Plant Science Review

PLANT SCIENCE REVIEW

Review Article

Journal homepage: https://psr.crcjournals.org/

ISSN No: 3041-7279

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The Phytochemical Profile of Areca Nut and Its Role in Oral Potentially Malignant Disorders and Oral Carcinogenesis: A Review

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15 January 2026: Received | 11 February 2026: Revised | 14 March 2026: Accepted | 10 April 2026: Available Online

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Citation: Vinesh Raj.S, and Nur Syahirah Binti Mohd Nazar (2026). The Phytochemical Profile of Areca Nut and Its Role in Oral Potentially Malignant Disorders and Oral Carcinogenesis: A Review. ***Plant Science Review***.
DOI: https://doi.org/10.51470/PSR.2026.07.01.40

Abstract

Areca nut (Areca catechu) remains one of the most widely consumed psychoactive substances in South and Southeast Asia, deeply entrenched in cultural and social traditions. Despite its historical significance, chronic exposure is associated with severe deleterious consequences on oral health, as classified by the International Agency for Research on Cancer. This review explores the complex phytochemical profile of the areca nut and its role in the pathogenesis of oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC). The biological impact is driven by a synergistic interaction between pyridine-derived alkaloids, such as arecoline, and polyphenolic tannins, which disrupt the extracellular matrix by promoting fibroblast proliferation and inhibiting collagen degradation. Furthermore, high concentrations of soluble copper act as a biochemical catalyst for lysyl oxidase, accelerating mucosal rigidity in oral submucous fibrosis (OSF). On a molecular level, carcinogenesis is facilitated through the formation of DNA adducts, chronic oxidative stress, and the induction of the epithelial-mesenchymal transition (EMT) within a hypoxic microenvironment. These processes culminate in invasive malignancy, characterised by characteristic anatomical distributions in the oral cavity. Given the high malignant transformation rates of areca-induced lesions, this review emphasises the urgent need for a paradigm shift in public health strategies, integrating advanced molecular diagnostics with culturally empathetic cessation programs and proactive clinical surveillance to mitigate this global cancer burden.

Keywords: *Areca nut; Phytochemical; Oral potentially malignant disorders; Oral submucous fibrosis; Oral cancer.*

Introduction

Medicinal and psychoactive plants have long played important roles in traditional healthcare systems and cultural practices worldwide. Among these, Areca catechu, commonly referred to as areca nut or betel nut, remains one of the most widely consumed psychoactive substances in the South and Southeast Asia region [1]. The nut is commonly chewed alone or together with betel leaf, slaked lime, tobacco, and flavouring agents as part of betel quid preparations. The practice remains highly prevalent throughout South Asia, Southeast Asia, Taiwan, Papua New Guinea, and Pacific Island populations[2].

Historically, areca nut chewing has been associated with social interaction, cultural identity, ceremonial practices, stress relief, digestion, and traditional medicinal beliefs[2].

In Malaysia, areca nut chewing continues to be observed among selected rural, indigenous communities and Borneo tribal communities, despite increasing awareness regarding oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC) [3].

The International Agency for Research on Cancer (IARC) classified areca nut as carcinogenic to humans due to substantial evidence linking chronic chewing practices with OPMDs and OSCC [2]. Oral submucous fibrosis (OSF), one of the most recognised OPMDs associated with areca nut chewing, demonstrates significant malignant transformation potential. Historically, foundational longitudinal studies established a transformation rate intoOSCC of approximately 7.6% over a 15-year period[4].

However, recent comprehensive meta-analyses indicate that the global pooled malignant transformation rate generally falls between 4.2%[5] and 6.0% [6].

The biological and pathological effects of areca nut are largely related to its phytochemical composition. In a comprehensive review, Tilakaratne et al. detail the overwhelming epidemiological and in vitro evidence identifying areca nut as the primary, dose-dependent aetiological factor for OSF. The disease's pathogenesis is heavily driven by the nut's constituent alkaloids, most notably arecoline, and tannins, which synergistically disrupt the equilibrium of the extracellular matrix by promoting fibroblast proliferation, enhancing collagen synthesis, and inhibiting its subsequent degradation[7].

This review highlights the current evidence on the phytochemical properties of Areca catechu and its implications in OPMDs and OSCC.

Methodology

A literature search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar for studies published between 2000 and 2025. Keywords utilised with Boolean operators included "Areca catechu," "Areca nut," "Betel quid," "Oral cancer," "Oral submucous fibrosis," "Oral potentially malignant disorders," "Phytochemistry," "Oral carcinogenesis," and "Oral squamous cell carcinoma". Peer-reviewed articles addressing the phytochemical composition of areca nut and its role in oral potentially malignant disorders and oral carcinogenesis were included. Conversely, non-English publications, duplicate records, conference abstracts lacking full texts, and studies unrelated to oral health outcomes were excluded. Screening was performed by title/abstract and subsequent full-text review, with relevant data systematically extracted and classified according to phytochemical characteristics, clinical oral manifestations, and mechanisms of oral pathogenesis.

Literature review

Phytochemical Characteristics

Composition of Areca Nut

- Alkaloid

The areca nut possesses a highly complex phytochemical profile containing a diverse array of biologically active compounds. These constituents are responsible for a dual spectrum of effects: the systemic pharmacological properties (such as mild psychoactivity, autonomic stimulation, and addiction) and the severe, localised pathological consequences seen in the oral cavity [7]. Within this phytochemical profile, pyridine-derived alkaloids represent the most critical group of compounds concerning oral pathogenesis. The principal alkaloids identified in the areca nut are arecoline, arecaidine, guvacoline, and guvacine [7]. During the mastication process, these agents not only exert direct cellular toxicity but also undergo nitrosation in the presence of saliva to form highly potent, areca-nut-specific nitrosamines, which act as powerful carcinogens [8].

Among these constituents, arecoline is unequivocally the most abundant and biologically active alkaloid, playing a central, well-documented role in the initiation and progression of OPMDs and OSCC [7]. Due to its chemical structure, arecoline readily penetrates the mucosal barrier of the oral cavity, binding to cellular receptors and initiating a cascade of adverse molecular and genetic events, including DNA damage, oxidative stress, and impaired DNA repair mechanisms [9].

In the specific context of OSF, arecoline acts as the primary fibrogenic catalyst. It directly triggers the abnormal proliferation of buccal mucosal fibroblasts and heavily upregulates the synthesis of Types I and III collagen [7]. Furthermore, arecoline disrupts the critical homeostasis of the extracellular matrix by actively preventing collagen degradation. This is mechanistically achieved by altering the expression of key regulatory enzymes, specifically, by downregulating collagen-degrading matrix metalloproteinases (MMPs) while simultaneously upregulating tissue inhibitors of metalloproteinases (TIMPs) [7]. This profound enzymatic imbalance, often mediated through the transforming growth factor-beta (TGF-β) signalling pathway, results in the continuous, irreversible deposition of dense, inelastic fibrotic tissue within the lamina propria, which is the clinical hallmark of OSF [7].

- **Polyphenols and Tannins**

Beyond its alkaloid content, the areca nut is exceptionally rich in polyphenolic compounds, which account for a substantial portion of the nut's dry weight. This phytochemical group primarily comprises flavonoids, catechins (such as epicatechin), and complex polymeric tannins[10]. While dietary polyphenols are frequently associated with antioxidant properties[11], in the specific context of areca nut chewing, they paradoxically act as potent pro-oxidants and fibrogenic agents, significantly contributing to oral pathogenesis[12].

The role of tannins is particularly critical in the progression of OSF [7]. While arecoline initiates excessive collagen synthesis, tannins work synergistically to stabilise the newly formed collagen network [7]. They actively cross-link collagen fibres, rendering them highly resistant to degradation by endogenous collagenase enzymes. This biochemical stabilisation directly accelerates the accumulation of dense, inflexible fibrotic bands within the oral mucosa [7]. Furthermore, areca nut polyphenols and catechins are primary drivers of genotoxicity in the oral cavity [13]. During the mechanical process of mastication, especially when the nut is chewed alongside slaked lime (calcium hydroxide), which creates a highly alkaline local environment, these polyphenols undergo rapid auto-oxidation [14]. This chemical reaction leads to the continuous, localised generation of massive amounts of reactive oxygen species (ROS), including superoxide anion radicals and hydrogen peroxide.

The resulting state of chronic oxidative stress overwhelms the oral mucosa's natural antioxidant defence systems, triggering lipid peroxidation, protein denaturation, and severe, direct damage to cellular DNA [14]. The progressive accumulation of these DNA single- and double-strand breaks, alongside subsequent genetic mutations, provides a primary mechanistic pathway for the malignant transformation of OPMDs into OSCC [15].

- Trace Elements (Copper)

In addition to its organic phytochemical constituents, the areca nut contains significant concentrations of inorganic trace elements that play a pivotal role in its localised pathogenicity [7]. Notably, areca nut preparations possess an unusually high concentration of copper compared to other commonly consumed nuts [16]. During mastication, substantial amounts of soluble copper are released into the saliva and are readily absorbed by the adjacent oral mucosa. This localised accumulation of heavy metal acts as a crucial biochemical catalyst in the initiation and progression of OSF [16].

Mechanistically, copper serves as an essential, obligate cofactor for lysyl oxidase (LOX), an extracellular enzyme responsible for the covalent cross-linking of collagen and elastin fibres [17]. The chronic mucosal influx of areca-derived copper significantly upregulates both the production and the functional activity of LOX within the lamina propria. Consequently, this hyperactive enzyme mediates extensive cross-linking of the newly synthesised collagen fibres. This highly cross-linked, mature collagen network becomes structurally rigid and profoundly resistant to proteolytic degradation by endogenous collagenases [18]. Ultimately, this copper-driven disruption of extracellular matrix remodelling accelerates the continuous, pathological accumulation of dense, inelastic connective tissue, severely exacerbating the clinical symptoms of OSF [18].

The primary active constituents of the areca nut, alongside their specific molecular mechanisms and resulting pathological consequences in the oral cavity, are summarised in Table 1.

Table 1: Major Areca Nut Constituents and Their Distinct Pathological Contributions

Phytochemical Class	Major Constituents	Cellular & Molecular Effects	Pathological Consequence
Alkaloids	Arecoline, Arecaidine, Guvacoline, Guvacine	• ↑ Fibroblast proliferation & collagen synthesis	Initiation of mucosal fibrogenesis; direct genotoxic and mutagenic initiation.
		• Altered MMP/TIMP ratio (↓ collagen degradation)	
		• Precursors to areca-nut-specific nitrosamines	
Polyphenols & Tannins	Flavonoids, Catechins, Polymeric tannins	• Rapid auto-oxidation generating high levels of ROS	Severe cellular oxidative stress; progression of malignant transformation; resistance to tissue remodelling.
		• Induction of lipid peroxidation and DNA damage	
		• Direct stabilization of newly formed collagen	
Trace Elements	Copper	• Obligate cofactor for LOX	Accelerated covalent cross-linking of collagen, driving rigid tissue maturation in OSF.
		• ↑ LOX expression and enzymatic activity	

**DNA: Deoxyribonucleic acid; LOX: lysyl oxidase; MMP: Matrix metalloproteinases; OSF: Oral submucous fibrosis; ROS: Reactive oxygen species; TIMP: Tissue inhibitors of metalloproteinases; ↑: Increased; ↓: Decreased.*

Clinical Oral Manifestation

Oral Submucous Fibrosis (OSF)

OSF is a chronic, insidious, and progressively debilitating OPMDs that is unequivocally linked to the habitual chewing of areca nut [13]. Clinically, the disease presents as a continuous spectrum of deteriorating oral health. Early manifestations are frequently characterized by a severe, localized burning sensation in the oral mucosa, particularly heightened upon exposure to spicy or hot foods, accompanied by pronounced mucosal blanching. This distinct, marble-like pallor is a direct result of localized ischemia caused by early fibrotic changes and impaired vascularity in the underlying tissue [19].

As the disease advances, the hallmark clinical feature of OSF emerges: the formation of palpable, inelastic, and firm fibrous bands that typically traverse the buccal mucosa, soft palate, and labial tissues [19]. This relentless fibroelastic deposition inevitably leads to a severe restriction in mandibular mobility, culminating in progressive trismus. This restricted mouth opening drastically impairs fundamental physiological functions, complicating mastication, deglutition, phonation, and routine dental care [19]. Crucially, OSF is not merely a restrictive fibrotic condition but a high-risk precancerous state [6]. The continuous cellular stress, chronic inflammation, and genomic instability within this hypoxic microenvironment create a highly favourable niche for malignant transformation, frequently leading to the development of OSCC [20].

Histopathologically, the architecture of OSF is distinct and clearly reflects its clinical severity.

Microscopic evaluation typically demonstrates profound atrophic changes in the overlying stratified squamous epithelium, which significantly thins the mucosal barrier and increases its vulnerability to salivary carcinogens [21]. Beneath the epithelium, the lamina propria and deeper connective tissues reveal a severe, chronic inflammatory cell infiltrate [21]. This is accompanied by massive, unyielding dense collagen deposition, extensive loss of blood vessels, and progressive connective tissue hyalinization, which collectively obliterate the normal elasticity of the oral mucosa and physically lock the tissue into a rigid state [21].

Oral Epithelial Dysplasia

In addition to fibrotic degeneration, chronic areca nut exposure is strongly associated with the induction of oral epithelial dysplasia (OED)[22]. This precancerous state arises from the cumulative genotoxic effects of areca alkaloids and chronic oxidative stress, which drive abnormal cellular proliferation, loss of epithelial stratification, and prominent nuclear atypia[7]. Clinically, these dysplastic changes frequently manifest as distinct mucosal alterations, classically presenting as leukoplakia, erythroplakia, or erythroleukoplakia. These distinct clinical phenotypes are categorised as OPMDs and harbour a highly variable, yet significant, potential for malignant transformation, with erythroplakia generally exhibiting the highest risk[23]. Because clinical appearance alone cannot accurately predict the underlying cellular atypia, these lesions mandate rigorous, continuous clinical surveillance and prompt histopathological assessment via incisional biopsy to definitively grade the dysplasia and guide proactive patient management[24].

Oral Squamous Cell Carcinoma

The ultimate and most devastating consequence of long-term areca nut exposure is the exponentially increased risk of developing OSCC[5, 6, 9, 12]. This malignancy represents the culmination of a progressive, multi-step carcinogenic cascade, frequently evolving from pre-existing OPMDs such as OSF or severe epithelial dysplasia into an invasive malignant phenotype[4,5,6]. The anatomical distribution of areca-induced OSCC is highly characteristic and closely mirrors the physical mechanics of the chewing habit. Tumours predominantly arise in regions subjected to the most intense, prolonged physical contact with the areca quid, specifically the buccal mucosa, the lateral borders of the tongue, the retromolar trigone, and the gingivobuccal sulcus [25]. Because users frequently hold the quid stationary in the buccal vestibule for extended periods, the localised pooling of concentrated arecoline, areca-derived nitrosamines, and oxidative metabolites triggers profound DNA damage and malignant clonal expansion[26].

Periodontal and Dental Hard Tissue Effects

Beyond its direct role in OSF and OSCC, chronic areca nut chewing is heavily implicated in severe, localised deterioration of the periodontium and dental hard tissues [27]. Epidemiological and clinical studies consistently demonstrate a strong positive correlation between habitual areca nut use and the accelerated progression of periodontal disease, characterised by deep periodontal pocket formation, pronounced gingival recession, and subsequent alveolar bone loss [27]. Furthermore, the habit invariably leads to profound extrinsic dental staining, a characteristic reddish-black discolouration of the enamel and exposed cementum resulting from the rapid auto-oxidation of areca polyphenols and tannins within the oral environment [27].

The pathogenesis of these structural oral changes is multifactorial, driven by a synergistic combination of intense physical trauma and chronic chemical cytotoxicity [28]. The inherently coarse, fibrous nature of the raw areca nut requires prolonged, forceful mastication, which exerts excessive mechanical stress on the dentition. This persistent friction leads to severe occlusal attrition, enamel wear, and direct physical abrasion of the delicate gingival margins, frequently resulting in recurrent mucosal trauma [28]. Concurrently, the constant exposure to the nut's alkaloid and heavy metal constituents induces a state of chronic, localised inflammation. This continuous chemical irritation impairs periodontal fibroblast function, compromises tissue vascularity, and weakens the local immune response against periodontal pathogens, creating a highly hostile microenvironment that significantly accelerates periodontal breakdown and structural degradation [27].

Mechanisms of Oral Carcinogenesis

The pathogenesis of areca nut-associated carcinogenesis is a complex, multi-stage process driven by the integration of genetic, epigenetic, and microenvironmental alterations[13]. Central to this transformation is the metabolic activation of areca alkaloids; during mastication, salivary nitrites facilitate the nitrosation of arecoline into areca-nut-specific nitrosamines, which form bulky DNA adducts[9]. When these adducts overwhelm cellular repair mechanisms, they induce critical mutations in proto-oncogenes and tumour suppressor genes, such as p53, effectively initiating the malignant cascade[9]. This genotoxic stress is further compounded by a shift in the cellular microenvironment; the dense fibrosis seen in OSF creates a state of localised hypoxia that triggers the "angiogenic switch." By upregulating Hypoxia-Inducible Factor-1 (HIF-1) and Vascular Endothelial Growth Factor (VEGF), the stressed tissues promote neo-angiogenesis, providing the necessary nutrients for clonal expansion[20]. Furthermore, arecoline facilitates the Epithelial-Mesenchymal Transition (EMT) by downregulating E-cadherin and upregulating Vimentin, a process that grants dysplastic epithelial cells the migratory capacity to breach the basement membrane.

Simultaneously, chronic exposure to ROS and epigenetic remodelling, specifically the hypermethylation of tumour suppressor promoters like p16INK4a, allows these damaged cells to evade apoptosis and bypass natural senescence checkpoints[29]. Ultimately, this synergy between mechanical trauma, chemical mutagenicity, and a pro-inflammatory, hypoxic niche creates a highly receptive environment for the evolution of invasive OSCC.

Public Health Implications

Despite the increasing awareness regarding oral cancer, areca nut chewing remains culturally accepted among many Asian populations.In Malaysia, areca nut and betel quid chewing practices continue to be observed among selected rural, indigenous communities and the Borneo tribal community [30]. The cultural acceptance and intergenerational exposure contribute towards continued usage despite increasing awareness regarding increase risk of oral cancer[31].Public health programmes should therefore focus onoral cancer awareness,culturally sensitive education, behavioural modification, early oral screening, and youth-targeted intervention. The oral medicine practitioners play important roles inearly diagnosis of oral potentially malignant disorders, biopsy referral, behavioural counselling, and long-term oral surveillance.

Future Perspectives

Further studies are required toidentify biomarkers for malignant transformation,investigate molecular pathways involved in fibrosis,evaluate preventive strategies, and develop culturally appropriate cessation programmes. Emerging technologies, including molecular diagnostics and artificial intelligence, may additionally contribute towards early detection of oral potentially malignant disorders associated with areca nut exposure.Further phytochemical and pharmacological studies may additionally contribute towards a better understanding of areca nut-associated carcinogenesis and disease progression.

Conclusion

The habitual chewing of Areca nut is a deeply entrenched cultural practice that acts as an insidious catalyst for oral devastation. As this review highlights, the synergistic toxicity of arecoline, polyphenols, and copper creates a highly mutagenic microenvironment, inexorably driving the progression of oral submucous fibrosis into oral squamous cell carcinoma. Confronting this unequivocal public health crisis demands a paradigm shift. Eradicating the areca nut epidemic is an urgent, life-saving imperative that requires integrating advanced molecular diagnostics with culturally empathetic cessation strategies, placing oral healthcare professionals at the very vanguard of global cancer prevention.

Acknowledgement

The authors have no acknowledgements to declare.

Funding Statement

The authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

VR: Conceptualisation, Literature search, Data visualisation (figures/tables), Writing – Original draft.

NSBMN: Conceptualisation, Literature search, Critical analysis, Writing – Review & Editing.

Availability of Data and Materials

The data supporting the findings of this review are available within the article.

Ethics Approval

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

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