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Phytochemicals as modulators of programmed and non-programmed cell death pathways in head and neck cancer: molecular mechanisms and translational challenges

Fitoquímicos como moduladores de vias de morte celular programada e não programada no câncer de cabeça e pescoço: mecanismos moleculares e desafios translacionais

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RESUMO

O câncer de cabeça e pescoço (CCP), predominantemente representado pelo carcinoma de células escamosas de cabeça e pescoço (CCECP), permanece um importante desafio em saúde pública em razão de sua elevada morbimortalidade e das limitações terapêuticas associadas aos tratamentos convencionais. Evidências crescentes indicam que fitoquímicos de origem natural apresentam efeitos antiproliferativos promissores em modelos pré-clínicos, além da capacidade de modular vias moleculares-chave envolvidas na iniciação tumoral, progressão da doença e resistência terapêutica. Esta revisão narrativa integrativa tem como objetivo sintetizar criticamente as evidências atuais sobre o papel dos fitoquímicos como moduladores de vias de morte celular programada e não programada no CCECP. Foram analisados estudos científicos revisados por pares, recuperados em bases de dados internacionais, visando identificar as principais classes de fitoquímicos investigadas, seus mecanismos moleculares de ação e suas potenciais aplicações terapêuticas. Os achados indicam que compostos como curcumina, resveratrol, epigalocatequina-3-galato, quercetina, luteolina e apigenina exercem efeitos pleiotrópicos por meio da regulação de vias de sinalização críticas, incluindo PI3K/AKT/mTOR, MAPK/ERK, NF-κB e STAT3, resultando em parada do ciclo celular, indução de apoptose e redução da invasividade tumoral. Apesar do robusto conjunto de evidências pré-clínicas, persistem desafios translacionais relevantes, especialmente relacionados à baixa biodisponibilidade, à heterogeneidade tumoral e à escassez de ensaios clínicos bem delineados. Conclui-se que os fitoquímicos emergem como agentes adjuvantes promissores no manejo do CCECP, desde que estudos futuros avancem na superação de limitações farmacocinéticas e no fortalecimento da validação clínica por meio de abordagens translacionais e de medicina de precisão. De forma conjunta, esses achados reforçam a relevância dos fitoquímicos como um campo promissor de pesquisa na farmacologia oncológica, ao mesmo tempo em que destacam a necessidade de reduzir a lacuna entre a evidência experimental e a aplicação clínica.

Palavras-chave: Flavonoides; Polifenóis; Medicina herbária; Compostos bioativos.

ABSTRACT

Head and neck cancer (HNC), predominantly represented by head and neck squamous cell carcinoma (HNSCC), continues to represent a major global health challenge due to its high morbidity, mortality, and limited therapeutic efficacy of conventional treatments. Increasing evidence indicates that phytochemicals derived from natural sources exhibit promising antiproliferative effects in preclinical models and the ability to modulate key molecular pathways involved in tumor initiation, progression, and therapeutic resistance. This narrative integrative review critically synthesizes current evidence on the role of phytochemicals as modulators of programmed and non-programmed cell death pathways in HNSCC. Peer-reviewed studies retrieved from major

international databases were analyzed to identify the main classes of phytochemicals investigated, their molecular mechanisms of action, and their potential therapeutic applications. The findings suggest that compounds such as curcumin, resveratrol, epigallocatechin-3-gallate, quercetin, luteolin, and apigenin exert pleiotropic effects by regulating critical signaling pathways, including PI3K/AKT/mTOR, MAPK/ERK, NF-κB, and STAT3, leading to cell cycle arrest, apoptosis induction, and attenuation of tumor invasiveness. Despite the robustness of preclinical evidence, translational challenges persist, particularly related to low bioavailability, tumor heterogeneity, and the scarcity of well-designed clinical trials. Overall, phytochemicals emerge as promising adjuvant agents in the management of HNSCC, provided that future studies address pharmacokinetic limitations and strengthen clinical validation through translational and precision oncology approaches. Collectively, these findings reinforce the relevance of phytochemicals as a promising research field in oncological pharmacology, while emphasizing the necessity of bridging the gap between experimental evidence and clinical application.

Keywords: Flavonoids; Polyphenols; Herbal medicine; Bioactive compounds

INTRODUCTION

Head and neck cancer (HNC) comprises a group of malignant neoplasms that predominantly arise from the squamous epithelium lining the oral cavity, oropharynx, hypopharynx, larynx, and adjacent anatomical structures. Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 90% of all cases, representing one of the most prevalent and clinically challenging cancer types worldwide (Aggarwal *et al*., 2021).

The multifactorial etiology of HNC involves classical risk factors such as chronic tobacco use and alcohol consumption, as well as persistent infection with human papillomavirus (HPV), particularly in oropharyngeal tumors. These factors contribute substantially to the biological and clinical heterogeneity observed in HNC (Kaushik, Tiku, 2023).

From an epidemiological perspective, HNC remains associated with high morbidity and mortality rates, exerting a profound impact on essential functions, including speech, mastication, swallowing, and respiration. Despite significant technological and therapeutic advances over recent decades, the overall five-year survival rate remains relatively low, especially in developing countries, where late diagnosis is common and access to specialized therapies is often limited (Santiago *et al*., 2025). Moreover, conventional treatment modalities such as surgery, radiotherapy, and chemotherapy, although effective in local disease control, are frequently associated with substantial systemic toxicity and permanent functional impairments, severely compromising patients' quality of life.

In this context, the search for innovative, less toxic, and biologically targeted therapeutic approaches has become a priority in contemporary oncological research. Bioactive compounds of natural origin, particularly phytochemicals, have attracted increasing scientific interest due to their ability to modulate multiple molecular pathways involved in carcinogenesis, tumor progression, and therapeutic resistance. Phytochemicals are generally associated with lower toxicity profiles compared to conventional chemotherapeutic agents, although this may vary depending on compound and dosage (Katiyar, 2016).

Phytochemicals comprise a broad class of secondary metabolites produced by plants, including polyphenols, flavonoids, terpenoids, alkaloids, and sulfur-containing compounds. Accumulating experimental evidence indicates that these compounds can modulate fundamental cellular processes such as proliferation, apoptosis, angiogenesis, inflammation, and tumor microenvironment remodeling. In HNSCC models, several phytochemicals have demonstrated the ability to inhibit critical signaling pathways, including PI3K/AKT/mTOR, MAPK/ERK, NF-κB, and STAT3, as well as to restore the activity of tumor suppressor genes such as

p53 (Aggarwal *et al*., 2021; Santiago *et al*., 2025).

Given this landscape, it is essential to compile, organize, and critically analyze the existing knowledge regarding the role of phytochemicals as emerging antiproliferative agents in HNC. Accordingly, this integrative narrative review aims to provide an in-depth discussion of the main phytochemicals investigated to date, their molecular mechanisms of action, proposed therapeutic strategies, and the translational challenges associated with their clinical application.

METHODS

The present study was designed as an integrative narrative literature review, a methodological approach widely used in the health sciences for the synthesis and critical interpretation of scientific evidence derived from heterogeneous experimental designs. This approach was selected due to the biological and molecular complexity of head and neck cancer (HNC), as well as the methodological diversity of studies investigating the effects of phytochemicals, including *in vitro*, *in vivo*, and preclinical studies (Bastos; Deslandes, 2005).

Unlike strictly systematic reviews, which typically focus on homogeneous clinical outcomes, integrative narrative reviews allow the incorporation of diverse types of evidence, enabling a comprehensive and interpretative analysis of molecular mechanisms, signaling pathways, and translational implications. This methodological framework is particularly suitable for identifying research trends, knowledge gaps, and emerging therapeutic perspectives in HNSCC.

A structured literature search was conducted in the PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect databases, selected due to their broad coverage of biomedical and pharmacological literature. Controlled and non-controlled descriptors were combined using Boolean operators (AND/OR), including: "phytochemicals," "head and neck cancer," "HNSCC," "cell death," "apoptosis," "ferroptosis," "necroptosis," and "molecular mechanisms."

The search included studies published between 2013 and 2025, with emphasis on recent evidence (2020–2025). Inclusion criteria comprised peer-reviewed articles written in English that investigated the effects of phytochemicals in HNC or relevant preclinical models, particularly those addressing molecular mechanisms, modulation of signaling pathways, and induction of programmed or non-programmed cell death.

Exclusion criteria included duplicate records, articles without full-text availability, studies not directly related to HNSCC, and those lacking mechanistic evaluation of phytochemical activity.

Data analysis was performed qualitatively and interpretatively. The findings were organized into predefined analytical categories: (i) classes of phytochemicals; (ii) molecular mechanisms of action; (iii) modulation of signaling pathways associated with proliferation and cell death; (iv) combined therapeutic strategies; and (v) translational challenges and clinical limitations.

To minimize bias inherent to narrative reviews, the analysis prioritized convergent evidence from independent studies and different preclinical models. Additionally, methodological limitations commonly identified in the literature—such as the use of supra-physiological concentrations, heterogeneity of experimental designs, and limited availability of clinical trials—were critically considered throughout the analysis to enhance transparency and scientific rigor.

Although this review does not follow a formal systematic review protocol, efforts were made to ensure methodological transparency and reproducibility of the search strategy.

RESULTS AND DISCUSSION

The study selection process resulted in the identification of approximately 120 records. After removal of duplicates and screening of titles and abstracts, 65 studies were selected for full-text evaluation. Of these, 21 articles met all inclusion criteria and were included in the final analysis. The main reasons for exclusion were: (i) focus on other cancer types, (ii) absence of mechanistic evaluation of phytochemicals, and (iii) methodological limitations.

Overall, the included studies were predominantly preclinical, consisting mainly of *in vitro* and *in vivo* models, with a strong emphasis on mechanistic investigations rather than clinical efficacy. Therefore, the findings discussed below should be interpreted within the context of experimental evidence, highlighting the need for cautious extrapolation to clinical settings, particularly due to the absence of robust randomized clinical trials.

Modulation of the PI3K/AKT/mTOR Pathway in HNC

The PI3K/AKT/mTOR pathway is one of the most frequently dysregulated signaling cascades in HNSCC, being closely associated with uncontrolled cell proliferation, apoptotic evasion, angiogenesis, and therapeutic resistance (Porta, Paglino, Mosca, 2014; Aggarwal *et al*., 2021). Although numerous studies identify this pathway as a central target of phytochemical action, considerable heterogeneity exists regarding molecular intervention points, the extent of pathway inhibition, and experimental conditions employed, which hampers direct comparisons among the compounds evaluated (Leemans, Snijders, Brakenhoff, 2018; Johnson *et al*., 2020; Li *et al*., 2023).

Activation of phosphatidylinositol 3-kinase (PI3K) leads to phosphorylation of protein kinase B (AKT), which subsequently activates the mechanistic target of rapamycin (mTOR), promoting increased protein synthesis, cell growth, and inhibition of apoptosis (Porta, Paglino, Mosca, 2014). In HNC, this pathway is frequently hyperactivated, contributing to enhanced tumor aggressiveness and poor prognosis. Evidence indicates that inhibition of this signaling axis results in reduced cell survival and increased susceptibility to programmed cell death (Leemans, Snijders, Brakenhoff, 2018; Li *et al*., 2023).

Experimental studies demonstrate that curcumin significantly reduces AKT and mTOR phosphorylation in HNSCC cell lines, leading to cell cycle arrest and induction of apoptosis (Aggarwal *et al*., 2021; Kaushik, Tiku, 2023). These findings reinforce the role of phytochemicals as promising modulators of the PI3K/AKT/mTOR pathway in preclinical models (Aguayo *et al*., 2023; Rajendran *et al*., 2024). However, these effects are largely derived from mechanistic studies, and their clinical applicability remains to be further validated.

Despite mechanistic consistency, many studies employ phytochemical concentrations exceeding those achievable in vivo, imposing limitations on the clinical translation of these findings. Furthermore, crosstalk between the PI3K/AKT/mTOR pathway and other signaling axes, such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), suggests that the therapeutic efficacy of phytochemicals depends on integrated rather than isolated modulation of these cascades, highlighting the need for combinatorial approaches (Aggarwal *et al*., 2021; Li *et al*., 2023). Similarly, resveratrol has been reported to interfere with AKT activation and restore tumor suppressor activity, reinforcing the modulatory potential of phytochemicals within this pathway.

Interference with the MAPK/ERK pathway

The mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway plays a fundamental role in regulating cell proliferation, differentiation, and survival and is frequently aberrantly activated in HNC. The literature indicates that phytochemicals exert relevant effects

on this cascade, although the magnitude of inhibition varies substantially among compounds and preclinical models (Katiyar, 2016).

Activation of the Rapidly Accelerated Fibrosarcoma RAF/MEK/ERK signaling axis leads to transcription of genes associated with cell cycle progression and tumor invasiveness (Ngan *et al*., 2022; Li *et al*., 2023). In HNSCC, this pathway is often linked to overexpression of the epidermal growth factor receptor (EGFR) and resistance to targeted therapies. Inhibition of ERK1/2 phosphorylation compromises cellular progression and favors the induction of apoptosis (Duma, Santos, Rodriguez, 2016; Veeraraghavan *et al*., 2024).

Epigallocatechin-3-gallate (EGCG) acts as a functional EGFR inhibitor, reducing downstream activation of the MAPK/ERK pathway and limiting cell proliferation (Thomas *et al*., 2014; Katiyar, 2016). Similarly, flavonoids such as quercetin and luteolin have demonstrated the ability to suppress ERK phosphorylation, resulting in cell cycle arrest and reduced tumor cell viability in HNSCC models (Cheng *et al*., 2022).

These findings reinforce the potential of phytochemicals as modulators of aberrant proliferative signaling; however, dependence on the specific molecular context of each cell line limits extrapolation of results. The lack of tumor stratification, such as distinction between HPV-positive and HPV-negative tumors, remains a relevant gap (Kaushik, Tiku, 2023).

Importantly, most of these findings are derived from preclinical models, and variability in experimental conditions, including phytochemical concentration and cell line characteristics, limits the direct translation of these results into clinical practice.

Regulation of NF-κB and tumor inflammation

Chronic inflammation is a major driver of tumor progression in HNC, with NF-κB serving as a central regulator of this process (Hayden, Ghosh, 2011). Constitutive activation of this transcription factor is associated with apoptotic evasion, angiogenesis, and therapeutic resistance, making it a strategic target for pharmacological interventions (Li *et al*., 2023).

NF-κB regulates the expression of genes involved in cell survival, inflammation, and angiogenesis. In HNSCC, its continuous activation contributes to tumor progression and resistance to chemotherapy and radiotherapy. Inhibition of NF-κB nuclear translocation results in reduced expression of pro-inflammatory cytokines and anti-apoptotic proteins (Gupta *et al*., 2010).

Curcumin stands out as one of the most effective phytochemicals in inhibiting NF-κB by preventing phosphorylation and degradation of inhibitor of nuclear factor kappa B alpha (IκBα). This effect leads to increased apoptosis and reduced cell viability in HNC models. Flavonoids such as quercetin and luteolin also exhibit relevant anti-inflammatory effects, contributing to modulation of the tumor microenvironment (Aggarwal *et al*., 2021).

Although NF-κB modulation represents a promising mechanism, most evidence remains restricted to preclinical models and lacks robust clinical validation (O'leary *et al*., 2024). Moreover, interactions between tumor inflammation and other signaling axes suggest that isolated NF-κB inhibition may be insufficient in complex clinical contexts (Aggarwal *et al*., 2021).

It is important to note that the majority of evidence regarding NF-κB modulation by phytochemicals is based on preclinical studies, reinforcing the need for well-designed clinical trials to validate these anti-inflammatory and antitumor effects.

Induction of apoptosis in HNC

Apoptosis is the most extensively investigated cell death mechanism in the context of the antiproliferative action of phytochemicals in HNC (El-Deiry, 2003; Fulda, Debatin, 2006; Aggarwal *et al*., 2021). The literature consistently demonstrates that these compounds

can activate both intrinsic and extrinsic apoptotic pathways; however, most studies focus on classical apoptotic markers, which may limit understanding of the complexity of the biological effects involved (Johnson *et al*., 2020; O'leary *et al*., 2024).

The intrinsic apoptotic pathway is primarily regulated by mitochondrial integrity and the balance between pro- and anti-apoptotic proteins of the BCL-2 family. Activation of this pathway culminates in cytochrome C release, apoptosome formation, and sequential activation of initiator and effector caspases. In HNC, dysfunction of these mechanisms contributes to apoptotic evasion and resistance to conventional therapies (El-Deiry, 2003; Fulda, Debatin, 2006).

Several phytochemicals have demonstrated the ability to restore apoptotic sensitivity in HNSCC cells. Curcumin, for instance, increases the BAX/BCL-2 ratio and activates caspases-3 and -9, while resveratrol induces apoptosis through p53 modulation and mitochondrial dysfunction. Flavonoids such as quercetin are also associated with activation of the intrinsic pathway, resulting in DNA fragmentation and reduced cell viability (Aggarwal *et al*., 2021; Kaushik, Tiku, 2023).

Despite strong mechanistic evidence, most studies assess apoptosis under highly controlled experimental conditions, frequently using high phytochemical concentrations. This limitation underscores the need for studies exploring apoptotic induction in models closer to clinical reality, including three-dimensional systems and *in vivo* models, to validate the translational relevance of these findings (Aggarwal *et al*., 2021).

Modulation of the cell cycle

Cell cycle dysregulation is a central event in head and neck carcinogenesis and is frequently associated with cyclin overexpression, aberrant activation of cyclin-dependent kinases (CDKs), and loss of cell cycle inhibitor function. In this context, phytochemicals emerge as relevant modulators of cell cycle progression, although observed effects vary according to compound, dose, and preclinical model (Thomas *et al*., 2014; Katiyar, 2016).

The cell cycle is regulated by a coordinated set of cyclins and CDKs, whose sequential activation ensures orderly progression through the G1 (Gap 1): initial cell growth and preparation for DNA synthesis; S (Synthesis): DNA replication; G2 (Gap 2): growth and preparation for mitosis; and M (Mitosis): cell division (mitosis and cytokinesis) phases. Disruptions in this system favor uncontrolled cell proliferation. Induction of cell cycle arrest, particularly at the G1/S and G2/M transitions, constitutes an important antiproliferative mechanism in tumor control (El-Deiry, 2003).

Phytochemicals such as quercetin, luteolin, and apigenin have demonstrated the ability to reduce expression of cyclins D and E while increasing expression of CDK inhibitors such as p21 and p27. These effects result in cell cycle arrest and reduced proliferative rates in HNSCC cell lines. Curcumin has also been associated with G2/M phase arrest, reinforcing its cytostatic potential (Thomas *et al*., 2014; Aggarwal *et al*., 2021).

Although cell cycle modulation represents a promising mechanism, reversibility of arrest in certain experimental contexts raises questions regarding sustained efficacy. Furthermore, the interaction between cell cycle control and cell death induction suggests that the cytostatic and cytotoxic effects of phytochemicals should be analyzed in an integrated manner (Katiyar, 2016; Aggarwal *et al*., 2021).

Emerging non-apoptotic cell death pathways: ferroptosis, necroptosis, and autophagy

In addition to apoptosis, recent evidence has highlighted the relevance of alternative cell death mechanisms, including ferroptosis, necroptosis, and autophagy, in cancer biology. These pathways represent promising therapeutic targets, particularly

in tumors resistant to conventional apoptosis-inducing strategies (Galluzzi *et al*., 2018; Stockwell *et al*., 2017).

Ferroptosis is characterized by iron-dependent lipid peroxidation and has emerged as a relevant mechanism in head and neck cancer biology, with potential therapeutic implications in apoptosis-resistant tumors (Dixon *et al*., 2012; Stockwell *et al*., 2022; Wang *et al*., 2023). Phytochemicals such as curcumin and resveratrol have been associated with modulation of oxidative stress, lipid metabolism, and intracellular redox balance, suggesting a potential role in ferroptotic regulation (Liu *et al*., 2020; Zhang *et al*., 2021).

Necroptosis, a regulated form of necrosis mediated by receptor-interacting protein kinases RIPK1 and RIPK3, has emerged as an alternative mechanism in apoptosis-resistant tumor cells (Galluzzi *et al*., 2018). Although evidence in HNSCC remains limited, the modulation of this pathway by bioactive compounds represents a promising field for future investigation, particularly in the context of resistance to conventional therapies.

Autophagy plays a dual role in cancer, acting as a cytoprotective or cytotoxic mechanism depending on the cellular context (Levy *et al*., 2017). Several phytochemicals have been shown to regulate autophagic pathways, influencing tumor cell survival and death through modulation of signaling pathways such as PI3K/AKT/mTOR and AMPK (Liu *et al*., 2020; Zhang *et al*., 2021). However, the specific role of autophagy in HNSCC remains incompletely understood.

Together, these findings indicate that the anticancer effects of phytochemicals extend beyond classical apoptotic pathways, involving a complex network of cell death mechanisms that require further investigation in translational and clinical models. These pathways may be particularly relevant in overcoming resistance to apoptosis-based therapies.

Cellular senescence as an alternative mechanism

Beyond apoptosis and cell cycle arrest, cellular senescence has been proposed as a relevant alternative mechanism in controlling tumor progression (El-Deiry, 2003; Fulda, Debatin, 2006). However, in the context of HNC, this process remains underexplored and is often mentioned only secondarily in the phytochemical literature (Ostrowska *et al*., 2024).

Cellular senescence is characterized by an irreversible proliferative arrest accompanied by morphological, metabolic, and secretory alterations. This process can be triggered by oxidative stress, DNA damage, and sustained activation of signaling pathways associated with cellular aging, functioning as a tumor suppressive mechanism (El-Deiry, 2003).

Evidence suggests that certain phytochemicals can induce senescence in tumor cells, particularly in contexts where apoptosis is limited. Activation of p53 and p21, as well as controlled increases in oxidative stress, have been associated with induction of this phenotype. However, few studies have systematically investigated this mechanism in HNSCC, representing a significant and underexplored area in the current literature (Aggarwal *et al*., 2021).

Exploration of cellular senescence as a complementary therapeutic strategy requires caution, as the senescence-associated secretory phenotype may, in certain contexts, promote tumor progression. Therefore, controlled induction of senescence by phytochemicals warrants in-depth investigation, particularly in translational models (Fulda, Debatin, 2006).

Combined therapeutic strategies involving phytochemicals

Although phytochemicals demonstrate consistent antiproliferative effects in preclinical models, their isolated use presents limitations in clinical settings. Consequently, interest has grown in combined

therapeutic strategies in which these compounds act as adjuvants to chemotherapy and radiotherapy, enhancing tumor response and reducing resistance mechanisms (Aggarwal *et al*., 2021).

Studies indicate that curcumin can increase the sensitivity of HNSCC cells to cisplatin by inhibiting pro-survival pathways such as NF-κB and PI3K/AKT (Anand *et al*., 2007; Yallapu, Jaggi, Chauhan, 2012). Similarly, resveratrol and EGCG have been associated with tumor radiosensitization, promoting increased DNA damage and reduced cellular repair capacity (Li *et al*., 2023; Veeraraghavan *et al*., 2024).

Despite promising results, lack of standardization regarding doses, therapeutic regimens, and evaluation criteria limits clinical application of these strategies (Aggarwal *et al*., 2021; Kaushik, Tiku, 2023). Moreover, potential pharmacological interactions and adverse effects remain insufficiently explored, reinforcing the need for well-designed clinical trials to validate combined use of phytochemicals in the management of HNC (Johnson *et al*., 2020; O'leary *et al*., 2024).

To integrate the main molecular mechanisms discussed, Table 1 summarizes the phytochemical classes investigated in HNC, their primary molecular targets, predominant cellular effects, and limitations associated with clinical translation.

Table 1 – Summary of major phytochemicals, molecular targets, and translational limitations in HNC.

Class of phytochemicals	Compound(s)	Main molecular targets	Observed cellular effects	Translational limitations and challenges
Polyphenols	Curcumin	NF-κB; PI3K/AKT/mTOR; p53; BCL-2/BAX	Induction of intrinsic apoptosis; cell cycle arrest (G2/M); reduction of tumor-associated inflammation	Low oral bioavailability; rapid metabolism; frequent use of supra-physiological concentrations; scarcity of robust clinical trials
	Resveratrol	p53; PI3K/AKT; MAPK/ERK	Mitochondrial apoptosis; cell cycle modulation; chemosensitization and radiosensitization	Chemical instability; rapid systemic clearance; cell line–dependent variability in response
Catechins (polyphenols)	Epigallocatechin-3-gallate (EGCG)	EGFR; MAPK/ERK; PI3K/AKT; MMP-2/9	Inhibition of cell proliferation; reduction of tumor invasion; induction of apoptosis	Low stability; dependence on tumor molecular context; limited clinical data
Flavonoids	Quercetin	CDKs; cyclins D/E; p21; p27	Cell cycle arrest (G1/S); mitochondrial apoptosis	Dose-dependent effects requiring high concentrations; limited physiological relevance of *in vitro* concentrations
	Luteolin	STAT3; MAPK/ERK; NF-κB	Reduction of cell viability; induction of apoptosis; modulation of inflammatory responses	Scarcity of *in vivo* studies; lack of experimental standardization
	Apigenin	CDKs; STAT3; oxidative stress pathways	Cell cycle arrest; cytostatic effect	Limited translational investigation; absence of clinical data
Terpenoids	Honokiol	PI3K/AKT/mTOR; NF-κB; angiogenesis	Induction of apoptosis; inhibition of tumor angiogenesis	Limited number of HNSCC-specific studies; predominantly preclinical data
Multiple phytochemicals	(combined use)	PI3K/AKT; NF-κB; MAPK	Chemosensitization and radiosensitization; reduction of therapeutic resistance	Lack of standardization of doses and treatment regimens; insufficiently explored potential pharmacological interactions

Legend: (MMP-2/9): [MMP-2: Matrix metalloproteinase-2; MMP-9: Matrix metalloproteinase-9].(STAT3): Signal transducer and activator of transcription 3. **Source:** Prepared by the author, 2026.

In an integrated manner, the main molecular mechanisms modulated by phytochemicals in head and neck cancer are summarized in figure 1, highlighting the convergence of the PI3K/AKT/mTOR, MAPK/ERK, and NF-κB pathways and their effects on apoptosis, cell cycle arrest, and senescence.

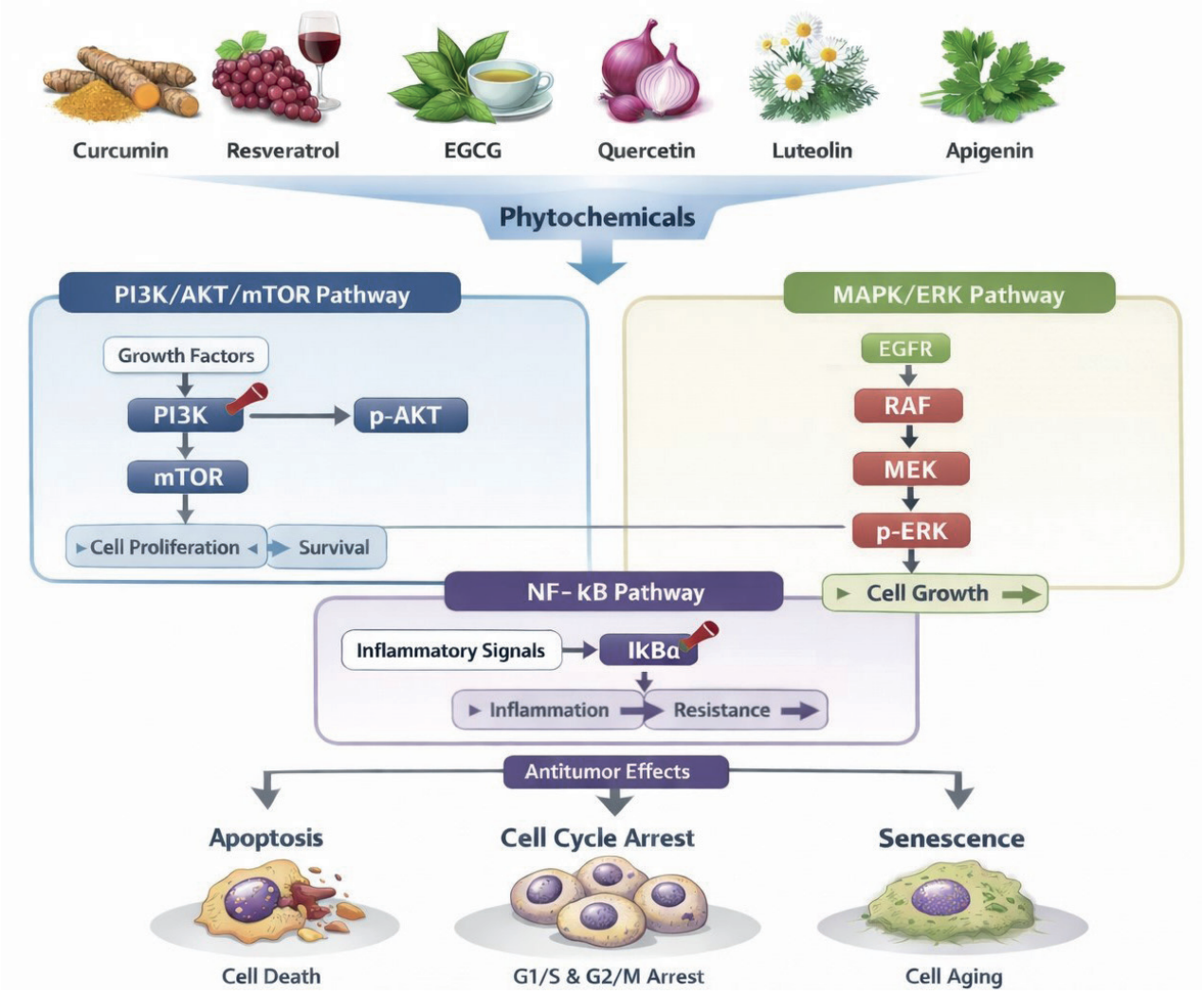


Figure 1 – Schematic representation of the main molecular mechanisms modulated by phytochemicals in HNC.

This reinforces the gap between mechanistic evidence and clinical validation, which remains one of the main challenges in the field. Nevertheless, recent studies have reinforced the relevance of phytochemicals in head and neck cancer, particularly regarding their ability to modulate multiple molecular pathways involved in tumor progression and therapeutic resistance (Singh *et al.*, 2023). This highlights the growing scientific interest in this field, while also emphasizing the need for more robust translational and clinical investigations.

CONCLUSION

The present study enabled the integration and critical analysis of current evidence regarding the role of phytochemicals as modulators of key molecular pathways involved in head and neck carcinogenesis and progression, with particular emphasis on mechanisms of cell death, cell cycle regulation, and therapeutic resistance. The synthesis of the literature indicates that these compounds exert consistent antiproliferative effects in preclinical models through the modulation of multiple signaling cascades, including PI3K/AKT/mTOR, MAPK/ERK, and NF-κB, as well as through the regulation of proteins associated with apoptosis and cell cycle progression. This multitarget activity highlights the biological relevance of phytochemicals in the context of HNSCC.

Mechanistic analysis further demonstrates that different classes of phytochemicals, such as polyphenols, flavonoids, and terpenoids, exhibit distinct and non-equivalent profiles of action across specific signaling pathways and cellular processes. Compounds such as curcumin, resveratrol, and epigallocatechin-3-gallate are particularly associated with the modulation of pro-survival pathways and tumor-associated inflammation, whereas flavonoids including quercetin, luteolin, and apigenin show a more pronounced impact on cell cycle regulation and proliferative arrest. These findings reinforce the importance of considering tumor molecular context and compound-specific mechanisms in the evaluation of phytochemical-based strategies.

Importantly, this review highlights significant limitations that restrict the clinical translation of phytochemicals. The predominance of in vitro and preclinical models, the frequent use of supra-physiological concentrations, and the heterogeneity of experimental designs limit the direct applicability of these findings to clinical settings. In addition, the scarcity of well-designed randomized clinical trials represents a major barrier to the validation of these compounds as therapeutic agents.

From a translational perspective, the available evidence suggests that phytochemicals may have greater potential when used as adjuvant agents in combination with conventional therapies, contributing to tumor sensitization and modulation of resistance-related pathways. However, the lack of standardization in dosing, delivery systems, and clinical evaluation protocols remains a critical challenge.

In summary, phytochemicals represent promising modulators of molecular pathways involved in HNSCC, particularly at the mechanistic and preclinical level. Nevertheless, their incorporation into clinical practice will depend on the advancement of well-designed translational studies, the development of strategies to overcome pharmacokinetic limitations, and the integration of precision medicine approaches, including molecular tumor stratification and combinatorial therapeutic strategies.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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