International Journal of Zoology and Applied Biosciences
Volume 11, Issue 1, pp: 50-60, 2026
https://doi.org/10.55126/ijzab.2026.v11.i01.008
ISSN: 2455-9571
http://www.ijzab.com
Research Article

RECENT ADVANCES IN SQUAMOUS CELL CARCINOMA THERAPY: BRIDGING CONVENTIONAL MODALITIES WITH PHYTOCHEMICAL NANOMEDICINE

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Article History: Received 27th October 2025; Accepted 22nd December 2025; Published 1st January 2026

ABSTRACT

Plant-derived phytochemicals have re-emerged as promising adjuvants and lead compounds in the management of squamous cell carcinoma (SCC). Over the past decade, extensive preclinical work shows that classes of phytochemicals including polyphenols (curcumin, resveratrol, quercetin), alkaloids, flavonoids, and terpenoids reduce SCC cell proliferation and invasion by modulating hallmarks of cancer: they induce apoptosis, cause cell-cycle arrest, suppress pro-survival signalling (EGFR/MAPK/PI3K-Akt), inhibit NF-κB driven inflammation, and impair angiogenesis and metastasis-related pathways. Advances in delivery (nano formulations, liposomes, and polymer conjugates) and combination strategies with standard chemotherapy/radiotherapy have improved phytochemical bioavailability and chemo-sensitization in vitro and in animal models. Translational progress includes metabolomics and molecular-target studies that clarify mechanisms (for example, effects on drug-efflux transporters and redox homeostasis) and several early-phase clinical or clinical-adjacent investigations exploring safety and chemo preventive potential in head-and-neck and cutaneous SCC. Despite promising efficacy signals, major barriers remain: inconsistent extract standardization, low oral bioavailability, limited large-scale clinical trials, and safety/interaction data when combined with conventional treatments. Future research priorities are rigorous standardization, mechanism-driven combination trials, optimized nano delivery systems, and well-designed clinical studies to establish efficacy, dosing, and safety profiles for integration into contemporary SCC care pathways.

Keywords: Nanodelivery, Nanoformulation, Chemoprevention, Clinical trials, Translational studies.

INTRODUCTION

Squamous cell carcinoma (SCC) is one of the most prevalent malignancies arising from keratinizing epithelial cells, contributing significantly to cancer-related morbidity and mortality worldwide(Alam & Ratner, 2001).It manifests in diverse anatomical regions including the skin, head and neck, oesophagus, and cervix; etiological factors include ultraviolet (UV) radiation, tobacco, alcohol, high-risk human papillomavirus (HPV) infection, and immunosuppression(Que *et al*.,2018; Chathurvedi *et al*.,2011). Recent epidemiological reports show rising absolute numbers of SCC diagnoses in many regions and a concerning increase in some younger cohorts, likely reflecting behavioural and environmental changes (Karia *et al*., 2013). In fair-skinned populations, cutaneous SCC is strongly linked to cumulative UV radiation, explaining the high burden reported in Australia, the United States, and Northern Europe (Lomas *et al*.,2012). Recent epidemiological estimates suggest that in the United States alone, more than 700,000 new cases of cutaneous SCC are diagnosed annually, with an associated 3,000–8,000 deaths, underscoring that while basal cell carcinoma is more common, SCC carries greater metastatic and mortality potential(Rischin *et al*., 2021).Similarly, head-and-neck SCC (HNSCC) accounts for over 600,000 new cases globally per year, with tobacco, alcohol, and high-risk human papillomavirus (HPV-16, HPV-18) infections identified as primary etiologic drivers(Chaturvedi *et al*., 2011). Cervical SCC, another HPV-associated malignancy, remains disproportionately prevalent in low- and middle-income countries due to limited access to screening and

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vaccination programs (Bray *et al*., 2011). Demographic analyses show SCC disproportionately affects older adults, with peak incidence beyond the sixth decade, reflecting cumulative carcinogen exposure and immune senescence (Hsu *et al*., 2011). However, there is an emerging trend of rising incidence among younger cohorts in high-income countries, attributed to increased tanning behaviors, lifestyle factors, and HPV-related oropharyngeal cancers (Chaturvedi *et al*.,2011; Lomas *et al*.,2012). Immunocompromised populations particularly organ transplant recipients and individuals with HIV/AIDS have a 65- to 250-fold increased risk of aggressive cutaneous SCC, often with multifocal presentation and high recurrence rates (Que *et al*., 2018).

The socioeconomic burden of SCC is substantial. Direct medical costs, including surgery, radiotherapy, systemic therapy, and long-term surveillance, contribute significantly to national cancer care expenditures. In the U.S., the annual cost of treating NMSC (of which SCC is a major contributor) exceeds USD 4.8 billion (Bray *et al*.,2018). Beyond economic impact, SCC also impairs quality of life due to disfiguring surgeries, speech and swallowing difficulties (in HNSCC), and psychosocial stress. Collectively, these data emphasize that SCC is not only common but also clinically and economically consequential, warranting continuous improvement in prevention, early detection, and therapeutic strategies (Alam & Ratner, 2001; Bray *et al*.,2018; Hsu *et al*., 2018; Loams *et al*., 2012).

Molecular Pathogenesis and Advances

Large-scale genomic and molecular studies over the last decade clarified key drivers of SCC: frequent TP53 mutations and CDKN2A loss, NOTCH family alterations in subsets, amplification/overexpression of receptor tyrosine kinases (notably EGFR), and recurrent PI3K/AKT pathway activation. The tumor microenvironment (TME), characterized by chronic inflammation and immunosuppressive myeloid/stromal populations, plays a critical role in progression and treatment resistance (Leemans *et al*.,2018). The molecular pathogenesis of squamous cell carcinoma (SCC) is complex, involving cumulative genetic mutations, epigenetic modifications, and dysregulation of signaling networks that collectively drive malignant transformation, progression, and therapeutic resistance(Pickering *et al*.,2013; Leeman *et al*., 2018).Next-generation sequencing studies, particularly The Cancer Genome Atlas (TCGA) and related large consortia, have provided comprehensive molecular profiles of SCC across anatomical sites, revealing both commonalities and site-specific variations(Johnson *et al*.,2020).

Key Genetic Alterations

One of the most consistent findings is the high frequency of TP53 mutations, present in up to 70–80% of head-and-neck SCC (HNSCC) and many cutaneous SCCs. These mutations impair DNA damage responses and apoptosis, creating a permissive environment for further genomic instability (Pickering *et al*.,2020).CDKN2A loss or inactivation is another hallmark, resulting in unchecked cell-cycle progression via deregulation of the p16INK4a–Rb axis (Leemans *et al*., 2018).Other recurrent events include NOTCH1/2 mutations, which paradoxically often act as tumor suppressors in SCC, contrasting with their oncogenic roles in other cancers (Johnson *et al*.,2020). Amplification and overexpression of receptor tyrosine kinases particularly EGFR drive hyperactivation of downstream pathways such as RAS/RAF/MEK/ERK and PI3K/AKT/mTOR, promoting cell proliferation, survival, and angiogenesis (Leemans *et al*., 2018) Mutations and amplifications in PIK3CA and loss of PTEN further potentiate aberrant PI3K signalling, while alterations in HRAS are enriched in subsets of oral SCC (Johnson *et al*.,2020).

Epigenetic and Transcriptomic Changes

Epigenomic studies demonstrate frequent promoter hypermethylation in genes controlling apoptosis, adhesion, and immune regulation, while transcriptomic profiling identifies overexpression of oncogenic transcription factors (SOX2, MYC) and immune checkpoint molecules (Leemans *et al*.,2018). Dysregulated microRNAs (miR-21, miR-155) also contribute to SCC pathogenesis by repressing tumor suppressor genes and enhancing pro-survival signaling (Johnson *et al*.,2020).

Tumor Microenvironment (TME)

Beyond intrinsic mutations, the SCC tumor microenvironment plays a pivotal role in disease progression. Chronic inflammation, often mediated by tobacco, alcohol, or UV exposure, induces cytokine-driven activation of NF-κB and STAT3, creating a pro-tumorigenic milieu(Leemans *et al*.,2018).The TME is enriched with immunosuppressive cells, including tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs), which collectively blunt cytotoxic immune surveillance(Johnson *et al*.,2020).Crosstalk between malignant keratinocytes and stromal fibroblasts enhances extracellular matrix remodeling and metastatic potential.

Molecular Advances and Clinical Translation

These molecular insights have translated into important clinical applications. Identification of PD-L1 expression and tumor mutational burden (TMB) as predictive biomarkers has guided the use of PD-1 inhibitors in SCC therapy (Johnson *et al*.,2020). Similarly, recognition of EGFR overexpression led to the clinical development of cetuximab, an anti-EGFR monoclonal antibody, which remains part of standard care in defined settings. Emerging research on genomic instability and DNA damage repair (DDR) pathway defects is opening opportunities for synthetic lethality-based treatments, such as PARP inhibitors in subsets of SCC (Leemans *et al*., 2018).

Diagnostics and Biomarkers

Beyond histology, immuno-oncology biomarkers (PD-L1), tumor mutational burden (TMB), and emerging immune gene signatures are used to stratify patients for immune checkpoint inhibitors (ICIs), though assay heterogeneity and cutoffs vary by study and indication. Liquid biopsies (ctDNA) and multiplex immune profiling are promising for monitoring minimal residual disease and predicting recurrence, but remain largely investigational (Lomas *et al*.,2012).

Immunohistochemistry (IHC) and Protein Biomarkers

Immunohistochemistry supplements morphology, especially in small biopsies or poorly differentiated tumors. Commonly used markers include: p63 and cytokeratin (CK) 5/6 to confirm squamous differentiation. p16INK4a as a surrogate biomarker for high-risk HPV-driven oropharyngeal SCC, where overexpression correlates with better prognosis and responsiveness to therapy (Johnson *et al*.,2020). EGFR overexpression, frequently observed in HNSCC, which provides both diagnostic and therapeutic information.

1.Immune Biomarkers

The advent of immunotherapy has brought PD-L1 expression into routine diagnostic practice. PD-L1 immunohistochemistry, measured as combined positive score (CPS) or tumor proportion score (TPS), guides eligibility for PD-1 inhibitors like pembrolizumab and nivolumab in recurrent/metastatic SCC. However, inter-assay variability, different cutoff thresholds, and intratumoral heterogeneity limit its reliability. Tumor mutational burden (TMB) and specific immune gene signatures are emerging predictors of response to immune checkpoint blockade, though clinical implementation remains investigational (Johnson *et al*.,2020).

2.Molecular Profiling

Genomic profiling using next-generation sequencing has identified recurrent mutations (TP53, CDKN2A, NOTCH1, PIK3CA) and copy number alterations in SCC, which not only provide biological insight but also guide inclusion in precision oncology trials. HPV DNA and RNA testing further refine diagnosis in oropharyngeal cancers, where HPV-positive SCC has distinct biology and therapeutic response compared to HPV-negative disease (Johnson *et al*.,2020).

3.Liquid Biopsy and Circulating Biomarkers

Liquid biopsy approaches including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomal RNA represent promising non-invasive modalities for monitoring disease burden, detecting minimal residual disease, and predicting relapse. While early studies demonstrate feasibility, liquid biopsies for SCC are not yet standardized in clinical practice, requiring further validation in prospective trials (Lomas *et al*.,2012).

Conventional and Emerging Therapies

Surgery and radiotherapy remain curative for many early-stage tumors; systemic therapies—primarily platinum-based chemotherapy regimens are used for locally advanced and metastatic disease. EGFR-directed therapy (cetuximab) and other targeted approaches have been used in defined settings, while photodynamic therapy has niche uses based on site and tumor characteristics (Chaturvedi *et al*.,2011; Rischin *et al*.,2021; Vermorken *et al*.,2008).

1.Surgery

Surgery remains the cornerstone curative modality for most localized SCC across sites (cutaneous, oral cavity, larynx, cervix). The primary goals are complete oncologic resection with negative margins and preservation of function and cosmesis where feasible. In cutaneous SCC, surgical excision with appropriate margins or Mohs micrographic surgery for cosmetically or functionally sensitive areas provides excellent local control for early lesions; advanced or recurrent disease may require wider resection with complex reconstruction and sometimes lymphadenectomy when nodal spread is suspected (Alam *et al*.,2001; Que *et al*.,2018). In head-and-neck sites, transoral robotic surgery (TORS) and function-sparing resections have advanced the ability to achieve oncologic control while reducing morbidity, though multimodality treatment is often required for locally advanced presentations (Pickering *et al*.,2013).

2.Radiotherapy

Radiotherapy (external beam) is a mainstay for primary treatment of unresectable lesions, adjuvant therapy after surgery when risk factors exist (positive margins, perineural invasion, nodal extracapsular spread), and palliative control. Advances over the last decade include intensity-modulated radiotherapy (IMRT) and image-guided RT, which improve dose conformity, spare normal tissues (salivary glands, mandible), and reduce long-term toxicity while maintaining tumor control. For selected early cutaneous lesions, localized modalities such as superficial RT or photodynamic therapy have niche roles when surgery is impractical (Rischin *et al*.,2021).

3.Chemotherapy

Cytotoxic chemotherapy remains important for locally advanced, unresectable, and metastatic SCC. Platinum-based agents (cisplatin or carboplatin) combined with 5-fluorouracil (5-FU) or with taxanes are commonly employed; induction regimens such as TPF (docetaxel, cisplatin, 5-FU) have been used to downstage bulky locally advanced head-and-neck tumors prior to definitive local therapy in selected patients. Chemotherapy is also used in combination with targeted agents or as the backbone for combination with immunotherapy in first-line systemic regimens for recurrent/metastatic disease when appropriate (Vermorkan *et al*.,2008; Wang *et al*.,2012).

Key practical considerations with chemotherapy include selection based on patient performance status and comorbidities (renal function, hearing for cisplatin), toxicity mitigation (hydration, antiemetics, growth-factor support where indicated), and coordination with local therapies to avoid excessive cumulative toxicity (Vermorkan *et al*.,2008).

4.Targeted therapy

Understanding of SCC molecular biology has enabled targeted approaches, although single-agent targeted therapy has had variable success. EGFR is frequently overexpressed in HNSCC and some mucosal SCCs; cetuximab (an anti-EGFR monoclonal antibody) combined with platinum-based chemotherapy showed improved outcomes versus chemotherapy alone in recurrent/metastatic HNSCC and remains an option in selected patients who are candidates for EGFR-directed therapy. However, benefit is modest and predictive biomarkers beyond EGFR expression remain limited, so patient selection is crucial (Leemans *et al*.,2018).

Other targeted strategies under investigation focus on the PI3K/AKT/mTOR axis (given PIK3CA alterations), cell-cycle regulators, and angiogenesis pathways, but these are mainly in clinical trials or early translational phases; durable single-agent activity has been limited, reinforcing the need for rational combination strategies supported by molecular selection (Pickering *et al*.,2013; Leemans *et al*.,2018).

5.Immunotherapy a paradigm shift

PD-1 pathway blockade has transformed management for subsets of advanced SCC. Nivolumab improved overall survival in recurrent/metastatic head-and-neck SCC compared with standard therapy in pivotal trials (Ferris *et al*.,2016). Pembrolizumab (KEYNOTE-048) produced durable responses as monotherapy in PD-L1–positive tumors and in combination with platinum-based chemotherapy, shifting first-line practice for many patients (Burtness *et al*.,2019). Cemiplimab produced clinically meaningful responses in advanced cutaneous SCC and is approved for locally advanced/metastatic cSCC when curative local therapy is not an option (Alam and Ratner, 2001). Despite these advances, many patients do not respond to ICIs and identifying predictive biomarkers and rational combinations remains a major research priority (Extermann *et al*.,2000; Johnson *et al*.,2020).

Nivolumab showed improved overall survival versus standard therapy in recurrent/metastatic HNSCC in a pivotal randomized trial, establishing PD-1 blockade as a standard option in the second-line setting for many patients (Ferris *et al*.,2016). Pembrolizumab (KEYNOTE-048) demonstrated that pembrolizumab monotherapy yields durable benefit in PD-L1–positive tumors and that pembrolizumab plus platinum-based chemotherapy improves survival in first-line recurrent/metastatic HNSCC, leading to changes in first-line practice for many patients (Burtness *et al*.,2019).

Biomarkers for immunotherapy

PD-L1 expression by immunohistochemistry (reported as TPS or CPS depending on assay and indication) is used to enrich for likely responders to pembrolizumab in HNSCC, but assay heterogeneity and variable cutoffs limit universal reliability. Tumor mutational burden (TMB) and composite immune gene signatures show promise as additional predictive tools but have not yet achieved universal standardization for routine clinical decision-making in SCC. As a result, biomarker-guided therapy is evolving but not yet definitive for all clinical scenarios (Johnson *et al*.,2020).

Combination strategies and rationale

To increase the fraction of patients benefiting from immunotherapy, numerous combination approaches are being tested: ICI + chemotherapy: chemotherapy may increase neoantigen release and alter the TME to Favour immune infiltration, providing rationale for combinations (as exemplified by pembrolizumab combination regimens). Clinical data support benefit in selected contexts, but toxicity profiles and patient selection remain important considerations (Burtness *et al*.,2019; Johnson *et al*.,2020). ICI + radiotherapy: radiotherapy can potentiate immune responses through immunogenic cell death and antigen release; combining RT with ICI is an active translational and clinical area (concurrent and sequential strategies) with promising early data in neoadjuvant and definitive settings (Rischin *et al*.,2021; Johnson *et al*.,2020). ICI + targeted agents: combining ICIs with agents targeting EGFR, VEGF, or the PI3K pathway is mechanistically attractive (modulating TME, improving antigen presentation), but clinical signals are mixed and require careful biomarker selection and toxicity monitoring (Leemans *et al*.,2018; Johnson *et al*.,2020).

Neoadjuvant and adjuvant immunotherapy

Neoadjuvant ICI trials use a window-of-opportunity model to give short preoperative immunotherapy and evaluate pathologic response; early studies report pathologic tumor regression in a subset of patients, suggesting potential for tumor downstaging and for using pathologic response as an early surrogate endpoint. Adjuvant immunotherapy is also being explored for high-risk resected disease to reduce recurrence risk, though definitive phase III evidence in many SCC settings is still accumulating (Johnson *et al*.,2020).

Immune-related adverse events (irAEs) and their management

ICIs produce unique immune-mediated toxicities affecting skin, gastrointestinal tract, liver, endocrine organs, lungs, and other systems. Management follows grade-based algorithms: immunotherapy may be withheld for moderate toxicities and permanently discontinued for severe or life-threatening irAEs; systemic corticosteroids (and other immunosuppressants for steroid-refractory cases) are the mainstay of treatment. Awareness and early recognition by

multidisciplinary teams is crucial to minimize morbidity and allow safe continued cancer care when possible (Postow *et al*.,2018).

Mechanisms of resistance and ongoing research

Primary and acquired resistance to ICIs arises from multiple mechanisms: lack of tumor antigenicity (low neoantigen burden), impaired antigen presentation (B2M or HLA alterations), immunosuppressive TME (TAMs, MDSCs, Tregs), upregulation of alternative checkpoints, and tumor intrinsic pathways (WNT/β-catenin). Translational research aims to identify predictive markers, reverse immunosuppression (e.g., TAM reprogramming), and rationally combine therapies to overcome resistance (Pickering *et al*.,2013; Johnson *et al*.,2020).

Newer Modalities and Combination Strategies

Neoadjuvant ICI trials (window-of-opportunity designs) aim to downstage tumors and use pathologic response as an early efficacy marker; several early-phase studies of pembrolizumab and cemiplimab in neoadjuvant settings show promise. Combination strategies (ICI + chemotherapy, ICI + radiation, ICI + targeted agents) are numerous; although some combinations have improved outcomes, other large trials have produced negative or equivocal results, underscoring the need for mechanistic rationale and biomarker selection before wide adoption(Khan *et al*.,2020; Johnson *et al*.,2020).

1.Neoadjuvant (window) immunotherapy and pathologic response paradigms

Neoadjuvant administration of immune checkpoint inhibitors (ICIs) prior to definitive surgery is an active area of investigation in SCC. The approach offers several theoretical and practical advantages: exposure of intact tumor antigens to the systemic immune system (potentially broadening T-cell repertoires), an in vivo readout of early pharmacodynamic effect via pathologic response, and opportunity to use pathologic response as a surrogate endpoint for long-term outcomes. Early-phase neoadjuvant trials using PD-1 inhibitors have reported pathologic tumor regression in a meaningful subset of patients, supporting further evaluation in larger trials and its incorporation into adaptive trial designs that use early pathologic or molecular signals to guide subsequent therapy choices. These efforts build on the durable systemic activity observed with PD-1 blockade in advanced settings (Alam & Ratner, 2001; Ferris *et al*.,2016; Burtness *et al*.,2019; Johnson *et al*.,2020).

2. ICI + chemotherapy: chemo-immunotherapy synergy

Combining cytotoxic chemotherapy with ICIs is among the most clinically advanced combination strategies. Chemotherapy can (a) increase neoantigen release through tumor cell killing, (b) deplete certain immunosuppressive cell subsets transiently, and (c) enhance antigen presentation thereby potentiating immune priming when combined with a PD-1/PD-L1 inhibitor. The KEYNOTE-048 program (pembrolizumab ± platinum/5-FU) exemplifies a chemo-immunotherapy regimen that improved outcomes compared with historical standards in recurrent/metastatic head-and-neck SCC, illustrating that rational chemo-immunotherapy combinations can expand benefit beyond single-agent ICI in appropriately selected patients. However, additive toxicities, optimal scheduling (concurrent vs sequential), and patient selection (PD-L1 status, performance status) remain crucial considerations (Burtness *et al*.,2019; Johnson *et al*.,2020).

3. ICI + radiotherapy: harnessing immunogenic cell death

Radiotherapy (RT) has well-characterized immunomodulatory effects inducing immunogenic cell death, increasing tumor antigen availability, and altering cytokine/chemokine gradients that recruit effector T cells. Combining RT with ICIs may produce local control benefits while also promoting systemic (abscopal) immune effects in selected cases. Clinical translation explores concurrent or sequential scheduling, dose-fractionation that maximizes immune stimulation, and RT targeting strategies to minimize lymphoid toxicity. Early translational and clinical data suggest promise, particularly in neoadjuvant or oligometastatic settings, but randomized evidence to define optimal parameters is still evolving (Rischin *et al*.,2021; Johnson *et al*.,2020).

4. ICI + targeted therapy: modulating the tumor microenvironment

Targeted agents (EGFR inhibitors, anti-angiogenics, PI3K pathway modulators) can remodel the tumor microenvironment (TME) to increase immunotherapy susceptibility for example, by normalizing tumor vasculature, reducing immunosuppressive cytokines, or inhibiting pathways that drive immune exclusion. Preclinical rationale supports combinations of PD-1 pathway inhibitors with EGFR or VEGF pathway agents; however, clinical results are heterogeneous and toxicity can be limiting. This underscores the importance of understanding on-tumor biology (e.g., EGFR/PIK3CA alterations, hypoxia signatures) and performing biomarker-guided trials rather than broad empiric combinations (Leemans *et al*.,2018; Johnson *et al*.,2020).

5. Multipronged combinations and the risk of antagonism or toxicity

While combining modalities is attractive, combinations can produce unexpected antagonism (e.g., immunosuppression from certain cytotoxics) or additive immune-related adverse events (irAEs). Each combination requires mechanistic justification, careful dose/schedule optimization, and staged clinical evaluation (phase I safety → phase II signal → randomized phase III). Safety frameworks and management algorithms for irAEs (early detection, steroid and steroid-sparing strategies) are essential when launching combination trials (Postow *et al*.,2018; Johnson *et al*.,2020).

6. Cellular therapies, oncolytic viruses, and bispecific agents early-phase innovation

Beyond ICIs and targeted agents, early-phase investigations are assessing novel biologics including oncolytic viruses that selectively lyse tumor cells while stimulating innate/adaptive immunity, bispecific T-cell engagers that redirect T cells to tumor antigens, and adoptive cellular therapies (engineered T-cells) adapted for solid tumors. These modalities are largely experimental in SCC but represent critical mechanisms to overcome low antigenicity or suppressive TMEs when rationally combined with checkpoint modulation. Translational endpoints (intratumoral immune infiltration, T-cell clonality) are vital to de-risk these strategies prior to large trials (Atanasov *et al*.,2015; Johnson *et al*.,2020).

7. Phytochemicals and adjuvant biologic modulation in combinations

Interest exists in integrating phytochemicals (with anti-inflammatory, antiproliferative, and TME-modulating properties) as adjuvants to sensitize tumors to chemotherapy, RT, or immunotherapy. Preclinical data demonstrate that certain phytochemicals can downregulate survival pathways and reduce oxidative stress, potentially enhancing cytotoxic or immune effects; however, rigorous PK, toxicity, and herb–drug interaction studies are prerequisites before clinical combination testing. The concept of co-delivery (e.g., nanoparticle co-encapsulation of a phytochemical and a chemotherapeutic) aims to maximize intratumoral synergy while minimizing systemic interactions (Yellappu *et al*.,2012; Bansal *et al*.,2011).

8. Biomarker-driven, adaptive, and window-of-opportunity trials

Adaptive trial designs including biomarker-enriched cohorts, platform trials, and window-of-opportunity studies that assess early molecular or pathologic response are increasingly used to triage promising combinations efficiently. These designs enable rapid signal detection (e.g., pharmacodynamic immune changes, pathologic complete response rates) and rationally eliminate ineffective combinations before large-scale investment. Crucially, harmonized biomarker collection (tissue, peripheral blood, ctDNA) must accompany these trials to refine predictive signatures for patient selection (Atanasov *et al*.,2015; Johnson *et al*.,2020).

Role of Phytochemicals: Mechanisms and Evidence

Phytochemicals plant-derived small molecules such as curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) display pleiotropic antitumor effects in SCC models. Mechanistically they induce apoptosis and cell-cycle arrest, inhibit pro-survival kinase cascades (EGFR/MAPK, PI3K/AKT), suppress NF-κB and STAT3 inflammatory signalling, modulate matrix metalloproteinase (MMP)/TIMP balance to reduce invasion and metastasis, and alter redox/mitochondrial function; some also modulate immune phenotypes in the TME. Preclinical studies in oral, cutaneous, and head-and-neck SCC models report reduced proliferation, invasion, angiogenesis, and enhanced chemosensitivity with various phytochemicals (Greenwell & Rahman, 2015; Fasinu *et al*.,2012).

1.Direct tumor-cell effects

a. Induction of apoptosis and pro-death signalling

Many phytochemicals activate intrinsic (mitochondrial) and/or extrinsic apoptotic pathways in SCC cells by upregulating pro-apoptotic proteins (Bax, Bak), downregulating anti-apoptotic factors (Bcl-2, Bcl-XL), and activating caspases (caspase-3/7). Curcumin, resveratrol and EGCG consistently show apoptosis induction across oral and cutaneous SCC in vitro and in vivo models (Aggarwal *et al*.,2007; Shukla & Singh,2011; Andrea,2015; Fasinu *et al*.,2012).

b. Cell cycle arrest

Phytochemicals frequently cause G0/G1 or G2/M arrest through modulation of cyclins (cyclin D1, cyclin E), cyclin-dependent kinases (CDKs), and CDK inhibitors (p21, p27), limiting proliferative capacity of SCC cells and sensitizing them to cytotoxics (Greenwell & Rahman, 2015; Salehi *et al*.,2019).

c. Inhibition of pro-survival kinase signalling (EGFR/MAPK, PI3K/AKT/mTOR).

Several phytochemicals downregulate EGFR phosphorylation or downstream MAPK and PI3K/AKT signalling, pathways highly relevant in SCC biology. This effect underlies part of the observed synergy between phytochemicals and EGFR-targeted or PI3K-pathway therapies in preclinical models (Salehi *et al*.,2019; Anand *et al*.,2007; Atanasov *et al*.,2015).

2. Anti-inflammatory and immunomodulatory actions

Chronic inflammation promotes SCC initiation and progression. Phytochemicals (notably curcumin, resveratrol, and flavonoids) inhibit NF-κB and STAT3 signaling, reducing pro-tumorigenic cytokines (IL-6, TNF-α) and COX-2 expression. By attenuating inflammatory signaling, these agents can reduce proliferation and may remodel the TME towards a less suppressive state, which is of particular interest when combining phytochemicals with immunotherapies (Salehi *et al*.,2019; Aggarwal *et al*.,2007; Hsu *et al*.,2019).

3. Anti-angiogenic and anti-metastatic effects

Phytochemicals downregulate angiogenic factors (VEGF) and matrix-remodeling enzymes (MMP-2, MMP-9) while modulating TIMPs, which together reduce neovascularization and invasive potential in SCC models. Several flavonoids have demonstrated suppression of

migration/invasion and reduced metastasis in animal studies (Atanasov *et al*.,2015; Newman and Cragg, 2007).

4. Epigenetic and transcriptional modulation

Certain phytochemicals affect DNA methylation patterns, histone modification enzymes, and microRNA expression—mechanisms that can re-activate tumor suppressors or downregulate oncogenic programs in SCC. These epigenetic effects support their potential as chemopreventive agents and as adjuncts to therapies targeting transcriptional dependencies (Salehi *et al*.,2019; Atanasov *et al*.,2015).

5. Radiosensitization and chemosensitization

Preclinical data indicate that phytochemicals can sensitize SCC cells to ionizing radiation and to cytotoxic drugs by (a) impairing DNA damage repair pathways, (b) enhancing ROS-mediated damage, and (c) inhibiting survival signalling that mediates resistance. Nano formulated phytochemicals have shown enhanced radiosensitizing / chemosensitizing effects in animal xenografts compared with free compounds, making them attractive candidates for combined modality studies (Yallappu *et al*.,2012; Wang *et al*.,2012; Williamson, 2001).

6. Effects on the tumor microenvironment and immune cells

Beyond direct cytotoxicity, phytochemicals modulate stromal and immune components: they can reduce TAM polarization to M2 phenotypes, lower levels of immunosuppressive cytokines, and in some models increase dendritic cell activation and cytotoxic T-cell infiltration. These immunomodulatory effects provide a mechanistic rationale for combining phytochemicals with immune checkpoint inhibitors, though careful preclinical and clinical pharmacology studies are required to avoid unintended antagonism or immune suppression (Fasinu *et al*.,2012; Hsu *et al*.,2019; Karagiannis *et al*.,2019).

7. Representative phytochemicals with SCC-relevant evidence

Curcumin (Curcuma longa): strong preclinical literature showing apoptosis induction, NF-κB inhibition, radiosensitization, and reversal of chemoresistance; limited clinical PK due to poor bioavailability has driven nanoformulation research (Aggarwal *et al*.,2007; Yallappu *et al*.,2012; Anand *et al*.,2007; Talib *et al*.,2020). Resveratrol: anti-angiogenic, pro-apoptotic, and immune-modulatory effects in SCC models; nanoformulations improve stability and tissue delivery in animal studies (Shukla & Singh, 2011; Bansal *et al*.,2011). Quercetin: flavonol with evidence for inhibiting PI3K/AKT signaling, MMP activity, and invasion in oral SCC models; explored as a chemo-sensitizer in preclinical work (Andrea, 2015; Atanasov *et al*.,2015). EGCG (green tea catechins): antioxidant/pro-apoptotic actions, anti-angiogenic effects, and chemopreventive signals in mucosal SCC models (Salehi *et al*.,2019; Fasinu *et al*.,2012).

8.Clinical evidence & current status

To date, most evidence for phytochemicals in SCC is preclinical (cell lines, organoids, animal xenografts). A limited number of early-phase human studies and botanical trials (including nanoparticle formulations in oral cancer cohorts) report safety and preliminary signals—but no phytochemical has yet achieved routine, evidence-based use as a standard SCC therapy. The translational pathway requires rigorous phase I PK/safety work, followed by mechanism-driven phase II trials (preferably window or neoadjuvant designs with pathologic/immunologic endpoints) prior to large randomized efficacy trials (Postow *et al*.,2018; Pappo *et al*.,2005; Kim *et al*.,2014; Williamson, 2001; Fasinu *et al*.,2012).

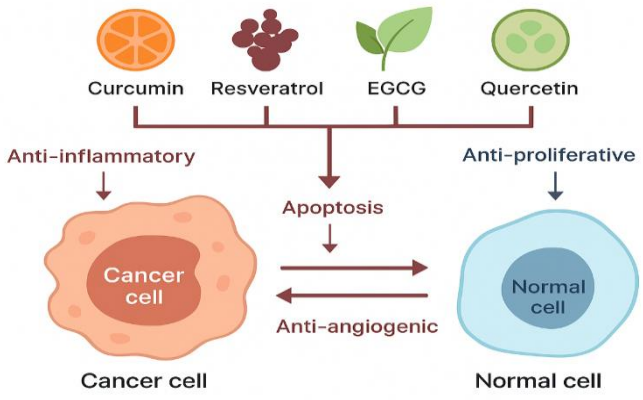

Figure 1. Mechanistic representation of phytochemical actions in SCC therapy. Plant-derived compounds such as curcumin, resveratrol, EGCG, and quercetin exert anticancer effects by inducing apoptosis, suppressing proliferation, inhibiting angiogenesis, modulating oxidative stress, and reducing inflammation. (Illustration self-designed using AI-based digital tools; free from copyright restrictions.).

Nanotechnology and Formulation Strategies

A principal translational barrier for phytochemicals is poor pharmacokinetics low oral bioavailability, rapid metabolism, and poor tissue penetration. Over the last decade, nanoparticle, liposomal, polymeric, and other delivery platforms (e.g., PLGA-PEG, solid lipid NPs) have been developed to enhance solubility, prolong circulation, and increase tumor accumulation via enhanced permeability and retention (EPR). Preclinical data show improved intratumoral delivery and efficacy of nano-curcumin, nano-resveratrol, and similar formulations versus free compounds; a few early-phase clinical trials are now testing selected nano formulations in oral SCC and related indications (Yellappu *et al*.,2012; Bansal *et al*.,2011; Williamson, 2001).

1.Major nanotechnology platforms

a. Liposomes

Liposomes are phospholipid vesicles that encapsulate hydrophobic or hydrophilic drugs. Curcumin-loaded liposomes demonstrate improved stability and solubility, prolonged circulation time, and enhanced uptake by SCC cells in vitro and in vivo. Surface modification with polyethylene glycol (PEGylation) increases half-life and reduces opsonization, while conjugation with ligands (e.g., folate, transferrin) enhances selective uptake in tumor cells expressing specific receptors (Yellappu *et al*.,2012; Anand *et al*.,2007).

b. Polymeric nanoparticles

Biodegradable polymers such as PLGA, chitosan, and polylactic acid have been widely used for phytochemical encapsulation. These nanoparticles allow controlled and sustained release, protection from enzymatic degradation, and enhanced tumor penetration. Curcumin-PLGA nanoparticles demonstrated increased apoptosis induction and radiosensitization in SCC xenografts compared to free curcumin (Yellappu *et al*.,2012; Wang *et al*., 2012; Williamson, 2001).

c. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)

SLNs and NLCs combine the advantages of lipids with solid matrices, enhancing drug loading, thermal stability, and sustained release. EGCG and quercetin encapsulated in SLNs/NLCs show enhanced cytotoxicity in SCC cell lines, improved systemic stability, and reduced rapid metabolism compared to free compounds (Bansal *et al*., 2011; Williamson, 2001).

d. Nanoemulsions and micelles

Self-assembling micelles and oil-in-water nanoemulsions solubilize hydrophobic phytochemicals, improve gastrointestinal absorption, and facilitate passive targeting via enhanced permeability and retention (EPR) effect. For example, resveratrol-loaded micelles improved bioavailability and antitumor efficacy in oral SCC animal models (Yellappu *et al*.,2012; Anand *et al*.,2007).

e. Targeted and stimuli-responsive nanoparticles

Recent developments include ligand-mediated targeting (e.g., EGFR, folate receptor) and stimuli-responsive systems that release the phytochemical payload under acidic tumor microenvironments, redox gradients, or in response to external triggers like light or heat. These strategies allow spatial and temporal control of drug release, maximizing antitumor effects while reducing systemic toxicity (Wang *et al*., 2012; Atanasov *et al*., 2015).

2.Mechanistic advantages of nanotechnology in SCC therapy

Enhanced cellular uptake – nanoparticles facilitate endocytosis-mediated entry into SCC cells, increasing intracellular drug concentrations and efficacy (Yellappu *et al*.,2012; Bansal *et al*.,2011). Improved pharmacokinetics and bioavailability – encapsulation protect phytochemicals from rapid metabolism and degradation, prolonging plasma half-life and systemic exposure (Anand *et al*.,2007; Williamson, 2001). Passive and active tumor targeting – nanoparticles exploit the EPR effect for preferential accumulation in tumors; surface modifications enable receptor-mediated targeting for enhanced specificity (Wang *et al*., 2012; Atanasov *et al*., 2015). Combination therapy facilitation – co-encapsulation of phytochemicals with chemotherapeutics, radiotherapy sensitizers, or immunomodulators allows synchronized delivery, enhancing synergy and minimizing off-target toxicity (Wang *et al*., 2012; Williamson, 2001). Overcoming multidrug resistance – nanoparticle delivery can bypass efflux pumps and enhance intracellular retention, improving efficacy against resistant SCC clones (Yellappu *et al*.,2012; Atanasov *et al*., 2015).

Future directions

Active targeting & multifunctional nanoparticles – incorporation of ligands or antibodies to enhance tumor-specific delivery and integration with diagnostic imaging (“theranostics”) (Atanosov *et al*.,2015). Co-delivery of phytochemicals and immunomodulators – combining tumor-cell killing with TME modulation to sensitize SCC to ICIs (Wang *et al*., 2012; Johnson *et al*.,2020). Stimuli-responsive and smart delivery systems – pH-, redox-, or light-responsive release to maximize intratumoral drug concentration while sparing normal tissues (Atanosov *et al*.,2015). Clinical translation – pilot studies of GMP-grade nanoformulations in SCC patients, with integrated biomarker analysis to guide dosing and evaluate efficacy (Yellappu *et al*.,2012).

Chemotherapy Regimens and Key Drugs

Platinum agents (cisplatin, carboplatin) remain cornerstone cytotoxics; TPF (docetaxel, cisplatin, 5-FU) is an

established induction regimen in selected locally advanced HNSCC. Cetuximab (anti-EGFR) combined with platinum-fluorouracil was shown to improve outcomes in recurrent/metastatic HNSCC and remains in use where appropriate. Selection of specific chemotherapeutic regimens is individualized based on tumor site, stage, prior therapy, performance status, and biomarker context (Chaturvedi *et al*.,2011; Yellappu *et al*.,2012; Wang *et al*.,2012).

Table 1. Evidence from preclinical studies of phytochemical nanoplatforms in squamous cell carcinoma (SCC).

Phytochemical	Nanoplatform	SCC model	Key outcomes	References
Curcumin	PLGA nanoparticles	Oral SCC xenografts	Enhanced apoptosis, radiosensitization, tumor growth inhibition	Yellappu *et al*.,2012; Wang *et al*., 2012
Resveratrol	PEGylated micelles	Cutaneous SCC cell lines	Improved bioavailability, anti-proliferative activity	Yellappu *et al*.,2012
EGCG	Solid lipid nanoparticles	Oral and skin SCC models	Increased cytotoxicity, reduced oxidative degradation	Bansal *et al*.,2011
Quercetin	Liposomes	Oral SCC	Inhibition of migration/invasion, enhanced cytotoxicity	Atonosov *et al*.,2015

Safety, Herb–Drug Interactions and Regulatory Considerations

Phytochemicals are not inherently risk-free: variability in extract composition, induction/inhibition of cytochrome P450 enzymes, and modulation of drug transporters raise potential for clinically relevant herb–drug interactions when combined with chemotherapy, targeted agents, or ICIs. Regulatory guidance for botanical drug development (FDA/EMA frameworks) emphasizes extract standardization, GMP manufacturing, and rigorous PK/toxicity testing prior to efficacy trials (Fasinu *et al*., 2012; Bray *et al*.,2018).

Special Populations: Paediatric SCC

SCC is uncommon in children and often linked to genetic photosensitivity syndromes (e.g., xeroderma pigmentosum) or immune deficiency. Management prioritizes cure while minimizing long-term toxicities; data are limited to case series and registry analyses. Molecular profiling in paediatric cases is sparse but may reveal actionable differences in some patients (Pappo *et al*.,2005; Kim *et al*.,2014).

Pregnancy and SCC

Treating SCC during pregnancy involves balancing maternal cancer control and fetal safety. Surgery is often feasible; systemic therapy decisions depend on gestational age and fetal risk. Experience with immunotherapy in pregnancy is limited and decisions are individualized by multidisciplinary teams including maternal-fetal medicine specialists (Cardonick *et al*., 2010).

Elderly Patients

Comorbidities, polypharmacy, and frailty influence treatment selection in older adults; less toxic or treatment-modified regimens and geriatric assessments are recommended to personalize therapy (Extermann *et al*., 2000).

CONCLUSION

Squamous cell carcinoma (SCC) remains a major health challenge due to its high incidence, recurrence, and resistance to conventional therapies. While advances in surgery, radiotherapy, chemotherapy, and immunotherapy have improved outcomes, their limitations highlight the need for safer, more effective alternatives. Phytochemicals such as curcumin, resveratrol, EGCG, and quercetin show strong anticancer potential by targeting apoptosis, angiogenesis, oxidative stress, and immune modulation, but their poor bioavailability has restricted clinical application. Nanotechnology-based delivery systems are addressing these barriers by enhancing stability, solubility, tumor targeting, and controlled release, thereby amplifying therapeutic efficacy. Integrating phytochemical nanomedicine with modern treatments and biomarker-driven strategies offers a promising path toward more personalized, less toxic, and more effective SCC management.

ACKNOWLEDGMENT

The authors express sincere thanks to the head of the Department of Microbiology, Nehru Arts and Science College, Coimbatore for the facilities provided to carry out this research work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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