



# Areca Nut an Irony for Mankind's Health



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## Abstract

Oral cancer is in the top five list of cancers occurring around. One of the leading causes is the excessive consumption of tobacco and areca nuts. This is mainly due to the active compound present in them such as arecoline present in areca nut. This not only affects the head and neck but also affects other vital organs as it is readily absorbed in blood stream and then gets transported to various parts of the body. This review article is written with the aim of providing complete detailed information about areca nuts. This will help in deliberating a complete picture of not only the harmful effects but also about its benefits. Thus, one can clear the misconception of considering betel nut just as a toxic and harmful compound.

**Keywords:** Beetal nut; Areca nut; Distribution; Chemical composition; Medicinal uses; Oral cancer

**Abbreviations:** ANE: Areca Nut Extract; Ig: Immunoglobulin; GABA: Gamma-Amino Butyric Acid; NNK: 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanone; NNAL: 4-(methylnitrosamino)-1-(3-Pyridyl)-1-Butanol; NNAL-Gluc: 4-(Methylnitrosamino)-1-(3-Pyridyl) Butyl]-beta-O-Dglucosiduronic acid; OSMF: Oral Submucous Fibrosis; T-cells: T Lymphocytes or Thymus Cells, m- Meter; cm- Centimeter

## Introduction

The two main chewing habits prevailing in India especially in, Gujarat are, first Mava which is mixture of tobacco, areca nut and lime and second is pan masala which is prepared by companies who claim it contains only areca nut and catechu. With time its consumption is increasing as pan masala is frequently promoted by media. Looking back into our ancient Ayurveda, the main ingredients such as areca nut and tobacco were used for curing many diseases i.e., it was used as medicine by our ancestors. Slowly and gradually, it started getting used to welcoming guests as a gesture of hospitality and these days it is one of the most addictive materials that has affected the health of the people consuming it. Oral cancer is in the top five list of cancers occurring around. One of the leading causes is the excessive consumption of tobacco and areca nuts. This is mainly due to the active compounds present in them such as arecoline and nicotine. They not only affect the head and neck but also affect other vital organs as it is readily absorbed in blood stream and then gets transported to various parts of the body. It is ironic that plants which were once considered as medicine are now treated as one of the worst toxins that is ruining the health of thousands as all that matters is its dose. We have neglected the thumb rule of toxicology i.e., anything in excess is poison, which leads to various health issues. The current scenario is such that thousands of people who are addicted feel helpless to quit and there are many who start consuming it out of curiosity and others who consider it as a matter of status and others who

use it to relax figure 1, for example, write "Magnetization (A/m)" or.

## Methodology

The purpose of this article is to comprehensively review the literature on areca nut its effects and uses. Literature search was performed using PubMed, Medline, Cochrane, and Google Scholar to search for articles published in English language. The following key words were used "Areca nut," "beetal nut" "supari" "Areca catechu," "cancer" "medicinal use" "habitat" and "chemical composition". All the papers were reviewed by two authors. The objective of this review was to compile the data and explore the lacunae in our current understanding which has withheld the medical community from its clinical use.

## Results

ARECANUT, Kingdom-Plantae, Subkingdom-Tracheobionta, Super division-Spermatophyta, Division-Magnoliophyta, Class-Liliopsida, Subclass-Arecidae, Order-Arecales, Family-Arecaceae

Genus-Areca, Species-Catechu.

Areca nut, seed of the fruit of the oriental palm, Areca catechu is the basic ingredient of a variety of widely used chewed products, which is more commonly named as betelnut. Areca nut is the seed of the oriental palm Areca catechu L. It has been

estimated that ~600 million people chew areca nut worldwide [1]. It is one of the most profitable cash crops in India. Combined with the leaf of the betel vine, piper betel and slaked lime, various preparations of areca nut are prepared in India, Taiwan, and Southeast Asia for the purpose of chewing. Areca nut is the fourth most abused substance after nicotine, ethanol, and caffeine [2]. It also has addictive potential and is reported to possess cytotoxic, mutagenic, and genotoxic properties [3,4].

### Description, habitat, distribution

Areca nut is an erect, unbranched palm reaching heights of 12-30m, depending upon the environmental conditions. The stem, marked with scars of fallen leaves in a regular annulated form, becomes visible only when the palm is about 3 years old. Girth depends on genetic variation and soil conditions. The root system is adventitious, typical of monocots. The adult palm has 7-12 open leaves, each with a sheath, a rachis, and leaflets. The leaf stalk extends as the midrib until the end of the leaf and ends as leaflets. Male flowers very numerous, sessile, without bracts; calyx 1-leaved, small, 3-cornered, 3-parted; petals 3, oblong, rigid striated; stamens 6, anthers sagittate. Female flowers are solitary or 2 or 3 at or near the base of each ramification of the spadix, sessile, without bracts; sepals permanent; staminodes 6, connate, styles scarcely any; stigmas [3], short, triangular. Fruit is a monocular, one-seeded berry, [3]. 8-5 cm long, smooth orange or scarlet when ripe, with a fibrous outer layer. The generic name is derived from the common name used by the people of the Malabar Coast in southwestern India [4]. It is distributed to various parts of Asia and U.S. It is known by various names in different countries and languages such as in English (areca nut, betel palm, betel-nut, supari palm, pinang palm)

### Chemical constituents

Areca nut (*Areca catechu*) is commonly used as an ingredient of betel quid, which also includes leaf of the creeping vine piper betel and lime with or without tobacco. Betel quid chewing has been popular, especially in many Southeastern Asian countries. Mostly, it is consumed for masticatory and psychoactive purposes [5]. It has been proven that addiction can be induced following prolonged chewing. Areca nut contents are very complex and controversial chemical entities having variable properties. The major compounds of it are polyphenolic compounds, alkaloids, tannin, arecoline, arecaidine and fibers. Areca nut contains the closely related alkaloids arecoline, arecaidine, guvacoline and guvacine [6,4]. Areca catechu is the only one of 54 areca species known to contain alkaloids. The arecaine is the active principle of the areca nut. Watery extract yields betel-nut catechu while the 'kernels' contain catechu, tannin 15%, gallic acid, oily matter (fat 14%), gum and alkaloids viz arecoline 0.07%, arecaine 1%, arecaidine and guvacoline, guvacine and choline occur in trace only. All these alkaloids are chemically related; arecoline is colorless volatile resembling nicotine [7]. The major constituents of the nut are carbohydrates, fats, proteins, crude fiber, polyphenols (flavonols and tannins), alkaloids and mineral matter. The role

of areca nut chewing in causation of oral cancer is established. Copper is implicated in tissues fibrogenesis via copper dependent enzyme (lysyl oxidase), which is crucial in stimulating fibroblasts in oral submucous fibrosis [8]. The habit of chewing areca nut preparations without tobacco has been reported to be associated with an increased risk of oral cancer in four epidemiologic studies, one each from India, Pakistan, Taiwan, China [6].

### Health effects and uses

Arecoline, the principal alkaloid in areca nuts, acts as an agonist primarily at muscarinic acetylcholine receptors and stimulates the central and autonomic nervous system. This leads to subjective effects of increased well-being, alertness, and stamina. It is known to improve concentration and relaxation, with other reported effects including lifting of mood, staving off hunger, aphrodisiac properties, and postprandial digestion. It has also been shown to have cario-static property. Areca nuts also exert a direct antimicrobial effect against bacteria, including *Streptococcus mutans*, *Streptococcus salivarius* and various other microorganisms in the oral cavity [5,9]. The cellular level of glutathione was diminished by areca nut extract (ANE) in splenic T-cells. Collectively, these results demonstrated that ANE markedly suppressed T-cell activation and Th1 cytokine production, which was mediated, at least in part, by the induction of oxidative stress [10]. Long-term exposure to sublethal doses of areca nut extract, intracellular anti-oxidative activity may also be enhanced in response to increased oxidative stress and genetic damage in human keratinocytes [11]. Substantial amounts of copper released from areca products induces lysyl oxidase activity up-regulating collagen synthesis by fibroblasts, facilitating its crosslinking and, thereby, inhibiting its degradation. The role of copper from areca products in the pathogenesis of oral sub-mucous fibrosis merits further investigation, particularly since it is thought to be involved in other fibrotic diseases, such as scleroderma and liver fibrosis [12].

Scientific teams from Taiwan, Malaysia and Papua New Guinea have reported that expectant mothers who chew pan (and/or other areca nut and betel leaf formulations) during pregnancy significantly increase adverse outcomes for the baby. The effects were like those reported for mothers who consume alcohol or tobacco during pregnancy. Incidences of lower birth weight reduced birth length and early term were found to be significantly higher [13]. Arecidine may have anxiolytic properties through inhibition of gamma-amino butyric acid (GABA) reuptake. The preferred route of administration, chewing, leads to rapid absorption of these alkaloids through the buccal mucosa, leading to an onset of these effects within 5 min, lasting for about 2 to 3 hours [9]. Areca tannin has been suggested as having a blood pressure regulatory effect through its ability to inhibit the precursor response to both angiotensin I and II [14]. Areca nut induced platelet aggregation is associated with iron-mediated reactive oxygen species production, calcium mobilization, phospholipase C activation, and TXB2 production. Various active

constituents like procyanidins, arecatannin B1 and extracts of seed showed HIV protease inhibition activity [15].

Various alkaloid constituents from areca nut, alkaloids in dichloromethane have antidepressant activity [16]. Betel nut may cause stimulant and euphoric effects. As a result, it is sometimes used recreationally. Betel nut was once used in toothpaste to prevent cavities. Areca nut contains several psychoactive alkaloids, one of which is arecoline and affects the parasympathetic nervous system and activates a sympathoadrenal response [17]. Areca nut chewing has been shown to affect nervous system [18,19] as well as cardiovascular system [20,21]. Peptic ulceration, reported to be increased in chewers of betel quid (with tobacco) [22]. Chewers secrete more saliva through chemical stimulation, diluting salivary amylase and potassium and tobacco aggravates this effect [23]. It was hypothesized that serum levels of immunoglobulins may play an important role in the pathogenesis of oral mucosal diseases or reflect clinical changes in these conditions [24].

Shah [25] found that oral submucous fibrosis patients had higher serum levels of immunoglobulin IgG, IgM and IgA, whereas Canniff [26] found an increase in serum IgG levels in oral submucous fibrosis patients relative to normal individuals, but no difference in IgM and IgA levels was found. These findings suggest that nicotine is a potent immunopharmacological agent regarding T-cell function [6]. Laboratory studies suggest that betel nut may have antibacterial effects, which may reduce the development of cavities. However, other therapies to prevent tooth decay are safer, and the risks associated with betel nuts likely do not outweigh the possible benefits. Areca nut is made into a dentifrice on account of its astringent properties [27]. It is considered to strengthen the gums and sweeten breath. The seed, reduced to charcoal and powdered, forms an excellent dentifrice [28]. Arecoline hydrobromide, a commercial salt, is a stronger stimulant to the salivary glands than pilocarpine and a more energetic laxative than eserine. In addition, chronic chewers also have marked attrition of cups of teeth leading to loss of occlusal pits and fissures, which may reduce the risk of pit and fissure caries by eliminating potential stagnation areas. The increased production of sclerosed dentine in response to attrition may confer protection against microbial invasion. Furthermore, the process of chewing itself brings copious amounts of saliva to the mouth and in the presence of added slaked lime may increase the pH in the oral environment; this may act as a buffer against acid formed in plaque on teeth [29].

The study demonstrating a detrimental influence of betel chewing on the periodontal tissues was carried out by Mehta [30]. They found a higher prevalence of periodontal disease among betel chewers than non-chewers. Gupta & Warnakulasuriya [2] found that the mean periodontal index (PI) for those who chewed betel nut was consistently greater than for those who did not chew. Waerhaug [31] found that betel nut chewers over the age of 20 years had a very high PI indicating greater periodontal breakdown among chewers 17 than non-chewers,

even when subgroups of equivalent oral hygiene were compared. A higher prevalence of gingivitis was reported among chewers of betel quid with tobacco [32]. Ling [33] found that the levels of two periodontal pathogens, *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*, were higher in betel quid chewers who show a higher gingival index (an indicator of gingival inflammation) than in non-chewers. In addition, 77–87% of those who have gingival recession also have evidence of related oral mucosal pathology [34]. In vitro studies by Chang & Jeng [35,36] pointed towards the adverse effects of areca nut on the gingiva and periodontium. Leukoplakia is the most common precancerous lesion associated with tobacco smoking and/or chewing. Tobacco smoking and chewing are the most important etiological factors associated with leukoplakia. Leukoplakia is a clinical term used to describe patches of keratosis [37]. It is visible as adherent white patches on the mucous membranes of the oral cavity, including the tongue. It is sometimes described as precancerous [38]. Tobacco, either smoked or chewed, is the main culprit in its development [39]. The WHO has classified these into two groups, homogeneous and non-homogeneous. Among non-homogeneous leukoplakias, nodular leukoplakia tends to show the highest rate of malignant transformation [40,41] carried out house-to-house survey in various villages in India and reported that leukoplakia was usually associated with higher prevalence of chewing of betel quid with tobacco than chewing of betel quid alone or than no chewing habit.

Earlier, Wahi [42] also showed that the habit of chewing was associated with higher prevalence of leukoplakia than no chewing habit. No distinction was made between those chewing betel nut alone and those chewing betel nut with tobacco. Gupta [43] reported a positive dose response relationship between tobacco habit and the prevalence of leukoplakia. The most convincing evidence for the etiological role of tobacco came from intervention studies which demonstrated that leukoplakia regressed significantly more often when tobacco habits were discontinued or reduced compared to when the habits remained unchanged [44]. This is supported by other studies also Mancini & Hirayama & Martin [45-47]. Later Kresty [48] reported an association between oral leukoplakia and two metabolites of the tobacco - specific nitrosoamine i.e., 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). These two metabolites are 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and [4-(methylnitrosamino)-1-(3-pyridyl) butyl]-beta-D-glucosiduronic acid (NNAL-Gluc). A significant association was found between the presence of leukoplakia and increasing levels of these metabolites demonstrating the role of smokeless tobacco in the causation of oral leukoplakia. Warnakulasuriya [49] reviewed four case-control studies that examined relative risk of oral leukoplakia in betel quid chewers. In one of the studies, chewing areca nut (in betel quid without tobacco) raised the relative risk by at least three-fold compared with non-tobacco users. Further, the results of a case-control study conducted in Taiwan, where areca nut is chewed without tobacco also demonstrated that the

cessation of areca nut chewing resulted in resolution of 62% of leukoplakias, suggesting that areca nut alone also has a significant etiologic role in the development of leukoplakia.

Oral submucous fibrosis is a precancerous condition characterized by a progressive stiffening of the oral mucosa to the point wherein affected 19 persons have difficulty of opening their mouths. Oral submucous fibrosis (OSMF) is a chronic condition characterized by mucosal rigidity of varying intensity due to fibro-elastic transformation of the juxta-epithelial layer [50]. OSMF is a high-risk precancerous condition [51] with a malignant transformation rate of about 7.6% [52]. Areca nut chewing could be one of the most important etiologic factors in OSMF [54]. One of the clinical symptoms of OSMF is trismus, a limitation of mouth opening. This may eventually impair the ability to eat and speak, and dental care may become difficult. Chewing betel quid has been recognized as one of the most important risk factors for OSMF [53-56] but only a fraction of betel quid chewers develops the disease. This disease affects 0.5% (5 million people) of the population in the Indian subcontinent and is a public health issue in many parts of the world, including the United Kingdom [27], South Africa [Seedat & Van [57] and many Southeastern Asian countries [58,59]. Lee & Chin [60] observed the effects of betel nut chewing on the buccal mucosa of Indians and Malays in West Malaysia. They found varying degrees of epithelial atrophy, reduction of rete pegs, sub epithelial inflammatory edema and fibrosis among chewers. A close association between OSMF and habituation to pan supari chewing was also reported by Dockrat & Shear et al. [61,62] found 0.49% prevalence of oral submucous fibrosis among the industrial workers in Gujarat, India. They observed that OSMF is more commonly associated with chewing plain supari, or with combination of pan with chuna (slaked lime), kattha (paste of catechu), supari (betel nut) and tobacco than with other combinations. Gupta [63] demonstrated that the incidence of submucous fibrosis was nil among people with no chewing habit, whereas the incidence rate among the people who chewed areca nut along with or as an ingredient of pan was 35 per 1,00,000 people per year. Canniff [26] also analyzed forty-four patients with oral submucous fibrosis. All were areca nut chewers, of which some of them chewed along with additives as pan supari. Out of these, 68%, 20 were heavy chewers while 37% were moderate chewers. Bhonsle [64] observed a variation in the pattern of occurrence of OSMF. In Pune, Maharashtra (India) OSMF affected more on the soft palate, uvula and retromolar region in contrast to patients in Ernakulam, Kerala (India) where the tongue, floor of the mouth and hard palate were more often involved. In addition, associated leukoplakia, oral cancer and petechiae were also observed in these groups of patients. The patients of Ernakulam, Kerala would spit out the juice macerated quid after chewing while the other group chewed for more time before swallowing the whole mixture. This could be the reason for the difference in sites of occurrence. A study was carried out among areca nut chewers in Taiwan showing that betel quid chewing is the main cause of OSMF and oral cancer [65].

Babu [66] reported that habitual chewing of pan masala or gutkha is associated with earlier presentation of OSMF than betel quid use. Oral lichen planus and leukoplakia were associated with smoking as well as betel quid chewing habits. Gupta [56] undertook a study to determine whether there was an increase in the incidence of OSMF in the Bhavnagar district, Gujarat, India. The reported prevalence of OSMF in Bhavnagar district during 1967 was 0.16%. Among 5018 men who reported the use of tobacco or areca nut, 164 were diagnosed as suffering from OSMF. Areca nut was used mostly in the form of mawa, a mixture of tobacco, lime and areca nut and 10.9% of mawa users had OSMF. The disease as well as areca nut use was about 85% , 21 among lower (<35 year) age group and concluded an increase in the prevalence of OSMF, especially in the lower age groups, directly attributable to the use of areca nut products. Meghji [67] investigated the effects of areca nut on the inhibition of collagenase and thereby aid in the deposition of excess collagen. They observed that areca nut extracts, purified tannins and catechin (the diphenol tannin precursor), all inhibited collagen lysis by both bacterial and mammalian collagenases in a dose-dependent manner. They concluded that tannin from the chewed areca nuts might enhance the development of fibrosis in oral submucous fibrosis by reducing the susceptibility to collagen degradation by collagenase. Harvey [68] suggested that the unnatural accumulation of collagen in the tissue of OSMF patient is due to fibroblast proliferation and stimulation of collagen synthesis by the alkaloids in the areca nut as well as an inhibition of collagen degradation by the tannins and flavanoids which are also contained in the nuts. The most serious aspect of OSMF is its high potential for development of cancer; the relative risk being 400 times [69]. Subsequent studies reported that the incidence of carcinoma varies in OSMF from 2 to 30% [70]. Awang [71] investigated the pharmacology of betel nut (Areca catechu) in relation to OSMF and found that boiling the nut, commonly used for softening before chewing removed most alkaloids. The variations in nut alkaloids and tannin content were probably due to plant variability and different procedures for the preparation of the areca nut for consumption. These variations in the pharmacologically active constituents of the betel nut may contribute to the regional difference in the incidence of the disease. It has been established that betel nuts (with or without paste of crude slaked lime and spices and/or tobacco) might play a role in the initiation and pathogenesis of OSMF. However, only a fraction of the betel nut chewers develops OSMF suggesting genetic susceptibility or lack of antifibrotic activity in OSMF cases. Canniff [26] demonstrated a genetic predisposition to the disease, involving raised frequencies of HLA antigens A10, DR3. The histopathological and clinical features of the oral mucosa gave the suggestion of an autoimmune basis for OSMF. The results supported that OSMF is a chronic autoimmune disease, initiated by constituents of betel nut and occurring in genetically susceptible individuals.

## Conclusion

The review article gives a clear picture of both medicinal uses as well as ill effects. In recent days due to over consumption areca nut is considered as a toxin thus its potential medicinal property is overlooked. More research needs to be done on the positive aspect. Keeping in mind the dosage this so-called toxic plant can again be considered as medicine for treating many illnesses.

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