Trends in Biomaterials and Artificial Organs
sbaoi
journal homepage: www.biomaterials.org.in/tibao
ISSN 0971-1198

Review Article

Integrative Role of Natural Bioactives in Oral Cancer Therapy: Mechanisms of Protection and Efficacy

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Received: *6 September 2025*
Accepted: *4 February 2026*
Published online: *24 February 2026*

Keywords: *oral squamous cell carcinoma, bioactive compounds, chemoprotection, phytochemicals, mitochondrial dysfunction, apoptosis, natural antioxidants, oral mucositis*

Oral cancer, particularly oral squamous cell carcinoma (OSCC), remains a significant global health burden with high morbidity and mortality rates, largely due to late diagnosis and the cytotoxic side effects of conventional therapies. While chemotherapeutic agents remain central to oral cancer management, their lack of selectivity often damages healthy oral tissues, leading to adverse outcomes such as mucositis, xerostomia, myelosuppression, and systemic inflammation, apoptosis, and autophagy. Notably, agents such as curcumin, thymoquinone, resveratrol, quercetin and betanin have been shown to activate Nrf2/ARE antioxidant defences, inhibit NF-êB driven inflammation, preserve mitochondria membrane potential, and regulate apoptotic pathways selectively in cancer versus normal cells. Moreover, their influence on P13K/Akt/mTOR signalling, p53 modulation, and epigenic reprogramming further underscores their therapeutic relevance. This review critically examines the integrative role of bioactive compounds in enhancing treatment efficacy, minimizing off target toxicities, and supporting oral tissue homeostasis offering a framework for incorporating phytochemicals into multimodal oral cancer therapies.

Introduction

Oral cancer, particularly oral squamous cell carcinoma (OSCC), remains a formidable public health challenge globally, accounting for approximately 90% of all malignancies in the oral cavity [1]. Despite significant advancements in early detection and therapeutic approaches including surgery, radiation, and chemotherapy, the overall 5-year survival rate for OSCC hovers around 50-60%, primarily due to late-stage diagnosis, tumor recurrence, metastasis, and the onset of chemoresistance. Conventional chemotherapeutic regiments, such as cisplatin, 5-flurouracil, and doxorubicin, are integral to oral cancer management; however, their lack of selectivity results in collateral damage to healthy tissues, leading to severe side effects including mucositis, myelosuppression, nephrotoxicity, hepatotoxicity, and cardiotoxicity. This therapeutic dilemma underscores the need for adjunct strategies that can enhance treatment efficacy while minimizing systemic toxicity [2].

Over the past few decades, natural bioactive compounds derived from dietary and medicinal plants have garnered considerable attention for their chemopreventive and chemoprotective potential. Polyphenols, flavonoids, alkaloids, and terpenoids present in various botanicals such as green tea, turmeric, grapes, pomegranate, black tea, and beetroot possess a wide array of biological activities including antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, and anti-metastatic properties [3]. In oral cancer research, compounds like curcumin, resveratrol, quercetin, thymoquinone, epigallocatechin gallate (EGCC), and betanin have demonstrated promising results in both in vitro and in vivo models. Their ability to modulate multiple molecular targets and signalling cascades central to carcinogenesis, inflammation, oxidative stress, apoptosis, and immune responses provides a compelling rationale for their integration into oral cancer therapy [4].

A central hallmark of oral carcinogenesis is the persistent oxidative stress induced by tobacco, alcohol, microbial infections (such as HPV), and environmental pollutants. Oxidative stress, marked by excessive production of reactive oxygen species (ROS), causes DNA damage, lipid peroxidation, and protein modifications, ultimately contributing to genetic instability, epigenetic alterations, and cellular transformation. Chemotherapeutic agents, while effective against rapidly dividing cancer cells, exacerbate this redox imbalance, inflicting oxidative damage on non-malignant tissues. Natural compounds like curcumin and resveratrol counteract this burden by activating the Nrf2/Keap1/ARE pathway, which enhances the transcription of antioxidant genes such as HO-1, NQO1, SOD, and catalase. This induction of endogenous antioxidant defenses not only protects healthy oral tissues from chemotherapy induced damage but also augments the redox sensitivity of cancer cells, enhancing their vulnerability to oxidative collapse [5].

Inflammation constitutes another pathological driver in oral cancer initiation, progression, and therapeutic resistance. The NF-κB signal-

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https://doi.org/10.65795/xmgwda06

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ling axis, activated by pro-inflammatory stimuli such as IL-6, TNF-α, and COX-2, orchestrates the transcription of genes involved in cell proliferation, survival, angiogenesis, and immune evasion. In the context of chemotherapy, sustained NF-κB activation contributes to treatment resistance and promotes inflammation associated side effects such as mucositis and systemic inflammatory responses. Bioactive agents such as EGCG, thymoquinone, and quercetin have been shown to inhibit the phosphorylation and degradation of IκB, thereby preventing NF-κB nuclear translocation and transcriptional activity. This results in the downregulation of inflammatory mediators and attenuation of inflammatory responses in the oral mucosa and surrounding tissues [6,7].

Apoptotic dysregulation is central to oral cancer pathogenesis and treatment outcomes. While pro-apoptotic signaling in cancer cells is a desirable effect of chemotherapy, inadvertent activation of apoptosis in healthy epithelial, hepatic, cardiac, and bone marrow cells results in dose limiting toxicities. Natural compounds help in achieving selective cytoprotecting by modulating both the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways. For example, thymoquinone and betanin preserve mitochondrial membrane potential, inhibit cytochrome c release, and enhance Bcl-2 expression in normal oral cells. Simultaneously, they suppress pro-apoptotic proteins such as Bax, caspase-3, and caspase-8, thus conferring protection to non-cancerous cells without impeding the pro-death effects in cancer cells. This duality offers a significant therapeutic edge in balancing efficacy and safety during oral cancer treatment [8,9].

Another promising avenue lies in the modulation of P13K/Akt/mTOR pathway, a major signaling axis implicated in oral cancer growth, chemoresistance, and metabolic reprogramming. While the inhibition of this pathway is beneficial in curbing tumor progression, its activation in healthy tissues may be desirable for cryoprotection. Compounds such as resveratrol and curcumin exhibit context dependent activity suppressing Akt/mTOR signalling in malignant oral keratinocytes while enhancing it in normal epithelial or fibroblast cells to promote survival and mitigate chemotherapy induced apoptosis. This selective modulation exemplifies the precision and adaptability of phytochemicals in orchestrating complex cellular responses [10].

Furthermore, bioactives regulate autophagy - a catabolic process critical for maintaining cellular homeostasis under stress conditions. Chemotherapy induced damage results in the accumulation of dysfunction organelles and protein aggregates, particularly in the oral mucosa, liver, and neurons. By activating AMPK and inhibiting mTOR, compounds like EGCG and resveratrol enhance autophagic flux, promoting the clearance of toxic cellular components and improving stress tolerance in normal cells. This cytoprotective autophagy also reduces inflammation, enhances tissue regeneration, and delays the onset of oral mucositis and neurotoxicity, common complications associated with oral cancer therapy [11,12].

Epigenic dysregulation, including aberrant DNA methylation and histone modifications, plays a pivotal role in oral tumor progression and resistance. Chemotherapeutic agents can induce global epigenic changes that silence tumor suppressor genes and activate oncogenes. Several bioactive compounds function as epigenic modulators, restoring gene expression patterns through HDAC inhibition, DNA demethylation, and histone acetylation. Curcumin, for instance, modulates the expression of p21, p16, and GSTP1 through epigenic reprogramming, thereby reinstating tumor suppressive functions while protecting normal oral cells from genotoxic stress [10].

Collectively, the integrative application of bioactive natural compounds in oral cancer therapy represents a multifaced approach that targets both tumor eradication and host protection. By intervening in key hallmarks of cancer oxidative stress, inflammation, apoptosis, metabolic reprogramming, and epigenetic instability these compounds serve not only as chemoprotective agents but also as adjuvants that enhance the therapeutic index of conventional treatments. Their low toxicity profiles, widespread dietary availability, and multitargeted mechanisms make them ideal candidates for translational research and clinical integration [13].

However, despite the promising preclinical evidence, several challenges remain. The bioavailability of many natural compounds is limited by poor solubility, rapid metabolism, and systemic clearance. Strategies such as nanoformulations, prodrug development, and combination therapies are being explored to overcome these limitations. Moreover, comprehensive clinical trials are warranted to validate the efficacy and safety of these agents in oral cancer patients, particularly in the context of chemoradiotherapy. Future research must also delineate the molecular contexts in which these compounds exert beneficial effects to avoid potential interference with anticancer efficacy. Hence, natural bioactives present a unique opportunity to transform oral cancer therapy by reducing treatment related toxicity, enhancing tumor sensitivity, and preserving normal tissue function. Their integration into standard care

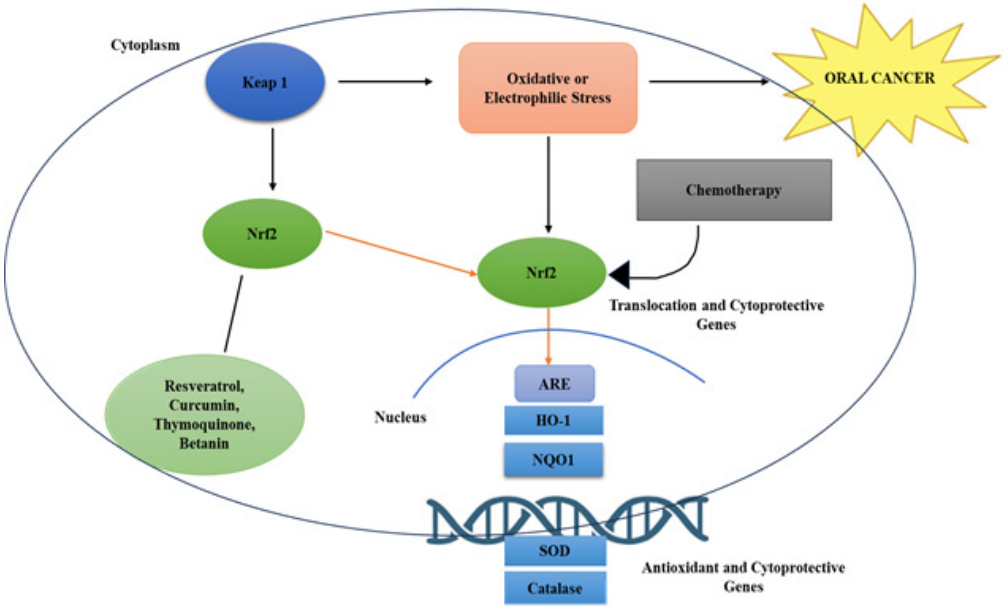

Figure 1: Activation of the Nrf2/Keap1/ARE pathway by natural compounds enhances antioxidant defence and protects normal oral tissues while modulating chemoresistance in oral squamous cell carcinoma

paradigms could revolutionized supportive oncology and pave the way for precision phytotherapy in head and neck cancers [14].

Activation of Antioxidant Defence via Nrf2/ Keap1/ARE Pathway in Oral Cancer Context

Oxidative stress is a hallmark of oral squamous cell carcinoma and plays a dual role in both tumor progression and chemotherapy induced toxicity. Reactive oxygen species (ROS) generated intrinsically by malignant cells or induced by chemotherapeutic agents contribute to DNA damage, inflammation, and metabolic reprogramming within the tumor microenvironment. However, this same oxidative stress can also lead to off target injury in adjacent healthy oral tissues, exacerbating side effects such as oral mucositis, dysgeusia, and ulceration. In this context, modulation of redox balance becomes a critical therapeutic strategy, and natural bioactive compounds that activate the Nrf2/Keap1/ARE pathway have emerged as promising adjuncts in oral cancer therapy (figure 1).

The transcription factor nuclear factor erythroid 2 related factor 2 (Nrf2) serves as the master regulator of cellular antioxidant defense. Under normal conditions, Nrf2 is bound in the cytoplasm by its inhibitor Keap 1 (Kelch like ECH associated protein 1), which targets it for ubiquitin mediated degradation. However, in response to oxidative or electrophilic stress such as that caused by cisplatin or 5 fluorouracil (5-FU) used in OSCC treatment critical cysteine residues on Keap 1 become oxidized, leading to the release and stabilization of Nrf2. Once translocated to the nucleus, Nrf2 binds to antioxidant response elements (AREs) in the promoter regions of cytoprotective genes, thereby enhancing the expression of detoxifying enzymes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [15].

Bioactive phytochemicals such as resveratrol, curcumin, thymoquinone, and betanin have shown potent Nrf2 activating properties in preclinical models of oral cancer. These compounds can restore redox balance in normal oral mucosa, reduce ROS accumulation, and prevent the activation of downstream inflammatory mediators such as NF-κB and COX-2. Importantly, these natural compounds do not uniformly activate Nrf2 in all cell types. In OSCC cells, where Nrf2 is often hyperactivated due to Keap 1 mutations and contributes to chemoresistance, these bioactive can also induce context dependent inhibition or modulation of the Nrf2 pathway, resensitizing tumor cells to chemotherapy [16].

Furthermore, studies in oral keratinocytes and animal models have demonstrated that Nrf2 activation by these compounds can protect against 5 FU induced oral mucositis by enhancing mitochondrial function, reducing lipid peroxidation, and preserving epithelial barrier integrity. This selective activation of antioxidant responses in non-malignant oral tissues without compromising the anti-tumor efficacy of chemotherapeutic agents underscores the therapeutic versatility of natural bioactives. Thus, targeted activation of the Nrf2/Keap1/ARE pathway by phytochemicals represents a dual function strategy in oral cancer management: it not only attenuates oxidative damage in healthy tissues but also fine tunes redox signaling within the tumor microenvironment to enhance treatment efficacy.

Suppression pf Pro-inflammatory Pathways via NF-κB Inhibition in Oral Cancer

The nuclear factor-kappa B (NF-κB) signaling pathway plays a pivotal role in regulating inflammation, immunity, cell proliferation, and survival. In the context of oral cancer, persistent activation of NF-κB is a hallmark of both tumorigenesis ad therapy induced tissue damage. While NF-κB contributes to the progression of OSCC by promoting inflammatory cytokine production, angiogenesis, epithelial to mesenchymal transition (EMT), and resistance to apoptosis, its unchecked activation in normal oral tissues following chemotherapy or radiotherapy exacerbates mucositis, tissue degradation, and delayed healing. Therefore, inhibition of NF-κB signaling represents a dual targeted strategy: it sensitizes cancer cells to apoptosis while simultaneously mitigating damage to adjacent healthy tissues[17].

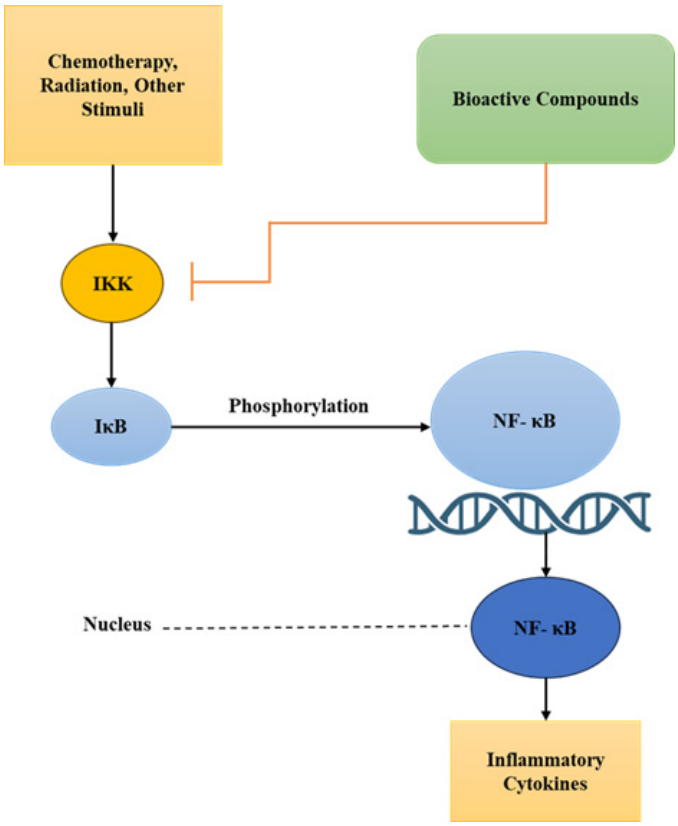

Figure 2: Natural compounds inhibit NF-kB activation, reducing inflammation and protecting normal oral tissues while suppressing tumor progression in oral cancer

Under basal conditions, NF-êB exists in the cytoplasm as a heterodimer bound to its inhibitor, IêBá. Upon exposure to external stressors such as chemotherapeutic agents, radiation, and bacterial toxins, IκB kinase (IKK) becomes activated. IKK phosphorylates IκBα, marking it for proteasomal degradation. This degradation releases NF-κB, allowing it to translocate into the nucleus where it binds specific κB sites in DNA promoter regions. The result is the transcription of numerous pro-inflammatory genes including TNF-α, IL-6, IL-1β, COX-2, and MMP-9, which perpetuate the inflammatory cycle and promote tumor supportive microenvironmental changes (figure 2).

Bioactive phytochemicals such as curcumin, resveratrol, theaflavin, thymoquinone, and quercetin exert potent inhibitory effects on NF-κB activation. In OSCC models, curcumin has been shown to inhibit IKK activity, thereby preventing IκBα degradation and nuclear translocation of NF-κB. Resveratrol modulates upstream kinases and suppresses NF-κB regulated gene expression in both cancerous and inflamed oral epithelial cells. Thymoquinone not only inhibits IKK but also interferes with NF-κB DNA binding, suppressing transcription of downstream pro-inflammatory mediators. Theaflavin has demonstrated a synergistic ability to reduce NF-κB activation when combined with other chemotherapeutics, aiding in the reducing of inflammatory cytokines and protecting oral mucosa from treatment induced injury.

The clinical relevance of targeting NF-κB is especially significant in oral cancer, where the local inflammatory milieu contributes to carcinogenesis, enhances resistance to therapy, and fosters recurrence. NF-κB inhibition through natural compounds results in the downregulation of cyclin D1, Bcl-2, VEGF, and MMPs- key mediators of proliferation,

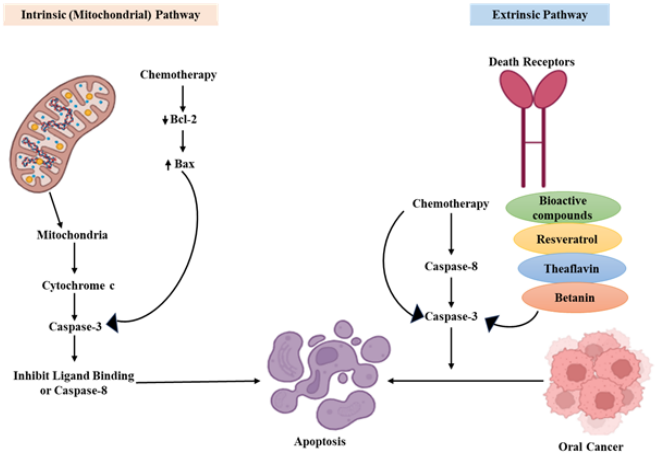

Figure 3: Natural bioactives modulate intrinsic and extrinsic apoptotic pathways, inducing cancer cell death while protecting normal oral cells from chemotherapy induced apoptosis

angiogenesis, and metastasis. Simultaneously, suppression of NF-κB in non-malignant oral mucosal cells helps reduce chemotherapy associated associated mucositis, ulceration, and fibrosis by limiting inflammatory cytokine storm and oxidative stress. Thus, selective modulation of the NF-κB pathway using natural bioactives represents a promising adjunct in oral cancer therapy, offering cytoprotection to normal tissues while impairing tumor promoting mechanisms within cancer cells. This dual advantage underscores the therapeutic potential of incorporating these compounds into standand oral oncology regiments [17,18].

Modulation of Apoptotic Pathways by Natural Bioactives in Oral Cancer Therapy

Apoptosis, or programmed cell death, is a fundamental biological process responsible for maintaining cellular homeostasis by eliminating damaged or potentially dangerous cells. In oral squamous cell carcinoma, dysregulation of apoptotic pathways plays a central role in tumor development, progression, and resistance to therapy. Chemotherapeutic agents induce apoptosis of non-cancerous cells, thereby contributing to treatment associated toxicity such as mucositis, myelosuppression, and salivary gland dysfunction. In this context, natural bioactive compounds have emerged as promising agents capable of selectively modulating apoptotic pathways, promoting apoptosis in oral cancer cells while protecting healthy tissues [19].

Apoptosis occurs via two primary pathways: the intrinsic (mitochondrial) pathway nd the extrinsic (death receptor -mediated) pathway. The intrinsic pathway is activated by intracellular stress signals such as DNA damage and oxidative stress, leading to mitochondrial outer membrane permeabilization (MOMP). This results in the release of cytochrome c into the cytoplasm, formation of the apoptosome complex, and activation of caspase-9, followed by downstream activation of caspase-3, a key executioner caspase. The balance between pro-apoptotic proteins and anti-apoptotic proteins determines the fate of the cell [20].

Natural compounds like thymoquinone, resveratrol, and betanin have been reported to restore the dysregulated apoptotic balance in oral cancer. In OSCC cells, these agents induce apoptosis by increasing the Bax/Bcl-2 ratio, facilitating mitochondrial dysfunction and caspase activation. Importantly, in normal oral epithelial cells and fibroblasts, these compounds exhibit cytoprotective effects, often by stabilizing mitochondrial membrane potential, suppression excessive ROS accumulation, and upregulating Bcl-2, thereby preventing chemotherapy induced apoptosis (figure 3).

The extrinsic pathway involves the activation of death receptors such as Fas, TNFR1, and TRAIL-R upon ligand binding, which subsequently triggers caspase-8 activation. Bioactives like quercetin and curcumin have been shown to sensitize OSCC cells to TRAIL induced apoptosis by upregulating death receptor expression and downregulating inhibitors of apoptosis proteins (IAPs), such as surviving and c-FLIP. These actions restore the responsiveness of OSCC cells to immune mediated or drug induced apoptosis. Moreover, some compounds demonstrate dual regulatory properties. For example, EGCG (epigallocatechin gallate) and theaflavin can induce caspase-3 activity in OSCC cells while concurrently suppressing caspase activation in non-malignant oral keratinocytes exposed to chemotherapeutic stress. This context dependent action is believed to be mediated through differential modulation of ROS levels and p53 signaling. Collectively, these findings suggest that natural bioactives can fine tune apoptotic signaling in a cell specific manner potentiating apoptosis in oral cancer cells while safeguarding adjacent normal tissues. This selective modulation makes them attractive adjuvants in OSCC therapy, offering the potential to reduce side effects and improve overall therapeutic efficacy [21].

Regulation of P13K/Akt/mTOR Pathway in Oral Cancer by Natural Bioactives

The phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway plays a pivotal role in regulating cell growth, proliferation, metabolism, and survival. In the context of oral squamous cell carcinoma (OSCC), this pathway is frequently dysregulated, leading to uncontrolled tumor progression, resistance to apoptosis, and chemotherapeutic resistance. Activation of PI3K leads to phosphorylation of Akt, a serine/threonine kinase, which subsequently activates downstream effectors including mTOR complex 1 (mTORC1). mTORC1, in turn, promotes protein synthesis, angiogenesis, and cellular proliferation by phosphorylating targets such as p70S6 kinase and 4E-BP1. Aberrant activation of this signaling cascade is observed in a significant proportion of oral cancers and is associated with poor prog-

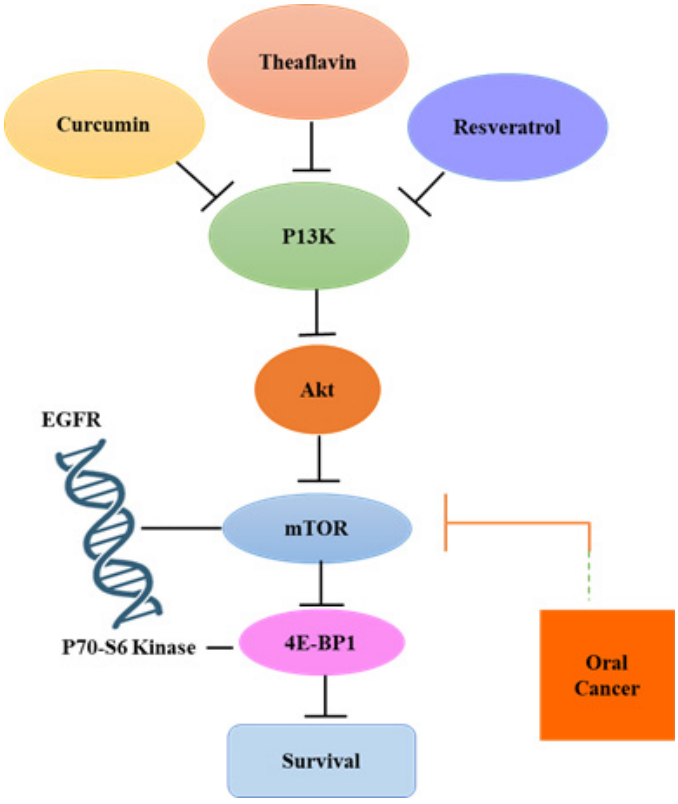

Figure 4: Natural bioactives modulate the P13k/Akt/mTOR pathway by inhibiting tumor growth and inducing apoptosis in oral cancer cells while protecting normal tissues from chemotherapy induced damage

nosis, increased invasiveness, and reduced response to conventional therapies (figure 4).

Natural bioactive compounds have emerged as promising modulators of the P13K/Akt/mTOR axis, offering dual advantages: suppressing tumor growth in OSCC while preserving or even enhancing the survival of non-malignant cells affected by chemotherapy. Curcumin, for instance, has been extensively studied for its ability to inhibit PI3K activity and prevent Akt phosphorylation in oral cancer cells. This inhibition results in decreased mTOR signaling, thereby halting cancer cell growth and inducing apoptosis. Similarly, resveratrol has been shown to interfere with the phosphorylation of Akt and mTOR, leading to autophagy induction and growth arrest in oral cancer models. These effects are often associated with downregulation of anti-apoptotic proteins such as Bcl-2 and surviving, along with upregulation of pro-apoptotic markers like Bax and Caspase-3 [22].

Interestingly, the action of these compounds appears to be context specific. While they supress the PI3K/Akt/mTOR pathway in OSCC cells, in non-cancerous tissues exposed to chemotherapeutic insults, they may activate or stabilize this pathway to promote survival and tissue repair. This is particularly important in protecting oral mucosal cells, fibroblasts, and keratinocytes from chemotherapy induced cytotoxicity. For example, quercetin and EGCG have demonstrated the ability to enhance Akt activation in normal cells, thereby supporting mitochondrial integrity, reducing ROS generation, and preventing apoptosis. Moreover, modulation of upstream and downstream regulators of this pathway further enhances the therapeutic efficacy of bioactives. Certain polyphenols downregulate growth factor receptors such as EGFR, which are often overexpressed in OSCC, leading to decreased P13K signaling. Others, like betanin and thymoquinone, influence transcription factors such as NF-κB and c-Myc that intersect with PI3K/Akt signaling, amplifying anti-cancer effects. Henceforth, natural bioactives offer a promising strategy to selectively modulate the P13K/Akt/mTOR signaling cascade in oral cancer. Their ability to inhibit oncogenic signaling in malignant cells while safeguarding normal tissues from chemotherapeutic toxicity represents a significant therapeutic advantage. Future research and clinical trials should focus on optimizing combinations, delivery systems, and dosages to fully harness the cytoprotective and anticancer potential of these compounds in oral oncology [23].

Epigenetic Modulation by Natural Bioactives in Oral Cancer: A Protective Mechanism Against Chemotoxicity

Epigenetic regulation plays a crucial role in the onset, progression, and therapeutic response of oral cancer. Epigenetics refers to heritable modifications in gene expression that do not alter the DNA sequence but affect chromatin structure and transcriptional activity. These modifications include DNA methylation, histone acetylation/deacetylation, and non-coding RNA regulation. In oral squamous cell carcinoma (OSCC), abnormal DNA hypermethylation often silences tumor suppressor genes such as p16INK4a, DAPK, and E-cadherin, while global hypomethylation can lead to genomic instability. Furthermore, overexpression of histone deacetylases (HDACs) in OSCC promotes oncogenic gene expression, supporting proliferation, inflammation, and resistance to chemotherapy [24].

Chemotherapeutic agents such as cisplatin and 5-fluorouracil have been associated with widespread epigenetic dysregulation, contributing to both therapeutic resistance and toxicity in normal tissues. In this context, natural bioactive compounds offer a promising avenue for epigenetic modulation. Molecules such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) have been demonstrated to function as epigenetic modifiers, capable of reversing aberrant methylation and acetylation patterns. Curcumin, for instance, inhibits HDACs and DNA methyltransferases (DNMTs), leading to re-expression of silenced tumor suppressor genes in oral cancer cells. Resveratrol also downregulates HDAC1 and modulates microRNA expression profiles, restoring normal gene regulation (figure 5).

The epigenetic effects of these compounds extend beyond tumor

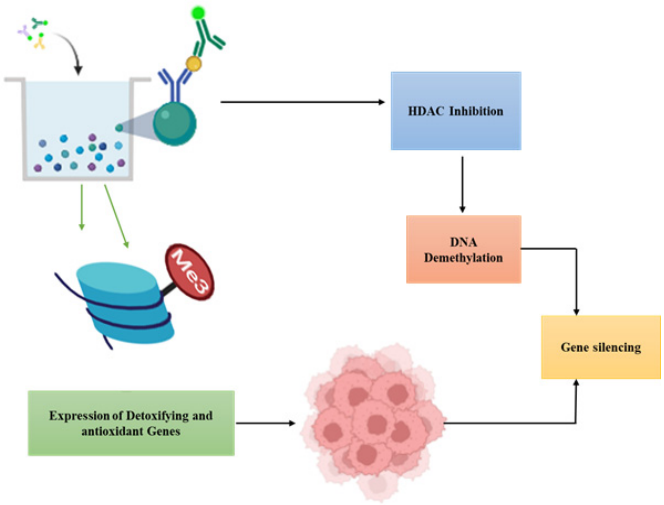

Figure 5: Natural bioactives regulate epigenic changes in oral cancer by correcting abnormal methylation and acetylation, reactivating tumor suppressor genes, and protecting healthy tissues from chemotoxic stress

cells to offer chemoprotective benefits in non-cancerous tissues. By restoring the expression of antioxidant and detoxifying genes such as NQO1, HO-1, and GST through demethylation or histone acetylation, these bioactive enhance the cellular defense against reactive oxygen species (ROS) and genotoxic insults. Furthermore, they reduce inflammation by downregulating pro-inflammatory gene expression epigenetically, thereby preserving oral mucosal integrity during chemotherapy. Importantly, these natural compounds exhibit selective activity promoting epigentic reprogramming in cancer cells while sparing normal tissues. For example, in OSCC cells, curcumin and EGCG promote apoptosis via the upregulation of p21 and downregulation of surviving through epigenetic mechanisms, whereas in non-malignant oral keratinocytes, they reinforce antioxidant pathways and maintain cell viability. This differential regulation highlights the dual protective and therapeutic potential of epigenetic modulators [25].

Overall, the integration of natural bioactive compounds as epigenetic therapeutics in oral cancer offers a strategy to not only suppress tumor progression but also mitigate the side effects of chemotherapy. Their ability to remodel the cancer epigenome while preserving genomic and epigenomic stability in normal cells positions them as potent adjuvants in oral cancer management. Further research and clinical trials are needed to validate the efficacy of these compounds in patient specific epigenetic landscapes and to optimize their use in combinatorial therapies for personalized oral cancer care [26].

Phytochemical Mediated Attenuation of Wnt/β-Catenin Signalling in Oral Cancer Therapy

The Wnt/β-catenin signaling pathway is a highly conserved molecular cascade that plays a vital role in embryonic development, cell fate determination, and tissue homeostasis. However, its aberrant activation is closely associated with carcinogenesis, particularly in oral squamous cell carcinoma, where it promotes uncontrolled cell proliferation, epithelial mesenchymal transition, metastasis, and chemoresistance. In normal conditions, β-catenin is tightly regulated by a destruction complex composed of adenomatous polyposis coli (APC), Axin casein kinase 1α (CK1α), and glycogen synthase kinase 3β (GSK-3β). This complex phosphorylates β-catenin, marking it for ubiquitin mediated degradation, thus preventing its accumulation and transcriptional activity [27].

In OSCC, however, this regulation becomes disrupted due to mutations or epigenetic alterations that stabilize â-catenin or impair the com-

ponents of the destruction complex. Consequently, β-catenin escapes degradation, accumulates in the cytoplasm, and translocates into the nucleus. Once in the nucleus, β-catenin partners with T-cell factor/lymphoid enhancer binding factor (TCF/LEF) transcription factors, initiating the transcription of oncogenes such as c-Myc, Cyclin D1, VEGF, and matrix metalloproteinases (MMPs). This transcriptional reprogramming not only drives tumorigenesis but also facilitates angiogenesis and resistance to therapy by enhancing the survival and self-renewal of cancer stem like cells (figure 5).

Natural bioactive compounds such as theobromine, curcumin, and sulforaphane have demonstrated promising regulatory effects on the Wnt/β-catenin pathway in oral cancer. Curcumin, a polyphenol derived from *Curcuma longa*, inhibits Wnt signalling by activating GSK-3β, which enhances β-catenin degradation. It also disrupts the nuclear translocation of β-catenin, thereby suppressing downstream oncogenic transcription. Sulforaphane, an isothiocyanate found in cruciferous vegetables, facilitates the stabilization of the destruction complex by increasing the expression of Axin and APC. This leads to reduced cytoplasmic β-catenin levels and diminished transcriptional activation of Wnt target genes. Additionally, sulforaphane has been shown to supress CD44 and ALDH1 markers of oral cancer stem cells indicating its capacity to target the Wnt dependent cancer stemness phenotype. Theobromine, a methylxanthine alkaloid found in cocoa, has recently garnered attention for its Wnt-inhibitory effects. It interferes with β-catenin's interaction with TCF/LEF and reduces its nuclear accumulation, thereby attenuating proliferation and enhancing apoptosis in OSCC models [28].

The modulation of Wnt/β-catenin signaling by these bioactives not only curtails tumor progression but also sensitizes oral cancer cells to conventional chemotherapy and radiotherapy. Importantly, these compounds exhibit selective cytotoxicity, sparing non-cancerous oral epithelial cells, which highlights their potential as safe adjuvants. By mitigating EMT, reducing metastasis, and preventing therapeutic resistance, Wnt-targeting bioactives provide a multifaced approach to oral cancer management. Their natural origin and low toxicity profile make them especially suitable for long term use as chemopreventive agents. Overall, the suppression of Wnt/β-catenin signaling represents a promising strategy in the integrative treatment of OSCC, aligning with the growing interest in plant derived compounds for cancer therapy (figure 6).

Discussion

Oral squamous cell carcinoma remains a challenging malignancy, characterized by its aggressive invasion, frequent metastasis, and limited responsiveness to conventional chemotherapy. Despite advances in surgical techniques and targeted therapeutics, the prognosis for advanced stage oral cancer remains poor. Moreover, chemotherapeutic agents such as cisplatin and 5-flurouracil, though effective against proliferating cancer cells, indiscriminately damage normal tissues resulting in mucositis, myelosuppression, and nephrotoxicity. This dual burden necessitates the exploration of adjunctive strategies that not only enhance anticancer efficacy but also protect healthy tissues. Natural bioactive compounds, due to their multifaceted molecular properties, have emerged as promising modulators in oral cancer therapy [29].

Among the key protective mechanisms, the activation of the Nrf2/Keap1/ARE antioxidant defense pathway stands out. Nrf2 activation enhances the transcription of cytoprotective genes such as HO-1, NQO1,

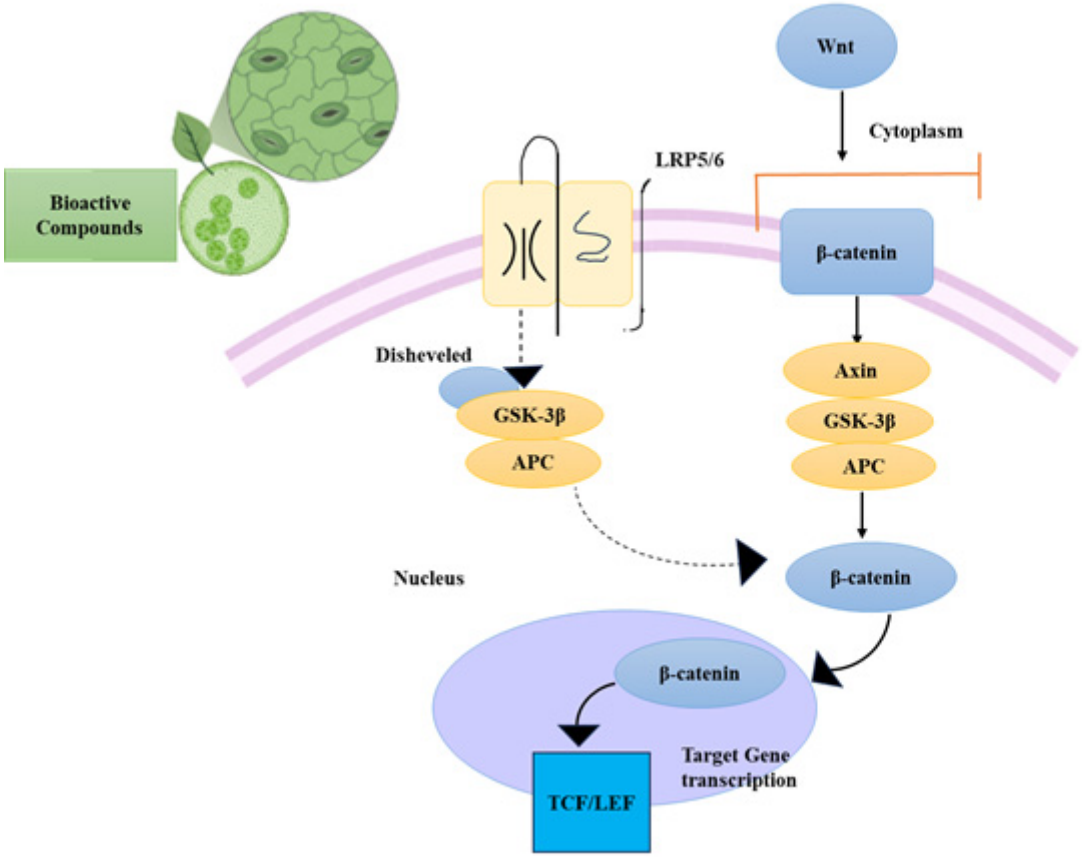

Figure 6: Natural bioactive supress Wnt/â catenin signalling, reducing â-catenin activity and oncogenic gene expression to inhibit oral cancer growth and metastasis

and GCLC, which collectively scavenge reactive oxygen species (ROS) and restore redox balance. In oral epithelial cells, bioactives like betanin and theaflavin upregulate Nrf2 signaling, mitigating oxidative damage induced by chemotherapy. Simultaneously, Nrf2 activation in OSCC cells can supress tumor progression under specific oxidative microenvironments, thus serving dual protective and anti-tumor functions [30].

Another major axis targeted by natural compounds is NF-κB signaling, a central driver of inflammation, angiogenesis, and resistance to apoptosis in OSCC. Chronic NF-κB activation in the tumor microenvironment enhances the secretion of cytokines such as IL-6 and TNF-α, promoting immune evasion and therapeutic resistance. Resveratrol, thymoquinone, and theobromine have demonstrated the ability to inhibit NF-κB nuclear translocation, thus suppressing the inflammatory milieu associated with OSCC. This regulation not only reduces tumor progression but also ameliorates inflammation driven mucosal toxicity in non-cancerous oral tissues.

Apoptosis modulation, both intrinsic and extrinsic, is critical in balancing cancer cell elimination and healthy tissue preservation. Chemotherapy induced mitochondrial dysfunction activates the intrinsic apoptotic pathway, characterized by cytochrome c release and caspase - 9 activation. Extrinsically, death receptors such as Fas and TRAIL-R1/R2 activate caspase-8. In OSCC, compounds like curcumin and sulforaphane selectively promote apoptosis in malignant cells enhancing Bax and caspase expression, while preserving Bcl-2 in non-transformed keratinocytes, thus preventing collateral cell death. Furthermore, the P13K/Akt/mTORaxis, which governs survival, proliferation, and metabolic regulation, is frequently dysregulated in OSCC. While chemotherapeutic agents target this pathway to reduce tumor cell viability, normal cells require its function to recover from cytotoxic insult. The dual action of curcumin and resveratrol suppressing this pathway in cancer cells while activation it in normal epithelium demonstrates the contextual adaptability of natural bioactives. Their ability to modulate upsteam regulators like PTEN and downstream mediators like mTORC1 allows for selective protection [31].

Epigenic modulation represents another critical protective mechanism. Chemotherapy disrupts DNA methylation and histone acetylation, silencing tumor suppressors and activating oncogenes. Natural HDAC inhibitors such as theaflavin and quercetin restore histone acetylation patterns, upregulating genes like p21 and Nrf2 while downregulating oncogenes like cyclin D1. This reprogramming supports both tumor suppression and normal tissue repair. Moreover, epigenetic flexibility ensures sustained chemoprotective gene expression without altering DNA sequences.

A particularly aggressive hallmark of OSCC is the activation of Wnt/â catenin signaling, which drives epithelial mesenchymal transition (EMT), invasion, and resistance. Natural compounds such as theobromine and sulforaphane inhibit Wnt signaling by destabilizing â-catenin, suppressing target genes like c-Myc and Cyclin D1. This reduces the metastatic potential of OSCC cells while allowing epithelial differentiation and regeneration in non-cancerous tissues.

Additionally, regulation of autophagy serves as a cytoprotective process under chemotherapeutic stress. Bioactives like EGCG and resveratrol activate AMPK and inhibit mTOR to promote autophagic clearance of damaged mitochondria and proteins. This autophagic modulation reduces inflammation, oxidative stress, and cellular senescence, particularly in the oral mucosa and salivary glands subjected to genotoxic stress. Lastly, the suppression of p53 overactivation in normal tissues is crucial. While p53 activation facilitates cancer cell apoptosis, excessive activation in healthy cells promote tissue injury. Compounds like thymoquinone and quercetin maintain physiological levels of p53 by modulating its post-translational regulation, preventing undue apoptosis and preserving tissue integrity [32].

Altogether, these mechanisms highlight the nuanced, cell context specific activity of bioactive compounds. Their ability to differentially modulate pathways such as inducing apoptosis in cancer cells while protecting normal cells, underscores their value in integrative oral cancer therapy. However, several challenges remain. The bioavailability of these compounds, potential interactions with chemotherapeutics, and dose dependent effects warrant further investigation. Future research must focus on clinical translation, pharmacokinetics, and formulation strategies, including nano delivery systems that enhance targeting and reduce systemic toxicity.

Moreover, the tumor microenvironment in OSCC, rich in cancer associated fibroblast (CAFs), inflammatory cytokines, and altered metabolic conditions, provides both a barrier and an opportunity. Bioactive compounds can modulate this microenvironment by suppressing CAF activation, inhibiting glycolytic reprogramming, and restoring immune surveillance, thereby transforming a chemoresistant niche into a more responsive one. In conclusion, natural bioactives represent a compelling adjunct to conventional therapy in oral cancer. Their pleiotropic actions, ranging from redox regulation to epigenetic remodeling enable selective protection and antitumor efficacy. Integrating these compounds into chemotherapeutic regiments may not only improve treatment outcomes but also reduce the debilitating side effects that compromise quality of life in oral cancer patients [33].

Conclusion

Natural bioactive compounds offer a promising avenue in oral cancer therapy by modulating multiple molecular pathways involved in oxidative stress, inflammation, apoptosis, survival signaling, epigenetics, and autophagy. Their ability to differentiate between malignant and healthy cells allows for selective cytoprotection during chemotherapy, mitigating off target toxicities while enhancing anticancer efficacy. Compounds such as resveratrol, theaflavin, thymoquinone, and curcumin demonstrate synergistic effects by activating protective pathways like Nrf2 in normal tissues and simultaneously suppressing oncogenic signals like NF-κB, P13K/Akt, and Wnt/β-catenin in cancer cells. These dual effects position them as ideal adjuncts in oral cancer treatment protocols. Moving forward, refining delivery systems and validating these compounds through rigorous clinical studies will be crucial for translating their therapeutic potential into standard clinical practice. Their integrative use not only enhances chemotherapeutic outcomes but also aligns with the broader goals of personalized and precision medicine in oral oncology.

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