependent on target - risk of broader transcriptional dysregulation
Ease of administration	IV/SC mAb (less frequent dosing)	IV/SC mAb	Oral small molecule (easy dosing)	Depends (small molecules, peptides, delivery challenges)
Biomarker dependency	High - receptor expression/mutation	High ligand expression, vascular risk	High - activating NOTCH mutations, PD signatures	High - NICD transcriptional dependency
Resistance patterns	Receptor redundancy, downstream activation	Compensatory angiogenesis, ligand redundancy	PK loss, bypass signaling, and downstream mutations	Mutation of interaction domains, epigenetic bypass
Clinical advantages	Potentially better tolerability vs pan-Notch	Targeting microenvironment/angiogenesis	Systemic, oral, proven in a specific disease (e.g., desmoid)	Theoretical precision; spares γ-secretase substrates
Clinical disadvantages	Limited single-agent efficacy in unselected cohorts	Safety (vascular) concerns limit systemic use	Class toxicities; PK challenges seen historically	Early stage; delivery and specificity hurdles

8. Future Direction

Future research should move toward a more precise, biologically stratified framework for the development of Notch-targeted interventions in cervical cancer. A central priority is the establishment of biomarker-driven patient stratification strategies, including the identification and validation of robust molecular markers that reflect Notch pathway activation status, receptor- and ligand-specific dependencies, and downstream transcriptional programs. Such biomarkers are essential for selecting patients most likely to benefit from Notch-modulating therapies and for monitoring treatment response. Equally important is the development of HPV-status–specific experimental and translational models. Given the profound influence of viral oncogenes on host signaling networks, systematic comparisons between HPV-positive and HPV-negative disease models are required to define how HPV reshapes Notch pathway activity, pathway crosstalk, and therapeutic vulnerability. This approach will enable a more accurate interpretation of Notch biology in clinically relevant disease contexts.

In parallel, the design of rational combination therapy should be prioritized. Integrating Notch pathway modulation with standard chemo radiotherapy, immunotherapy, or other molecularly targeted agents offers a potential strategy to overcome pathway redundancy and adaptive resistance mechanisms. Such combinations should be guided by functional genomics, pathway interaction analyses, and predictive biomarkers to maximize therapeutic synergy while minimizing toxicity. Finally, for phytochemical-based strategies, future studies must place greater emphasis on standardized compound characterization, formulation optimization, pharmacokinetic profiling, and rigorous validation in clinically relevant models. Only through well-designed translational studies and biomarker-guided clinical trials can the true therapeutic value of Notch-targeting phytochemicals be established and integrated into precision treatment strategies for cervical cancer.

9. Conclusion

Targeting the Notch signaling pathway represents a promising yet biologically complex therapeutic strategy in cervical cancer. There is substantial experimental evidence linking irregularities in the Notch signaling pathway to cancer progression, stem cell proliferation, epithelial-mesenchymal transition, and resistance to therapy. However, ongoing debates over the mechanisms of Notch signaling and their clinical applications persist due to its context-dependent nature. Notch ligands and receptors may play different roles depending on the cancer subtype, disease stage, and cell location. Additionally, the fact that Notch receptors may share functional properties with one another leads to confusion about which Notch receptor should be prioritized as a target when designing therapy. As a result, patients may respond inconsistently to therapies that target components of the Notch pathway. In parallel, uncertainty remains regarding the optimal mode of Notch pathway modulation. Although γ-secretase inhibitors and receptor- or ligand-targeted antibodies demonstrate antitumor efficacy in preclinical models, their clinical applicability is limited by dose-limiting, on-target toxicities and restricted therapeutic windows. Conversely, phytochemicals and other natural products exhibit multitarget regulatory properties and comparatively favorable safety profiles in experimental systems; however, the specificity, reproducibility, and durability of their effects on Notch signaling remain insufficiently validated. Importantly, the translational promise of phytochemicals must be interpreted with caution. Major barriers include poor and variable bioavailability, limited molecular selectivity, formulation and batch variability, incomplete

pharmacokinetic and toxicological characterization, and a strong dependence on *in vitro* and small-scale *in vivo* models. Moreover, direct causal evidence linking individual phytochemicals to clinically relevant and sustained Notch pathway modulation in cervical cancer remains sparse, collectively constraining reproducibility, dose optimization, and regulatory progression.

Author Contributions

Conceptualization, S.S., A.M., and P.P.; methodology, S.S., A.M., and P.P.; investigation, S.S., A.M., and P.P.; resources, S.S., A.M., and P.P.; writing—original draft preparation, S.S., A.M., and P.P.; writing—review and editing, S.S., A.M., and P.P.; visualization, S.S., A.M., and P.P.; supervision, S.S., A.M., and P.P.; project administration, S.S., A.M., and P.P. All authors contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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