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Review Article

Upregulation of extrinsic and intrinsic apoptosis pathways in head and neck squamous cells by promotion of caspase activation by P13K inhibitor HCD – A systematic review.

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Abstract

Background
Constitutive activation of the phosphoinositide-3-kinase/protein kinase B (PI3K/Akt) pathway promotes tumor cell survival and resistance to apoptosis in head and neck squamous cell carcinoma (HNSCC). 16-Hydroxycleroda-3,13-dien-15,16-olide (HCD), a clerodane diterpene isolated from *Polyalthia longifolia*, has demonstrated pro-apoptotic activity through inhibition of PI3K signaling. This systematic review evaluated whether HCD activates intrinsic and extrinsic apoptotic pathways through caspase signaling in HNSCC models.

Methods
A systematic review was conducted according to PRISMA 2020 guidelines. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched using predefined Boolean combinations related to HCD, PI3K inhibition, and apoptosis. Two reviewers independently screened studies and extracted data. Eligible studies were original experimental investigations evaluating apoptosis-related endpoints, including caspase activation, Bax/Bcl-2 modulation, cytochrome-c release, PARP cleavage, reactive oxygen species generation, and PI3K/Akt signaling alterations. Due to heterogeneity in experimental models and outcome reporting, findings were synthesized using structured qualitative narrative analysis.

Results
Five in vitro studies met the inclusion criteria. HCD consistently reduced PI3K/Akt phosphorylation, increased oxidative stress, altered Bax/Bcl-2 balance, induced mitochondrial membrane depolarization, and activated caspase-9 and caspase-3. In oral squamous cell carcinoma models, activation of caspase-8 and upregulation of death receptor signaling indicated concurrent engagement of extrinsic apoptosis.

Conclusion
Available preclinical evidence indicates that HCD induces caspase-dependent apoptosis through suppression of PI3K/Akt signaling and activation of both mitochondrial and death receptor pathways.

Future research
Further experimental and translational studies, including in vivo investigations and clinical validation, are required to determine the therapeutic potential of HCD in head and neck squamous cell carcinoma.

Keywords: *Head and neck squamous cell carcinoma; Oral squamous cell carcinoma; PI3K/Akt signaling pathway; 16-Hydroxycleroda-3,13-dien-15,16-olide; Apoptosis; Intrinsic apoptotic pathway; Extrinsic apoptotic pathway; Caspase activation; Polyalthia longifolia.*
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Introduction

Head and neck squamous cell carcinoma (HNSCC) remains one of the most common and aggressive malignancies worldwide, contributing substantially to global cancer-related morbidity and mortality [1]. It encompasses cancers arising from the mucosal epithelium of the oral cavity, oropharynx, hypopharynx, and larynx, with oral squamous cell carcinoma (OSCC) constituting the majority of cases [1,2]. Despite major advances in surgical techniques, radiotherapy delivery, chemotherapy regimens, targeted therapies, and immunotherapy, overall survival rates have shown only modest improvement over the past several decades. Patients with advanced-stage disease continue to experience high rates of local recurrence, regional lymph node metastasis, distant spread, and therapeutic resistance. These challenges underscore the need for a deeper understanding of the molecular mechanisms driving tumor progression and survival [3,4].

The biological behavior of HNSCC is largely governed by dysregulation of intracellular signaling pathways that promote uncontrolled proliferation and suppress programmed cell death. Among these, the phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling axis plays a central oncogenic role. Activation of this pathway enhances cellular proliferation, promotes metabolic reprogramming, stimulates angiogenesis, and inhibits apoptotic mechanisms [5-7]. Genetic alterations such as PIK3CA mutations, amplification of PI3K catalytic subunits, loss of PTEN tumor suppressor function, and overexpression of upstream receptor tyrosine kinases contribute to constitutive activation of PI3K/Akt signaling in a significant proportion of HNSCC cases. Persistent pathway activation confers a survival advantage to malignant cells, enabling them to evade apoptotic stimuli and resist cytotoxic therapies [8-10].

Akt, a serine/threonine kinase downstream of PI3K, regulates numerous cellular processes critical for tumor survival. Through phosphorylation of pro-apoptotic proteins, modulation of transcription factors, and regulation of mitochondrial integrity, Akt suppresses programmed cell death and enhances tumor resilience. This anti-apoptotic effect is a hallmark of malignant transformation and represents a key barrier to effective therapy [11,12]. Consequently, targeted inhibition of PI3K/Akt signaling has emerged as an attractive therapeutic strategy in HNSCC. However, clinical application of selective PI3K inhibitors has been limited by toxicity, incomplete pathway suppression, and compensatory activation of parallel signaling networks [13]. These limitations highlight the need for alternative or multi-targeted approaches capable of simultaneously modulating survival pathways and restoring apoptotic sensitivity.

Apoptosis, or programmed cell death, is a tightly regulated physiological process essential for maintaining tissue homeostasis and eliminating damaged or transformed cells[14]. In cancer, evasion of apoptosis allows malignant cells to persist despite genomic instability and therapeutic intervention. Apoptotic signaling proceeds through two principal pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor-mediated) pathway. Both ultimately converge on activation of executioner caspases, particularly caspase-3, which orchestrates cellular dismantling and DNA fragmentation[15-17].

The intrinsic pathway is initiated by intracellular stressors such as oxidative damage, DNA injury, oncogenic signaling imbalance, or hypoxic stress. These stimuli disrupt mitochondrial membrane integrity through modulation of Bcl-2 family proteins. The balance between pro-apoptotic members such as Bax and Bak and anti-apoptotic proteins such as Bcl-2 and Bcl-xL determines mitochondrial outer membrane permeabilization. Once mitochondrial integrity is compromised, cytochrome c is released into the cytoplasm, where it participates in the formation of the apoptosome complex. This complex activates initiator caspase-9, which subsequently activates downstream executioner caspases, leading to irreversible apoptotic cell death[14,18].

The extrinsic pathway is triggered by activation of cell surface death receptors, including tumor necrosis factor receptor (TNF-R) and Fas (CD95). Binding of their respective ligands leads to assembly of the death-inducing signaling complex and activation of initiator caspase-8[19]. Caspase-8 can directly activate executioner caspases or amplify intrinsic apoptosis through cleavage of Bid, thereby linking both apoptotic pathways[20]. In HNSCC, dysregulation of death receptor signaling and overexpression of anti-apoptotic proteins frequently impair this pathway, further contributing to tumor persistence[21].

In recent years, increasing attention has been directed toward natural bioactive compounds as potential anticancer agents due to their ability to modulate multiple signaling networks simultaneously. Plant-derived diterpenes, particularly clerodane diterpenes, have demonstrated diverse biological activities, including anti-inflammatory, antimicrobial, and cytotoxic properties [22]. Among these compounds, 16-hydroxycleroda-3,13-dien-15,16-olide (HCD), isolated from the medicinal plant *Polyalthia longifolia*, has emerged as a promising candidate with anticancer potential [23].

Notably, HNSCC is not a biologically uniform disease. In addition to tobacco- and alcohol-associated carcinogenesis, a substantial subset of oropharyngeal cancers is driven by high-risk human papillomavirus

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(HPV) infection[24]. HPV-positive tumors are characterized by expression of viral oncoproteins that disrupt cell cycle regulation and promote genomic instability. Importantly, HPV-associated tumors also exhibit frequent alterations in the PI3K/Akt pathway, including increased prevalence of PIK3CA mutations and enhanced survival signaling[25]. Although HPV-positive HNSCC generally demonstrates improved response to therapy and better overall prognosis compared to HPV-negative disease, aberrant PI3K pathway activation remains a relevant contributor to tumor survival and recurrence. Thus, targeting PI3K-mediated anti-apoptotic signaling may hold therapeutic value across etiologic subtypes of HNSCC[26,27].

Despite accumulating experimental evidence demonstrating pro-apoptotic effects of HCD in different malignancies, the mechanistic findings remain dispersed and variably reported. Specifically, whether HCD consistently activates both intrinsic and extrinsic apoptotic pathways in head and neck squamous carcinoma cells through coordinated suppression of PI3K signaling requires systematic evaluation. Clarifying this mechanism is essential for determining its translational relevance as a potential targeted pro-apoptotic agent.

Therefore, the present systematic review aimed to comprehensively analyze available preclinical evidence regarding the ability of HCD to modulate PI3K/Akt signaling and activate intrinsic and extrinsic apoptosis pathways in head and neck squamous cell carcinoma models. By synthesizing mechanistic findings, this review seeks to provide a clear biological framework supporting further investigation of HCD as a novel therapeutic candidate in HNSCC.

Review question

What is the effect of 16-hydroxycleroda-3,13-dien-15,16-olide on caspase activation and apoptosis signaling pathways in head and neck squamous cell carcinoma, including modulation of intrinsic and extrinsic apoptotic mechanisms?

Materials and methods

Study design

This study was designed as a systematic review evaluating the mechanistic effects of 16-hydroxycleroda-3,13-dien-15,16-olide (HCD) on apoptosis signaling pathways in head and neck squamous cell carcinoma models. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[28].

Information Sources and Search Dates

A comprehensive literature search was performed in the following electronic databases:
PubMed/MEDLINE
Scopus
Web of Science Core Collection
Google Scholar

In addition to database searches, the reference lists of all eligible full-text articles were manually screened to identify additional relevant studies. No clinical trial registries yielded eligible records, as the review focused exclusively on preclinical mechanistic investigations.

The final search of all databases was conducted on 15 February 2026. No language restrictions were applied during the initial search; however, only studies published in English were included at the screening stage.

Search strategies combined controlled vocabulary (MeSH, where applicable) and free-text terms using Boolean operators. Core terms included: "16-hydroxycleroda-3,13-dien-15,16-olide" OR "HCD" OR "clerodane diterpene" AND "PI3K" OR "Akt" OR "mTOR" AND "apoptosis" OR "caspase" OR "intrinsic pathway" OR "extrinsic pathway" AND "oral squamous cell carcinoma" OR "head and neck squamous cell carcinoma." The complete search strategy is available from the corresponding author upon request.

Eligibility criteria

Inclusion criteria

- Studies were included if they met all of the following criteria:
- Original peer-reviewed experimental studies
- In vitro or in vivo cancer models
- Investigation of HCD or related clerodane compounds
- Evaluation of apoptosis-related outcomes, including caspase activation, PARP cleavage, cytochrome c release, Bax/Bcl-2 modulation, or reactive oxygen species generation
- Published in the English language

Exclusion criteria

- Studies were excluded if they met any of the following criteria:
- Review articles, editorials, or expert opinion papers
- Conference abstracts without full-text availability

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- Animal-only mechanistic studies not evaluating apoptosis endpoints relevant to cancer
- Non-experimental reports
- Studies lacking assessment of apoptotic or caspase-related outcomes

Study selection

Titles and abstracts of all retrieved records were screened to exclude irrelevant studies. Full-text articles were subsequently assessed for eligibility based on the predefined inclusion and exclusion criteria. Study selection was performed independently by two reviewers. Disagreements were resolved through discussion and consensus.

Data extraction

Data extraction was carried out using a standardized data collection framework. The following information was extracted from each included study:

- Author and year of publication
- Study design
- Cancer type and specific cell lines
- HCD concentration and exposure duration
- Experimental assays used to evaluate apoptosis
- Evidence of caspase activation
- Modulation of intrinsic and extrinsic pathway markers
- Effects on PI3K/Akt pathway signaling

Data synthesis

Given the heterogeneity in experimental models, dosage protocols, molecular endpoints, and outcome measurements, a quantitative meta-analysis was not performed. Instead, results were synthesized using a qualitative narrative approach.

Risk of bias assessment

The methodological quality and risk of bias of the included studies were assessed according to study design. Experimental studies were evaluated for adequacy of controls, presence of dose-response analysis, confirmation of molecular pathway activation through validated laboratory techniques, and reproducibility of findings. Risk-of-bias assessment was conducted independently by two reviewers.

Registration and Protocol

This systematic review was conducted in accordance with PRISMA 2020 reporting standards. The review was **not prospectively registered** in PROSPERO or any other international systematic review registry.
A formal review protocol was **not publicly registered or published** before commencement of the study. However, the research question, eligibility criteria, search strategy, data extraction framework, and outcome domains were predefined before data collection and remained consistent throughout the screening and synthesis stages.
No substantive methodological amendments were made after initiation of the review. Minor refinements were implemented during full-text screening to clarify operational definitions of apoptosis-related endpoints, specifically to ensure inclusion required documented assessment of caspase activation or validated mitochondrial or death receptor pathway markers. These clarifications did not alter the core research question, inclusion criteria, or primary outcomes of interest.

Results

Study selection

The electronic database search identified 268 records across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. After the removal of 82 duplicate records, 186 unique records remained for title and abstract screening. Of these, 154 records were excluded due to irrelevance to the review topic, absence of apoptosis-related outcomes, non-experimental study design, or lack of evaluation of HCD.
The full texts of 32 articles were assessed for eligibility. Following full-text review, 27 studies were excluded for the following reasons: review articles or expert opinions (n = 9), studies not evaluating HCD specifically (n = 8), studies lacking apoptosis or caspase-related endpoints (n = 6), and non-English publications (n = 4).
Ultimately, five studies met all inclusion criteria and were included in the final qualitative synthesis. (Figure 1)

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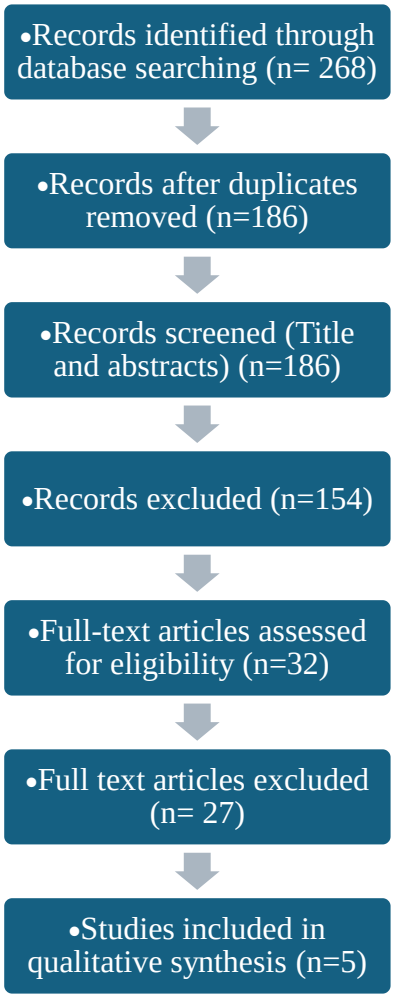

Figure 1: PRISMA Flowchart

Study characteristics

The five included studies comprised experimental in vitro investigations evaluating the effects of 16-hydroxycleroda-3,13-dien-15,16-olide (HCD) across multiple cancer models. These included oral squamous cell carcinoma cell lines (SCC25, SCC180, OECM1, SAS), bladder carcinoma (T24), leukemia and solid tumor cell models, and breast cancer cell lines.

All studies evaluated apoptosis-related molecular outcomes following HCD exposure, with varying concentration ranges and exposure durations. Key apoptosis markers assessed included reactive oxygen species (ROS), mitochondrial membrane potential (MMP), cytochrome c release, Bax/Bcl-2 modulation, caspase activation, and PARP cleavage. (Table 1)

Table 1. Characteristics of included studies

Author (Year)	Setting	Study Design	Cancer Model	HCD Concentration	Key Apoptosis Markers	Major Findings
Chan et al. (2026)[29]	In vitro	Experimental	SCC25, SCC180 (OSCC)	Dose-dependent	ROS, Bax/Bcl-2, cytochrome c, caspase-3/8/9	Dual intrinsic and extrinsic apoptosis activation; PI3K inhibition

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Chen et al. (2020)[30]	In vitro	Experimental	T24 bladder carcinoma	10–40 µM	MMP loss, cleaved PARP, caspase-3	Mitochondrial dysfunction and apoptosis induction
Velmurugan et al. (2018)[31]	In vitro	Experimental	Breast cancer cell lines	Variable	Bax, Bcl-2	Pro-apoptotic modulation; enhanced apoptosis signaling
Cheng et al. (2017)[32]	In vitro	Experimental	OECM1, SAS (OSCC)	1–10 µM	LC3, p62, apoptosis markers	Growth inhibition; autophagy involvement; PI3K/mTOR modulation
Lin et al. (2011)[33]	In vitro	Experimental	Leukemia & solid tumor cells	Dose-dependent	Caspase-3, PARP cleavage	PI3K/Aurora B inhibition; caspase-dependent apoptosis

Abbreviations: OSCC – Oral Squamous Cell Carcinoma; ROS – Reactive Oxygen Species; MMP – Mitochondrial Membrane Potential.

Risk of bias assessment

As all included studies were experimental in vitro investigations, risk of bias was assessed qualitatively based on methodological rigor, presence of appropriate controls, dose-response validation, and molecular confirmation of pathway activation.

All studies included appropriate untreated control groups. Most investigations incorporated dose-dependent analyses and validated apoptosis activation using molecular techniques such as Western blotting or RT-PCR. Overall, the risk of bias was considered low to moderate. (Table 2)

Table 2. Risk-of-bias assessment of included studies

Study	Control Groups	Dose-Response Analysis	Molecular Validation	Reproducibility	Overall Risk
Chan et al. (2026)[29]	Yes	Yes	Yes	High	Low
Chen et al. (2020)[30]	Yes	Yes	Yes	High	Low
Velmurugan et al. (2018)[31]	Yes	Partial	Yes	Moderate	Moderate
Cheng et al. (2017)[32]	Yes	Yes	Yes	Moderate	Moderate
Lin et al. (2011)[33]	Yes	Yes	Yes	High	Low

Intrinsic apoptosis activation

Across the included studies, consistent evidence supported activation of the intrinsic (mitochondrial) apoptosis pathway following HCD treatment.

In oral squamous cell carcinoma models, HCD induced mitochondrial ROS generation, depletion of intracellular glutathione, and release of cytochrome c into the cytoplasm. This was accompanied by upregulation of pro-apoptotic Bax and downregulation of anti-apoptotic Bcl-2, indicating mitochondrial membrane destabilization.

Similarly, in bladder carcinoma cells, HCD treatment resulted in loss of mitochondrial membrane potential, increased cleaved PARP expression, and activation of caspase-3, further supporting mitochondrial pathway involvement. Additional evidence from leukemia and solid tumor models demonstrated caspase-3 activation and PARP cleavage following suppression of PI3K signaling.

Collectively, these findings demonstrate consistent activation of intrinsic apoptotic signaling across different cancer cell types.

Extrinsic apoptosis activation

In head and neck squamous carcinoma models, HCD was shown to upregulate components of the death receptor pathway, including TNF-α/TNF-R and Fas/FasL signaling. This resulted in activation of initiator caspase-8, indicating involvement of the extrinsic apoptosis pathway.

The concurrent activation of caspase-8 alongside mitochondrial apoptotic markers suggests that HCD engages both intrinsic and extrinsic pathways in oral squamous cell carcinoma cells.

Caspase cascade activation

All included mechanistic studies demonstrated activation of executioner caspase-3 following HCD exposure. Caspase activation was confirmed through the detection of cleaved caspase forms and PARP cleavage. These findings confirm that apoptosis induced by HCD is

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caspase-dependent and culminates in activation of the apoptotic execution phase.

Pi3k/akt pathway suppression

Suppression of the PI3K/Akt pathway was consistently observed in studies evaluating upstream signaling modulation. HCD reduced phosphorylation of PI3K and Akt, linking inhibition of survival signaling to downstream apoptotic activation. In some models, additional inhibition of mTOR or Aurora B kinase signaling was reported, further reinforcing disruption of pro-survival pathways.

Taken together, the included studies demonstrated that HCD induces apoptosis through coordinated suppression of PI3K/Akt signaling and activation of both intrinsic and extrinsic apoptotic mechanisms.

Discussion

The present systematic review synthesized evidence from five experimental studies and demonstrated that 16-hydroxycleroda-3,13-dien-15,16-olide (HCD) consistently induced apoptosis through coordinated modulation of mitochondrial and death receptor–mediated pathways. When the findings of Chan et al. (2026)[29], Cheng et al. (2017)[32], Lin et al. (2011)[33], Chen et al. (2020)[30] and Velmurugan et al. (2018)[31] were analyzed collectively, a convergent mechanistic pattern emerged in which suppression of PI3K/Akt signaling preceded activation of intrinsic and in some models extrinsic apoptotic cascades.

The strongest mechanistic characterization in head and neck squamous models was provided by Chan et al. (2026)[29], who demonstrated that HCD induced mitochondrial ROS generation, intracellular glutathione depletion, cytochrome c release, and activation of both caspase-9 and caspase-8, ultimately converging on caspase-3 activation. This dual activation strongly supported engagement of both intrinsic and extrinsic pathways. Their findings closely aligned with the mitochondrial apoptosis framework described by Green and Reed (1998)[34] and Elmore (2007)[35] in which mitochondrial outer membrane permeabilization was considered the central irreversible step of intrinsic apoptosis. The shift in Bax/Bcl-2 ratio reported by Chan et al. (2026)[29] directly correlated with the regulatory model described by Oltvai et al. (1993)[36] and Cory and Adams (2002)[37], who established that the relative abundance of pro- and anti-apoptotic Bcl-2 family members determined mitochondrial susceptibility to apoptotic stimuli.

The mitochondrial findings of Chan et al. (2026)[29] were independently supported by Chen et al. (2020)[30], who observed loss of mitochondrial membrane potential and increased cleaved PARP and caspase-3 expression in bladder carcinoma cells. Although Chen et al.[30] investigated a non-head-and-neck model, the preservation of mitochondrial dysfunction and caspase activation suggested that HCD targeted conserved apoptotic machinery rather than tumor-specific pathways. This cross-model reproducibility strengthened biological plausibility and aligned with the oxidative stress–induced apoptosis mechanisms described by Simon et al. (2000)[38], Trachootham et al. (2009)[39], Ott et al. (2007)[40], and Circu and Aw (2010)[41] who demonstrated that ROS generation facilitated mitochondrial destabilization and apoptosome formation.

Lin et al. (2011)[33] further contributed to mechanistic clarity by demonstrating caspase-3 activation and PARP cleavage following PI3K pathway inhibition in leukemia and solid tumor models. Their findings were particularly important because they reinforced the upstream role of PI3K/Akt suppression in apoptosis induction. This observation correlated strongly with the foundational work of Datta et al. (1997)[42] and Cardone et al. (1998)[43], who showed that Akt-mediated phosphorylation inhibited pro-apoptotic proteins and caspase-9 activation. The broader signaling architecture outlined by Manning and Cantley (2007)[44] further contextualized the importance of Akt as a survival regulator. Given that genomic analyses by the Cancer Genome Atlas Network (2015)[45] and Lui et al. (2013)[46] demonstrated frequent PI3K pathway alterations in HNSCC, the suppression of this pathway by HCD provided mechanistic and translational relevance.

Cheng et al. (2017)[32] introduced an additional layer of complexity by demonstrating modulation of LC3, p62, and PI3K/mTOR signaling in OSCC cell lines (OECM1 and SAS), suggesting involvement of autophagy-related mechanisms. When compared with Chan et al. (2026)[29], who emphasized robust caspase activation, Cheng et al. (2017)[32] appeared to describe a cellular stress response that incorporated both apoptotic and autophagic signaling. This difference likely reflected intrinsic molecular heterogeneity among OSCC cell lines, consistent with the mutational variability reported by Stransky et al. (2011)[47] and Agrawal et al. (2011)[48]. The interplay between autophagy and apoptosis described by Cheng et al. (2017)[32] aligned with models proposed by Levine and Kroemer (2008)[49] and Maiuri et al. (2007)[50], which emphasized crosstalk between self-digestion and programmed cell death pathways.

Importantly, Velmurugan et al. (2018)[31] provided additional support for intrinsic pathway activation by demonstrating Bax upregulation and Bcl-2 suppression in breast cancer cell lines following HCD exposure. Although their model differed from HNSCC, their results mirrored the Bax/Bcl-2 modulation reported by Chan et

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al. (2026)[29] and indirectly supported mitochondrial involvement described by Chen et al. (2020)[30]. The recurrence of Bax/Bcl-2 modulation across OSCC, bladder carcinoma, leukemia, and breast cancer models suggested that mitochondrial sensitization was a reproducible hallmark of HCD activity. This observation was consistent with the central role of mitochondrial membrane permeabilization described by Kroemer et al. (2007)[51] and with apoptosis resistance being a core hallmark of cancer as articulated by Hanahan and Weinberg (2011)[52].

The extrinsic pathway activation described by Chan et al. (2026)[29], including TNF-R and Fas/FasL upregulation with caspase-8 activation, further strengthened the mechanistic model. This finding correlated with classical death receptor signaling described by Ashkenazi and Dixit (1998)[53] and Peter and Krammer (2003)[54]. The formation of the death-inducing signaling complex, characterized by Kischkel et al. (1995)[55] and the Bid-mediated cross-talk between extrinsic and intrinsic pathways described by Li et al. (1998)[56] and Luo et al. (1998)[57], provided a mechanistic explanation for the simultaneous activation of caspase-8 and mitochondrial events observed in OSCC cells. In the context of HNSCC, Gastman et al. (1999)[58] reported Fas ligand expression in squamous carcinomas, supporting the plausibility that restoration of death receptor signaling could overcome tumor immune evasion.

When all five included studies[29-33] were analyzed comparatively, several consistent features were observed: (1) suppression of PI3K/Akt survival signaling; (2) increased oxidative stress; (3) modulation of Bax/Bcl-2 balance; (4) mitochondrial membrane destabilization; (5) activation of initiator caspases-9 and/or -8; and (6) convergence upon executioner caspase-3 activation. Differences between studies were primarily attributable to tumor type, experimental conditions, and emphasis on specific signaling nodes rather than contradictory findings. Notably, none of the included studies reported anti-apoptotic effects or pathway activation inconsistent with the canonical apoptosis cascade.

Despite these mechanistic consistencies, limitations remained. All included investigations were conducted in vitro, and none incorporated in vivo validation or clinical correlation. Variations in HCD concentration ranges and exposure durations limited direct quantitative comparison. Furthermore, although mechanistic reproducibility across tumor types strengthened biological plausibility, tumor microenvironment interactions and pharmacokinetic considerations were not addressed.

In summary, comparison and correlation of all five included studies demonstrated a coherent and reproducible mechanism in which HCD suppressed PI3K/Akt signaling and activated both intrinsic and extrinsic apoptotic pathways, culminating in caspase-dependent cell death. The integration of these findings with established apoptosis and PI3K literature provided strong biological plausibility and supported further translational investigation of HCD in head and neck squamous cell carcinoma.

Limitations and implications for practice, policy, and future research

The present review has several limitations that should be considered when interpreting the findings. All included investigations were in vitro experimental studies and therefore lacked validation in animal models or clinical populations. Differences in HCD concentration ranges, exposure durations, and molecular endpoints limited direct comparison across studies. In addition, mechanistic observations were derived from isolated cell culture systems that do not fully reproduce tumor microenvironment interactions, pharmacokinetics, or systemic toxicity profiles.

Despite these constraints, the findings carry several implications. From a research perspective, the consistent suppression of PI3K/Akt signaling and activation of caspase-dependent apoptosis suggest that HCD represents a potential multi-targeted therapeutic candidate that warrants further investigation in preclinical animal models. Future studies should evaluate pharmacodynamic behavior, bioavailability, and toxicity profiles to determine translational feasibility. From a clinical and policy standpoint, identification of natural compounds capable of modulating major oncogenic pathways may contribute to the development of adjunctive targeted therapies for head and neck malignancies. Rigorous in vivo studies and early-phase clinical investigations will be required before any therapeutic application can be considered.

Conclusion

This systematic review demonstrated that 16-hydroxycleroda-3,13-dien-15,16-olide (HCD) consistently induced caspase-dependent apoptosis through coordinated suppression of PI3K/Akt survival signaling and activation of both intrinsic and extrinsic apoptotic pathways. Across the included studies, HCD promoted mitochondrial dysfunction, oxidative stress, modulation of the Bax/Bcl-2 balance, cytochrome c release, and activation of initiator caspases-9 and -8, culminating in executioner caspase-3 activation. The mechanistic consistency observed across different cancer models, particularly in oral squamous cell carcinoma, strengthened the biological plausibility of HCD as a multi-targeted pro-apoptotic agent. Although all available evidence was derived from in vitro investigations and

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clinical validation remains absent, the integration of mitochondrial, death receptor, and PI3K pathway modulation suggested a coherent and reproducible mechanism of action. These findings support further preclinical and translational studies to evaluate the therapeutic potential of HCD in head and neck squamous cell carcinoma.

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List of abbreviations

Akt – Protein kinase B
Aurora B – Aurora kinase B
Bax – Bcl-2-associated X protein
Bcl-2 – B-cell lymphoma 2
CD95 – Cluster of differentiation 95 (Fas receptor)
DISC – Death-inducing signaling complex
EGFR – Epidermal growth factor receptor
FasL – Fas ligand
HCD – 16-Hydroxycleroda-3,13-dien-15,16-olide
HNSCC – Head and neck squamous cell carcinoma
HPV – Human papillomavirus
LC3 – Microtubule-associated protein 1 light chain 3
MMP – Mitochondrial membrane potential
mTOR – Mammalian target of rapamycin
OSCC – Oral squamous cell carcinoma
PARP – Poly (ADP-ribose) polymerase
PI3K – Phosphoinositide 3-kinase
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTEN – Phosphatase and tensin homolog
ROS – Reactive oxygen species
TNF-R – Tumor necrosis factor receptor

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Conflict of interest

The authors declare that there are no conflicts of interest related to this work.

Availability of data

All data generated or analyzed during this study are included within the published article. The extracted dataset, search strategy details, and screening framework are available from the corresponding author upon reasonable request.

Author contributions

Dr. Karthik Shunmugavelu: Conceptualization, study design, literature screening, data extraction, methodological supervision, manuscript drafting, and final approval.
Dr. N. Parthiban: Independent screening and eligibility assessment, data validation, and critical revision of the manuscript for intellectual content.
Uma Bharathi S: Data extraction support, tabulation of study characteristics, preparation of PRISMA flow data, formatting, and reference verification.
All authors reviewed and approved the final manuscript.

Authors' biographies

Dr. Karthik Shunmugavelu is an Assistant Professor in the Department of Dentistry at PSP Medical College Hospital and Research Institute, Tamil Nadu, India. He holds BDS and MDS degrees in Oral and Maxillofacial Pathology and additional postgraduate qualifications from the United Kingdom. His academic interests include molecular oncology, apoptotic signaling pathways in head and neck malignancies, and translational cancer therapeutics.
Dr. N. Parthiban is an Assistant Professor in Oral Pathology and Microbiology at Government Medical College and Hospital, The Nilgiris, Tamil Nadu, India. His research focuses on molecular mechanisms of oral carcinogenesis, biomarker discovery, and diagnostic pathology.
Uma Bharathi S is an undergraduate medical student at PSP Medical College Hospital and Research Institute. Her academic interests include oncology research, molecular medicine, and translational therapeutic strategies.

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