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REVIEW ARTICALE

THERAPEUTIC POTENTIAL OF OCIMUM TENUIFLORUM PHYTOCHEMICALS IN ORAL CANCER-A COMPREHENSIVE REVIEW

Lakshmi Thangavelu[1*], Ramana Gangireddy[2], Raju Balaji[1*], Muthu Thiruvengadam[3,4], Rekha Thiruvengadam[1], Prathap Chandar Manivannan[5]

[1]Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Thandalam, Chennai, Tamil Nadu, India
[2]KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andra Pradesh, India
[3]*Department of Applied Bioscience*, College of Life and Environmental Science, *Konkuk University, South Korea*
[4]Centre of Research Impact and Outcome, Chitkara University, Rajpura, Punjab, India
[5]Faculty of Dentistry, MAHSA University, Bandar Saujana Putra, 42610 Jenjarom, Selangor, Malaysia

[*]***Corresponding author: Lakshmi Thangavelu and Raju Balaji****, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India*
E-mail: lakshmi@saveetha.com, balajir24.smc@saveetha.com

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ABSTRACT

Background: Oral cancer remains a significant global health challenge, characterized by high mortality rates and limited effective treatment options. There is a growing interest in natural bioactive compounds as potential therapeutic agents to overcome the limitations of conventional therapies.

Purpose: This review aims to explore the therapeutic potential of bioactive compounds derived from *Ocimum tenuiflorum* L. (Holy basil or Tulsi) in the management of oral cancer.

Methods: A comprehensive literature survey was conducted PubMed, Scopus, and Web od Science database to analyze the mechanisms through which key phytochemicals from *O. tenuiflorum*, such as eugenol, rosmarinic acid, apigenin, and linalool, exert anticancer effects. Keywords included: "*Ocimum tenuiflorum*," "Tulsi," "Bioactive Compounds," "Nanotechnology," "Oral Cancer," "Personalized Medicine." We focused on modulating oxidative stress, inducing apoptosis, and inhibiting metastasis by interfering with critical signaling pathways.

Results: The selected phytochemicals demonstrated potent anticancer properties against oral cancer cells in preclinical studies. They effectively modulated oxidative stress, promoted apoptosis, and inhibited metastatic progression. However, significant gaps persist regarding their clinical applicability and long-term safety profiles.

Conclusions: *Ocimum tenuiflorum* exhibits transformative potential in oral cancer therapy. Future research should prioritize clinical translation of these preclinical findings and focus on developing novel therapeutic agents tailored to individual patient needs.

KEYWORDS: Bioactive Compounds, Nanotechnology, *Ocimum tenuiflorum*, Oral Cancer, Personalized Medicine

1. INTRODUCTION

Oral cancer, a subset of head and neck cancers, poses a significant global health burden, particularly in developing countries. It is characterized by the malignant transformation of epithelial cells in the oral cavity and is often diagnosed at advanced stages, contributing to high morbidity and mortality.[1]

Key etiological factors include tobacco use, alcohol consumption, poor oral hygiene, viral infections such as Human Papilloma Virus (HPV), and genetic predisposition. Despite the availability of conventional treatments such as surgery, chemotherapy, and radiation, these interventions often have limited efficacy, serious side effects, and high recurrence rates. Consequently, there is a growing interest in alternative and complementary therapies, particularly those based on medicinal plants, to

address these limitations. Among the many botanicals studied for their anticancer properties, *Ocimum tenuiflorum* L., commonly known as Holy basil or Tulsi, has emerged as a prominent candidate. Revered in Ayurvedic and other traditional systems of medicine, Tulsi is known for its wide spectrum of therapeutic properties. The plant contains a diverse array of phytochemicals, including eugenol, rosmarinic acid, apigenin, linalool, and other phenolic compounds, which have demonstrated potent antioxidant, anti-inflammatory, antimicrobial, and anticancer effects.[2,3,4,5] These compounds interact with multiple cellular pathways and have been shown to exert a significant influence on tumor growth and progression.

One of the primary mechanisms through which *O. tenuiflorum* exerts its anticancer effects is oxidative stress modulation. Oxidative stress plays a pivotal role in carcinogenesis by damaging cellular components and inducing mutations. The phytoconstituents in Tulsi exhibit strong free radical scavenging activities and enhance endogenous antioxidant defenses, thereby reducing the risk of cancer initiation and progression.[6] Additionally, Tulsi compounds can inhibit inflammatory pathways implicated in tumor promotion and metastasis, such as NF-κB and PI3K/Akt signaling. These pathways are essential for cancer cell survival, proliferation, and resistance to apoptosis. Another critical anticancer mechanism of *O. tenuiflorum* is the induction of apoptosis, or programmed cell death, in malignant cells. Compounds like apigenin and eugenol have been shown to modulate signaling pathways such as MAPK and HIF-1α, which regulate cell cycle arrest and apoptosis.[7,8] This selective cytotoxicity towards cancer cells, while sparing normal cells, presents a distinct advantage over conventional chemotherapy. Furthermore, *O. tenuiflorum* has been reported to inhibit angiogenesis, the process of new blood vessel formation that tumors rely on for growth and metastasis by downregulating pro-angiogenic factors such as VEGF.[1,9]

The affordability and accessibility of *O. tenuiflorum* make it an attractive option, especially in resource limited settings where oral cancer prevalence is disproportionately high. However, despite promising in vitro and in vivo findings, significant challenges remain. Variability in phytochemical composition due to environmental factors, limited bioavailability of active compounds, and lack of clinical validation are major obstacles to its integration into mainstream oncology.[10] Innovative approaches such as nanotechnology-based drug delivery systems have shown promise in enhancing the solubility, stability, and targeted delivery of Tulsi phytochemicals, potentially overcoming these limitations.[11] This review consolidates the current understanding of *O. tenuiflorum*'s phytochemical profile and its anticancer activities against oral malignancies. It also highlights emerging technologies and future directions aimed at optimizing its therapeutic potential. By bridging traditional wisdom and modern scientific research, *O. tenuiflorum* holds promise as a safe and effective adjunct in oral cancer management.

2. ORAL CANCER: EPIDEMIOLOGY AND RISK FACTORS

Oral cancer constitutes approximately 3% of all cancers worldwide, with a disproportionate burden in LMICs.[12,13,14] Regions such as South Asia, Eastern Europe, and parts of Latin America report some of the highest incidence rates, largely attributed to sociocultural habits like tobacco and areca nut use.[15] For example, India and Sri Lanka report alarmingly high prevalence of oral cancer due to widespread tobacco chewing and betel quid consumption. In contrast, Western countries show relatively lower incidence, though late-stage diagnoses and healthcare access inequalities persist.[16,17] The five-year survival rate remains suboptimal between 50–60% and is heavily dependent on the stage of diagnosis.[18] Patients diagnosed at earlier stages exhibit markedly better outcomes compared to those with advanced disease, highlighting the critical need for timely detection and treatment.[16,19] Multiple risk factors contribute to oral cancer development. Tobacco use and smoking, chewing, or using snuffs, remains the most significant carcinogen, delivering mutagenic agents that induce DNA damage and chronic inflammation.[20] Prolonged and intense tobacco use elevates cancer risk up to 15-fold.[15,21] Alcohol further exacerbates this risk, particularly when combined with tobacco. Metabolism of ethanol into acetaldehyde, a known carcinogen, disrupts DNA repair mechanisms, promoting malignancy.[22,23] In recent years, HPV, especially type 16, has emerged as a major risk factor for oropharyngeal cancer. Unlike tobacco-related cancers, HPV-positive cases often affect younger individuals and are localized to the tonsillar region and tongue base. The virus integrates into host DNA, leading to deregulation of oncogenes and inhibition of tumor suppressor proteins.[24,25]

Genetic predispositions, particularly mutations in DNA repair genes, can also elevate susceptibility to oral malignancies.[26,27] Environmental and dietary factors including high intake of smoked meats, refined carbohydrates, and nutrient-deficient diets have been implicated in modulating cancer risk.[28,29] Furthermore, recent studies implicate microbial dysbiosis in chronic oral inflammation and

carcinogenesis, pointing to a role for the oral microbiome.[30,31]

Early symptoms of oral cancer such as non-healing ulcers, leukoplakia, and unexplained lesions are often mistaken for benign conditions, resulting in delayed diagnosis and reduced therapeutic efficacy.[18,32] Existing diagnostic tools suffer from limitations in sensitivity and specificity, underscoring the urgent need for non-invasive biomarkers and improved screening strategies.[33,34]

Treatment typically involves surgery, often accompanied by radiotherapy and chemotherapy. While effective in managing localized disease, these approaches can result in debilitating side effects, functional impairment, and disfigurement.[35,36] Hence, there is a growing interest in alternative therapeutic strategies that are safer, more effective, and tailored to individual patient profiles.

3. TULSI: AN OVERVIEW

Tulsi (*O. tenuiflorum*) is a distinguished member of the Lamiaceae family, mostly used for its aromatic leaves and multipurpose applications in culinary, spiritual, and medicinal contexts. Native to the Indian subcontinent, this perennial herb thrives in warm, humid climates, growing up to 1 meter in height depending on environmental conditions.[37,38]

Its distinct elliptical, serrated leaves not only serve an ornamental role but also play a central part in traditional medical systems such as Ayurveda and Siddha.[39,40]

Tulsi holds profound cultural and religious significance in Hinduism, being revered as a sacred plant. Ancient scriptures detail its use in spiritual rituals, attributing purifying and protective properties to it.[41,42]

Beyond religious importance, *O. tenuiflorum* has been widely employed in managing ailments such as respiratory conditions, fevers, bronchitis, and digestive issues. Decoctions made from its leaves and stems have long served as remedies across traditional healthcare systems.[43]

The herb’s antimicrobial properties are particularly notable, with historical usage in wound healing, treating ulcers, and controlling oral inflammation and toothache in rural populations.[44,45] Classified as an adaptogen, *O. tenuiflorum* is known to bolster the body’s resilience to physical and emotional stress by regulating cortisol levels.[46]

Consumed regularly as teas or herbal supplements, it is integrated into health-promoting diets aiming to support holistic well-being.[47,48] Its therapeutic potential is attributed to a rich phytochemical profile, including phenolic acids, flavonoids, terpenoids,
and essential oils.[49,50] Compounds like rosmarinic acid and caffeic acid exhibit strong antioxidant activity by neutralizing free radicals, chelating metal ions, and reducing lipid peroxidation, thereby mitigating oxidative stress.[51] Flavonoids such as apigenin and orientin contribute anti-inflammatory and anticancer activities, making them promising agents in cancer research.[52,53]

The essential oils of Tulsi, rich in terpenoids like eugenol and linalool, contribute analgesic, antibacterial, and anticancer activities. Eugenol, in particular, has demonstrated the ability to inhibit tumor growth and modulate immune responses.[54,55] Additional oil components like citral and camphor, along with alkaloids, glycosides, and saponins, enhance its pharmacological efficacy.[56,57]

Multiple studies affirm the herb's safety, with consistent evidence showing minimal adverse effects at therapeutic doses in both animal and human trials.[58,59] Nonetheless, caution is advised for individuals with known hypersensitivity or those on certain medications. Pregnant and lactating women are advised to moderate intake due to insufficient safety data.[60,61] In preclinical disease models, *O. tenuiflorum* extracts have demonstrated anti-inflammatory effects through the suppression of pro-inflammatory cytokines and NF-κB signaling pathways.[62,63]

Its anticancer potential is evidenced by its ability to inhibit tumor cell proliferation, induce apoptosis, and suppress metastasis, primarily through bioactive compounds like eugenol and rosmarinic acid, which regulate MMPs and VEGF, respectively.[64,65]

Advanced extraction techniques such as supercritical fluid extraction and ultrasound-assisted methods are being adopted to optimize the purity and potency of Tulsi based formulations.[66] These advancements bolster its value in modern integrative medicine and reaffirm its relevance in both traditional and contemporary healthcare systems.

4. BIOACTIVE COMPOUNDS IN TULSI

Tulsi contains multiple bioactive compounds, notably eugenol, rosmarinic acid, apigenin, and linalool, each contributing to its remarkable anticancer properties, especially in oral cancer. (**Figure 1, Table 1**).

Table 1. Anticancer properties of major bioactive compounds from *O. tenuiflorum* (Tulsi)

Compound	Key Mechanisms	Molecular Targets / Pathways	Cancer-Relevant Effects	References
Eugenol	Antioxidant, pro-apoptotic, anti-inflammatory, anti-metastatic	ROS scavenging, ↑SOD & catalase, ↓PI3K/Akt/mTOR, ↓NF-κB, ↓MMP-2/9, ↑cytochrome c	Induces apoptosis, inhibits proliferation, EMT, metastasis, and enhances chemosensitivity	38,67,68
Rosmarinic Acid	Antioxidant, anti-inflammatory, pro-apoptotic	↓IL-6, IL-8, TNF-α, ↓NF-κB, ↓STAT3, ↑Bax, ↓Bcl-2	Enhances intrinsic apoptosis, modulates tumor microenvironment, synergizes with eugenol	46,56,57
Apigenin	Cell cycle arrest, pro-apoptotic, anti-angiogenic	↓CDK2/4, ↑p21/p27, ↑caspase cascade, ↓VEGF	Induces G1/S arrest, promotes apoptosis, inhibits angiogenesis	60,69
Linalool	Antioxidant, mitochondrial apoptosis, anti-inflammatory	↓ROS, ↑SOD, ↓IL-6, ↓VEGF, ↓MMPs	Induces apoptosis, inhibits metastasis, angiogenesis	46,70,71
Synergistic Action	Multi-targeted effect	Combination of above pathways	Enhances therapeutic response, overcomes drug resistance, minimal cytotoxicity to normal cells	72,73

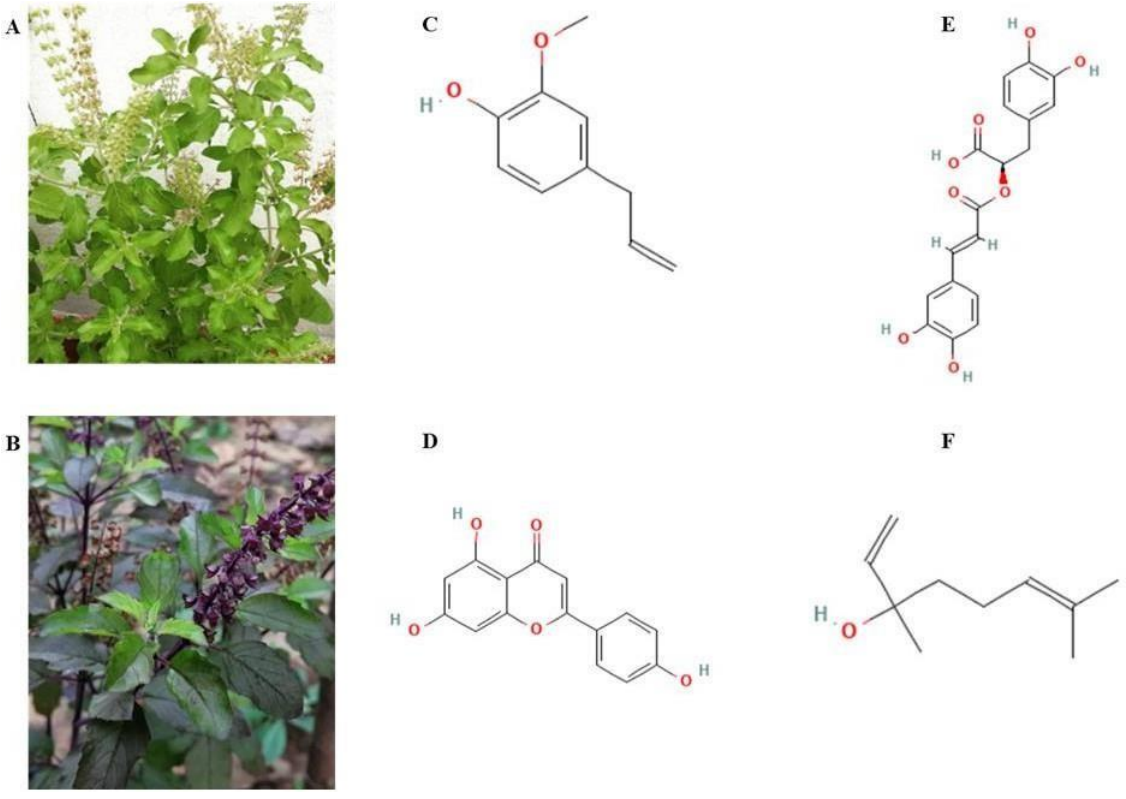

Figure 1. Key constituents of *O. tenuiflorum* with anticancer potential. (A) *O. tenuiflorum* (Green type); (B) *O. tenuiflorum* (Purple type); (C) Eugenol; (D) Apigenin; (E) Rosmarinic acid; (F) Linalool. These compounds contribute to oxidative stress modulation, apoptosis induction, metastasis inhibition, and oncogenic pathway regulation in oral cancer.

Eugenol, a phenylpropanoid, is the most extensively studied compound from *O. tenuiflorum*. It permeates cell membranes and targets mitochondrial pathways, disrupting oxidative stress balance and inducing apoptosis. Eugenol scavenges reactive oxygen species (ROS) and enhances antioxidant enzymes such as superoxide dismutase (SOD) and catalase, thus reducing oxidative stress implicated in carcinogenesis.[74,75] It also impairs the electron transport chain, promoting cytochrome c release and activating the intrinsic apoptotic pathway.[46]

Eugenol downregulates anti-apoptotic proteins (e.g., Bcl-2) while upregulating pro-apoptotic proteins (e.g., Bax), shifting the balance toward cell death.[73] Eugenol modulates critical oncogenic pathways like PI3K/Akt/mTOR and NF-κB. It inhibits Akt phosphorylation, reducing glucose uptake and halting tumor growth.[38] By suppressing NF-κB, it lowers inflammation and anti-apoptotic gene expression, both of which are central to cancer progression.[43] Eugenol also exhibits anti-metastatic properties by downregulating matrix metalloproteinases MMP-2 and MMP-9 and reversing epithelial-to-mesenchymal transition (EMT), enhancing E-cadherin while suppressing vimentin.[71] Particularly, eugenol enhances the efficacy of chemotherapeutics like cisplatin by inhibiting multidrug resistance (MDR) proteins, thereby increasing intracellular drug accumulation. Its selective cytotoxicity toward cancer cells, attributed to their altered redox states, and its lipophilic properties, enabling better mucosal penetration, make it ideal for oral cancer therapy.[56]

Rosmarinic acid, a polyphenol found in *O. tenuiflorum*, complements eugenol through its potent anti-inflammatory and antioxidant properties. It inhibits pro-inflammatory cytokines such as IL-6 and TNF-α, altering the tumor microenvironment.[76] At the molecular level, it suppresses STAT3 and NF-κB signaling pathways, reducing cancer cell proliferation and enhancing apoptosis.[57] Additionally, it modulates Bcl-2 family proteins, increasing Bax/Bak and decreasing Bcl-2 expression, leading to mitochondrial membrane destabilization and caspase activation. It also arrests the cell cycle at the G1/S checkpoint by downregulating cyclins and CDKs. [70]

Apigenin, a flavonoid in *O. tenuiflorum*, induces cell cycle arrest and apoptosis. It inhibits CDK2/CDK4 activity, halting the G1/S transition, and upregulates p21 and p27 to reinforce checkpoint control.[69] Like eugenol and rosmarinic acid, apigenin promotes cytochrome c release and caspase cascade activation. It also suppresses inflammatory mediators and reduces VEGF expression, impairing angiogenesis.[60]

Linalool, a monoterpene, exerts antioxidant and anti-inflammatory effects by scavenging ROS and downregulating cytokines, thereby reducing tumor-favoring inflammation.[70] It induces mitochondrial depolarization, cytochrome-c release, and apoptosis. Like other compounds in *O. tenuiflorum*, it inhibits MMPs and VEGF, limiting metastasis and angiogenesis.[46] The synergistic interactions among these phytochemicals offer a holistic and multi-targeted strategy against cancer. Their collective activities apoptotic induction, oxidative stress modulation, signaling pathway disruption, and metastasis inhibition highlight the therapeutic promise of *O. tenuiflorum*. Ongoing research continues to explore these compounds for future applications in integrative and localized oral cancer therapy.

5. MECHANISMS OF ACTION AGAINST ORAL CANCER

The bioactive compounds of *O. tenuiflorum*, notably eugenol, rosmarinic acid, and apigenin, exhibit promising chemo-preventive and therapeutic potential against oral cancer. These phytochemicals exert synergistic effects across multiple pathways, targeting oxidative stress, inflammation, cellular signaling, apoptosis, and metastasis, while sparing normal cells (**Figure 2**). Oxidative stress and chronic inflammation are critical contributors to oral carcinogenesis. Excessive reactive oxygen species (ROS) promote DNA damage, genomic instability, and tumor progression.[77] Eugenol, the major active component of *O. tenuiflorum*, demonstrates potent antioxidant activity by scavenging superoxide anions and hydroxyl radicals.[78,79]

It also enhances endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, thereby restoring redox homeostasis and reducing oxidative DNA damage.[78,80] Inflammation is another hallmark of cancer progression. Elevated levels of cytokines like IL-6 and TNF-α promote a pro-tumorigenic microenvironment.[77]

Rosmarinic acid and linalool, present in *O. tenuiflorum*, modulate inflammation by downregulating IL-6, IL-8, and TNF-α expression and inhibiting the NF-κB pathway, a central mediator of inflammation.[77,81]

This downregulation mitigates chronic inflammation and contributes to tissue homeostasis. Disruption of oncogenic signaling pathways further strengthens the anticancer efficacy of these phytocompounds. The PI3K/Akt/mTOR signaling axis, commonly activated in oral cancers, promotes proliferation and apoptosis resistance.[82] Eugenol and apigenin inhibit Akt phosphorylation, leading to downstream suppression of mTOR signaling and halting cell cycle progression.[81,83] Additionally, suppression of NF-κB phosphorylation and nuclear translocation by eugenol and rosmarinic acid blocks the transcription of anti-apoptotic and pro-inflammatory genes, sensitizing cancer cells to cell death.[84,85]

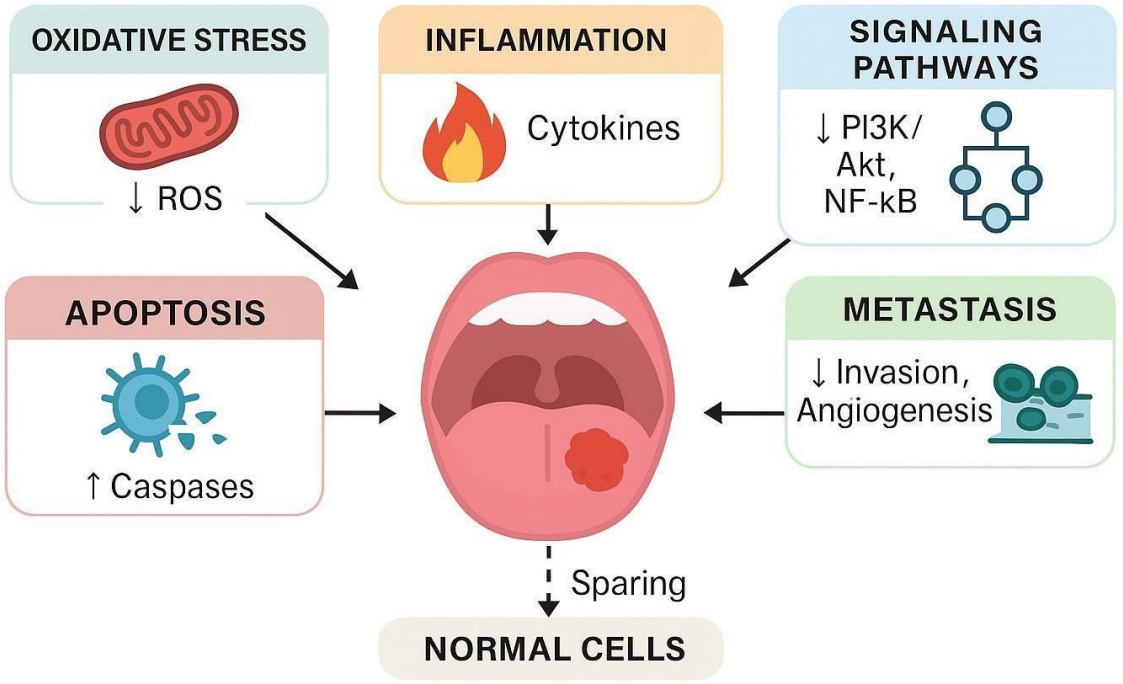

Figure 2. Mechanisms of *Ocimum tenuiflorum* bioactive compounds against oral cancer, including modulation of oxidative stress, suppression of inflammation, inhibition of PI3K/Akt and NF-κB signaling, induction of apoptosis, and prevention of metastasis and angiogenesis, while sparing normal cells.

Apoptosis induction through the intrinsic mitochondrial pathway is a pivotal mechanism. Eugenol disrupts mitochondrial membrane potential, triggering cytochrome c release and activating caspase-9 and caspase-3, culminating in apoptosis.[86,87] Apigenin complements this effect by upregulating pro-apoptotic proteins and downregulating anti-apoptotic Bcl-2, thus promoting selective apoptosis of cancer cells.[88,89] Cell cycle arrest is another key target. Apigenin inhibits G1/S phase transition by downregulating cyclin D1 and CDK4 while upregulating p21, a cyclin-dependent kinase inhibitor.[90,91] This blockade prevents uncontrolled cell proliferation and facilitates apoptotic signaling. The inhibition of metastasis and angiogenesis by *O. tenuiflorum* compounds further enhances its anticancer potential. Eugenol and linalool suppress matrix metalloproteinases MMP-2 and MMP-9, enzymes essential for extracellular matrix degradation and cancer cell invasion.[92,93] Eugenol also represses epithelial-to-mesenchymal transition (EMT) by restoring E-cadherin expression and reducing vimentin levels, thus reducing metastatic spread.[94,95] Angiogenesis, a process vital for tumor survival and expansion, is impeded by apigenin and rosmarinic acid, which inhibit vascular endothelial growth factor (VEGF) expression.[96,97,98] The inhibition of VEGF limits endothelial cell recruitment and neovascularization, depriving tumors of essential nutrients and oxygen. Collectively, these bioactive compounds act on diverse molecular targets to combat oral cancer. Their multi-modal mechanisms as antioxidant, anti-inflammatory, anti-proliferative, pro-apoptotic, anti-metastatic, and anti-angiogenic position, Tulsi as a potent natural adjunct in oral cancer therapy, warranting further exploration in clinical settings.

6. PRECLINICAL STUDIES ON *O. TENUIFLORUM* AND ORAL CANCER

Preclinical investigations provide strong evidence for the anticancer efficacy of *O. tenuiflorum* in oral cancer models (**Table 2**). These studies, involving both in vitro assays using oral cancer cell lines (e.g., SCC-9, SCC-25, CAL-27) and in vivo animal models, highlight the therapeutic potential of its bioactive compound's eugenol, rosmarinic acid, apigenin, and linalool. Eugenol, a dominant phytochemical in *O. tenuiflorum*, exhibits potent cytotoxic effects by inhibiting cancer cell proliferation and inducing apoptosis in a dose-dependent manner. The apoptotic effects are marked by morphological changes such as cell shrinkage and nuclear condensation.[38,99] Mechanistically, eugenol disrupts mitochondrial membrane potential, triggering cytochrome c release, and activation of caspase-9 and caspase-3, thereby initiating the intrinsic apoptotic pathway.[43] Importantly, eugenol demonstrates selective toxicity, preferentially targeting cancer cells while sparing normal cells, which enhances its therapeutic appeal.

Table 2. Preclinical Evidence Supporting the Anticancer Potential of *O. tenuiflorum* in Oral Cancer

Bioactive Compound	Experimental Model	Mechanisms of Action	Key Outcomes in Oral Cancer Models	References
Eugenol	*In vitro* (SCC-9, SCC-25, CAL-27); *In vivo* (4-NQO, DMBA models)	↓Mitochondrial membrane potential, ↑cytochrome c, ↑caspase-9/3, ↓Bcl-2, ↑Bax	Apoptosis induction, selective cytotoxicity, reduced lesion severity, no organ toxicity	38,43,99
Rosmarinic Acid	*In vitro*; *In vivo* (rat oral carcinogenesis models)	G1/S arrest, ↓Cyclin D1, ↓CDK4, ↑p21, ↓IL-6, TNF-α, ↑antioxidants	Inhibits proliferation, suppresses inflammation, enhances DNA protection	71,100
Apigenin	*In vitro* oral cancer cell lines	↑p21/p27, ↓Cyclin D1/CDK4, ↑Caspase-3, ↓Bcl-2	Cell cycle arrest, apoptosis promotion, synergy with eugenol/rosmarinic acid	71,89,101
Linalool	*In vitro* and *in vivo* models	↓IL-6, ↓TNF-α, ↓MMP-2/9, ↓NF-κB, ↓migration/invasion	Anti-inflammatory, anti-metastatic, inhibits EMT	43,102,103
Whole Extract (O. tenuiflorum)	Rodent carcinogen-induced oral cancer models (4-NQO, DMBA)	↑SOD, ↑catalase, ↓ROS, ↓hyperplasia/dysplasia	Reduction in tumor incidence and lesion grade; preserves liver/kidney health	71,104,100
Combination with Chemotherapeutics	Eugenol + Cisplatin / Rosmarinic Acid + Doxorubicin	↓MDR proteins, ↑chemosensitivity, ↓toxicity	Synergistic effects; enhanced efficacy and tolerability vs. standard chemotherapy alone	38,93,105

Rosmarinic acid further contributes to anticancer activity by inducing cell cycle arrest at the G1/S checkpoint through downregulation of cyclin D1 and CDKs, and upregulation of the CDK inhibitor p21.[71,100] It also cooperates with eugenol in modulating apoptosis-related proteins, upregulating Bax and downregulating Bcl-2.[60] These synergistic actions enhance the overall anticancer potency of *O. tenuiflorum* extracts. Apigenin, another bioactive flavonoid in *O. tenuiflorum*, complements these effects by reinforcing intrinsic apoptosis in oral cancer cells, amplifying the impact of eugenol and rosmarinic acid.[71,101] Collectively, these compounds present opportunities for combination therapy with enhanced efficacy and lower toxicity.[43] Linalool, a monoterpenoid component, provides anti-inflammatory and antimetastatic effects. It suppresses pro-inflammatory cytokines such as IL-6 and TNF-α and inhibits matrix metalloproteinases (MMPs), reducing tumor-promoting inflammation and cell invasion.[102,103] These effects underscore *O. tenuiflorum* role in preventing metastasis and promoting cancer cell containment.

The *in vivo* studies using rodent models with chemically induced oral cancer (e.g., 4-NQO and DMBA) validate the chemo-preventive effects of *O. tenuiflorum* extracts. Treatment results in reduced incidence and severity of precancerous lesions and histological improvements, including decreased dysplasia and hyperplasia.[71,101] These outcomes are linked to enhanced antioxidant defenses and reduced oxidative stress via free radical scavenging by eugenol and rosmarinic acid.[103,104]

Additional mechanistic insights show that pyrazine derivatives and linalool modulate pro-apoptotic signaling and downregulate inflammatory markers, improving organ health and supporting the systemic safety of the extract.[106,107,108] Toxicological evaluations confirm that therapeutic doses of *O. tenuiflorum* do not adversely affect the liver, heart, or kidneys, validating its biocompatibility.[99,104] Comparative analyses with chemotherapeutic agents reveal that eugenol matches or surpasses cisplatin in cytotoxic activity, while causing less damage to healthy tissues.[38] Moreover, rosmarinic acid and apigenin can enhance doxorubicin's effect by mitigating multidrug resistance mechanisms.[93,105] Co-administration of *O. tenuiflorum* with chemotherapeutics enhances overall cytotoxicity and reduces required dosages, thereby minimizing side effects and improving patient tolerance.[71] Overall, preclinical data firmly support the chemo-preventive and therapeutic potential of *O. tenuiflorum* in oral cancer. Its multi-targeted mechanisms, safety profile, and synergy with existing drugs make it a strong candidate for future clinical trials in oncology.

7. DRUG DELIVERY SYSTEMS FOR ENHANCING BIOAVAILABILITY

The therapeutic potential of *O. tenuiflorum* in treating oral cancer is limited by challenges in the bioavailability and stability of its bioactive compounds such as eugenol, rosmarinic acid, and apigenin. These phytochemicals possess low aqueous solubility, high lipophilicity, and are prone to rapid metabolic degradation, limiting their systemic absorption and clinical efficacy.[28,109,110] Due to their lipophilic nature, compounds like eugenol and apigenin are poorly absorbed in conventional oral formulations, reducing their therapeutic concentrations in target tissues.[111,112] In addition to poor solubility, many of these constituents undergo rapid enzymatic metabolism primarily via cytochrome P450 enzymes resulting in the formation of less active metabolites before they reach systemic circulation.[112] For example, rosmarinic acid is especially unstable when exposed to environmental stressors like pH fluctuations, light, and heat, requiring special formulation strategies to preserve its bioactivity.[111,113] These pharmacokinetic drawbacks result in subtherapeutic plasma levels that are inadequate for meaningful anti-cancer activity. Furthermore, the non-targeted nature of traditional delivery systems increases the risk of off-target effects. When administered orally or topically, these bioactives are dispersed non-specifically throughout the body, reducing their concentration at cancer sites and increasing the risk of side effects in healthy tissues.[114,115] This lack of site-specificity is a major limitation in cancer therapy, where precise drug delivery is essential.

Advancements in nanotechnology have introduced novel drug delivery systems that address these limitations. Nanocarriers such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles (SLNs) can encapsulate lipophilic phytochemicals, enhancing solubility, stability, and targeted delivery.[116,117,118] Liposomes protect compounds from degradation and improve membrane permeability. Functionalization with tumor-specific ligands enables targeted delivery, increasing therapeutic efficacy and minimizing systemic toxicity.[109,119,120,121] Polymeric nanoparticles made from biocompatible materials like chitosan and polylactic-co-glycolic acid (PLGA) offer controlled, sustained release of bioactives. PLGA-based systems have shown to enhance the bioavailability of rosmarinic acid, boosting cytotoxicity against tumor cells while protecting normal tissues.[122,123,124] SLNs provide a hybrid approach, stabilizing lipophilic compounds within a solid lipid matrix, improving pharmacological properties, and allowing for stimulus-responsive, localized release at tumor sites.[118,125,126] Combination therapies incorporating phytochemicals with conventional chemotherapeutics have shown synergistic effects, reducing the required doses of synthetic drugs and associated side effects.[127,128,129] Solubility enhancers like cyclodextrins and hydrocolloid carriers have also been effective in improving the pharmacokinetics of poorly soluble compounds.[130,131] While natural product-based therapies are attractive due to their low toxicity and rich pharmacological profiles, their success depends on innovative delivery systems that address inherent limitations in solubility, metabolism, and targeting.[132,133] Integrated therapeutic strategies combining nanocarriers and natural phytochemicals may be especially effective in complex conditions like oral cancer.[124,134] *O. tenuiflorum* holds immense potential for oral cancer treatment, but overcoming its bioavailability hurdles is essential. Advanced drug delivery platforms, particularly those leveraging nanotechnology, offer promising avenues to maximize its therapeutic value. Further *in vivo* and clinical validations are warranted to translate these promising results into effective cancer therapeutics.

8. INTEGRATION WITH CONVENTIONAL THERAPIES

The integration of *O. tenuiflorum* compounds with conventional cancer therapies has gained prominence for enhancing therapeutic efficacy and minimizing side effects from chemotherapy and

radiotherapy. This synergistic approach involves combining natural bioactive compounds from *O. tenuiflorum* with standard treatments to optimize outcomes tailored to individual patients. Eugenol, a major constituent of *O. tenuiflorum*, has shown promise in potentiating the effects of chemotherapeutics such as cisplatin. Preclinical studies indicate that the co-administration of eugenol with cisplatin significantly reduces tumor volume compared to cisplatin alone.[135] Eugenol's mechanism includes downregulation of multidrug resistance (MDR) proteins like P-glycoprotein (P-gp), thereby enhancing intracellular drug retention and efficacy.[136,137]

Additionally, its antioxidant properties may reduce cisplatin-induced nephrotoxicity, preserving renal function.[138] Other *O. tenuiflorum* compounds also contribute to combination therapy. Rosmarinic acid, for example, augments the cytotoxic effects of doxorubicin by inducing apoptosis and cell cycle arrest.[70] Linalool, another bioactive component, acts as a radiosensitizer, increasing radiation-induced cytotoxicity by elevating reactive oxygen species (ROS) and inhibiting DNA repair in tumor cells.[135,139,140] This dual effect enhances tumor cell mortality while potentially protecting normal tissues via antioxidant mechanisms.[141]

The rise of personalized medicine further advances the clinical utility of *O. tenuiflorum*. Tailored treatment regimens based on genetic polymorphisms in drug metabolism can optimize dosages and therapeutic response.[136,142] Proteomic and metabolomic profiling aids in identifying biomarkers predictive of responsiveness to *O. tenuiflorum*, supporting stratified treatment.[143] Additionally, combining eugenol with targeted therapies may offer enhanced outcomes in patients with mutations in specific signaling pathways.[144] Thus, incorporating *O. tenuiflorum* compounds into standard and personalized cancer treatments offers a promising strategy to boost efficacy and reduce toxicity. Continued research may solidify their role in integrative oncology.

9. CLINICAL RELEVANCE AND FUTURE DIRECTIONS

Compounds from *O. tenuiflorum* show significant potential in oral cancer therapeutics. Bioactive compounds like eugenol, linalool, and rosmarinic acid demonstrate antioxidant, anti-inflammatory, and chemoprotective effects, making them valuable for both prevention and treatment.[38,145] For instance, eugenol has been shown to reduce cisplatin-induced nephrotoxicity and potentially enhance its efficacy when co-administered.[38,45] Linalool, with radiosensitizing properties, may enhance radiation therapy effectiveness while reducing collateral tissue damage.[51,146]

The chemo-preventive role of *O. tenuiflorum* is compelling, particularly for individuals at risk due to tobacco, alcohol, or HPV exposure. Rosmarinic acid and apigenin may counteract chronic inflammation and oxidative stress, pivotal in oral cancer development.[147,148,149]

Additionally, localized applications, such as mouthwashes or lozenges, show promise for addressing precancerous lesions.[45,150] Challenges include standardizing extracts, considering variations in phytochemical composition.[75] Further exploration of pharmacokinetics and potential drug interactions, particularly with cytochrome P450 enzymes, is essential to ensure safety and efficacy.[151,152] Understanding molecular mechanisms via pathways like PI3K/Akt/mTOR and NF-κB is critical for optimizing therapeutic regimens.[153,154] Advancements in medicinal chemistry, nanotechnology, and theranostic platforms could revolutionize *O. tenuiflorum* clinical application.[155,156] Investigating its potential in combinatorial therapies, particularly with immunotherapy, could further enhance treatment outcomes.[45,157]

10. CONCLUSION

O. tenuiflorum, with its bioactive compounds such as eugenol, rosmarinic acid, apigenin, and linalool, offers a transformative approach to oral cancer treatment by targeting key cancer hallmarks like oxidative stress, inflammation, apoptosis, and metastasis. Preclinical studies demonstrate their potential in reducing tumor growth, enhancing the effects of conventional therapies, and reducing chemotherapy and radiation related toxicities. Nanotechnology-based drug delivery systems have helped overcome bioavailability challenges, ensuring efficient targeting of affected tissues. The synergy between *O. tenuiflorum* and conventional therapies highlights its potential to improve therapeutic outcomes while minimizing side effects. Personalized medicine approaches, utilizing genetic, proteomic, and metabolomic data, could further tailor treatments to individual patients, optimizing safety and efficacy. However, challenges remain, including the need for standardized extracts, long-term toxicity studies, and a deeper understanding of its mechanisms to enable clinical application. The development of novel therapeutic agents through synthetic modifications or advanced platforms, such as theragnostic nanoparticles, could enhance its impact. Beyond its anticancer potential, Tulsi shows promise in chemoprevention, palliative care, and integrative oncology, addressing both physical and psychosocial aspects of cancer management. As research

progresses, *O. tenuiflorum* holds great promise in revolutionizing oral cancer treatment, providing safer, more effective, and personalized solutions. This botanical powerhouse exemplifies the intersection of nature and technology, offering hope for better patient outcomes and a future where oral cancer can be managed with precision and compassion.

DECLARATIONS

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CONFLICT OF INTEREST

Authors declared that they do not have any conflicts of interest.

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