

# EXPLORING THE COMBINED USE OF ARECA NUT AND TOBACCO: FROM TRADITIONAL PRACTICES TO MODERN PUBLIC HEALTH CONCERNS

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## ABSTRACT

Areca nut and tobacco are widely used psychoactive substances, particularly in South and Southeast Asia, with deep cultural and traditional roots. However, their prolonged use is associated with serious health consequences. This integrative review synthesizes the current knowledge on the chemical composition, biological effects, addiction potential, and socio-cultural aspects of areca nut and tobacco use. Areca nut contains alkaloids, such as arecoline, and polyphenols, which exhibit both pharmacological and toxicological properties. Tobacco contains nicotine and numerous carcinogenic compounds, contributing to addiction and various life-threatening illnesses. The co-consumption of areca nut and tobacco increases the risk of oral submucous fibrosis, oral squamous cell carcinoma, cardiovascular diseases, and reproductive disorders. Arecoline and nicotine exert their effects through cholinergic receptors, leading to addiction and systemic toxicity. The prevalence of areca nut and tobacco use is further reinforced by cultural normalization in low- and middle-income countries, contributing to increased healthcare costs and premature mortality. Culturally-specific integrated public health measures, including smoking cessation programs, educational campaigns, and pharmacological and behavioral interventions, are urgently needed to control the high prevalence of areca nut and tobacco use. Future research should focus on identifying genetic susceptibility, evaluating long-term cessation interventions, and developing interdisciplinary policy frameworks to address these preventable health burdens effectively.

**Keywords** Areca nut, Tobacco, Squamous cell carcinoma, Health effects, public health, Cultural aspects, Policy interventions.

## INTRODUCTION

Around the globe, tobacco and areca nut (*Areca catechu*, AN) are the most widely used psychoactive drugs in the world, ranking first and fourth, respectively (Zdrojewicz et al., 2015). The areca palm (*Areca catechu* L) is a tropical and subtropical plant found mainly in South and Southeast Asia and in the Pacific islands of Bangladesh, Myanmar, China, India, Sri Lanka, and Thailand. Due to their unique taste and chewing properties, areca nuts are used as a chewing hobby (Papke et al., 2020). Since ancient times, it has been used as a mouth refresher and also included in the Chinese Pharmacopoeia in 1953; it is applied in more than 100 prescriptions against parasitic infections, dyspepsia, stomach distension, abdominal pain, diarrhoea, oedema, and jaundice (Sun et al., 2024). Chewing areca nut has become a habit of more than 600 million worldwide, next to the habits of Tobacco, alcohol, and caffeine. Areca Nut and Tobacco Product (ANTP) comprise smokeless tobacco products and is commonly used by 224 million Indians. Ten to twenty percent of the world's population consumes areca nut. In the last few years, especially within the young generation, the use of commercially available commodities containing areca nut has increased, such as gutka, pan masala, and mawa (Niaz et al., 2017). Both Areca Nut and Tobacco Product (ANTP) and AN are very commonly used; however, there is a major health hazard in both because of the incidence of cardiovascular diseases and oral cancer. areca nut chews are known to be associated with pharyngeal and oral malignancies; therefore, in 2003 the International Agency for Research on Cancer (IARC) classified areca nut chews as Group 1 carcinogens with or without the presence of tobacco (IARC, 2004, Runggay et al., 2024).

Several studies have indicated that one of the chief chemical components of areca nuts, arecoline, has caused genotoxicity, carcinogenicity, reproductive toxicity, neurotoxicity, hepatotoxicity, and nephrotoxicity. Arecoline was recently classified as a Group 2B carcinogen by the International Agency for Research on Cancer (Garg et al., 2014; Ali et al., 2020).

The harmful health effects of tobacco use and areca nut may be generalized into 3 major categories. To begin with, oral squamous cell carcinoma (OSCC) has a significantly higher probability of developing in case the onset of oral potentially malignant disorders such as leukoplakia, oral lichen planus, erythroplakia, oral submucous fibrosis (OSMF), and proliferative verrucous leukoplakia is caused by chronic consumption (Sivaramakrishnan and Sridharan, 2025).

Second, chronic exposure to the chemicals causes cancers like the oesophageal cancer and OSCC that remain the major causes of morbidity and mortality in Asia and Southeast in general (Akhtar, 2013). Third, some of the equally concerning non-malignant systemic effects of using areca nut and tobacco are the risk of coronary artery disease, hypertension, metabolic syndrome, and cerebrovascular stroke. Also, reproductive complications like still births, preterm birth and low birth weight have been seen in regular users. Combined, these results highlight the high cost to the population health of areca nut and tobacco consumption (Tsai et al., 2012). The prevalence of chewing areca nut among Sri Lankan adults is significantly higher in rural than in urban areas. Compared to lip and oral cavity cancers, which contributed to 9.5% of all registered cancers, oral-pharyngeal cancer contributed to 12.8% of all registered cancers in Sri Lanka, making the latter the most fatal cancer form (3 deaths per day), based on the country's data from 2020 on the national cancer incidence rate (Karunarathne & Ekanayake, 2016). Areca nuts affect the autonomic nervous system and stimulate the parasympathetic and sympathetic nervous systems simultaneously.

Pulse rate rises, pupil dilation occurs, intestinal peristalsis and tone increase, and skin temperature becomes hyperthermic due to this effect. Arecoline also decreases diastolic blood pressure and is cholinergic. Use of arecoline during pregnancy leads to neonatal withdrawal syndrome and placental damage (Lin et al., 2018; Thakur & Mehrotra, 2022). Therefore, the purpose of this review is to investigate the various impacts of tobacco, areca nut, and their combinations.

The use of tobacco and areca nut is very widespread in South and Southeast Asia. Cases of areca nut chewing have been reported in the practice of Many countries including Pakistan, Sri Lanka, Bangladesh, Thailand, Cambodia, Malaysia, Indonesia, China, East Timor, Taiwan, Papua New Guinea, and some Pacific Islands, as well as migrant populations in South Africa, Eastern Africa, North America, the United Kingdom and Australia (Kumar et al., 2021). Besides looking into the biological, toxicological and epidemiological issues of areca nut and tobacco, this review also emphasizes on their general public health implications. The socioeconomic disparities play an important role in the prevalence of these substances, with low income and less educated population showing higher rate of use (Singh et al., 2021). Furthermore, pharmacological and behavioural cessation methods like structured counselling, pharmacologic measures which have shown promising effects in regions with high areca nut consumption have attracted growing interest (Muralidhar & Madhivanan, 2023). The cultural and ritual significance of chewing areca nuts poses a great barrier to quitting, and the continuation of social acceptability. Lastly, new policy and regulatory actions, which include prohibition of gutkha and other smokeless tobacco, are some of the most crucial steps to reduce these health risks (Tami-Maury et al., 2019). All these considerations demonstrate the need to have a multidisciplinary approach that integrates the behavioural, cultural, biological, and policy perspectives to effectively address the global burden of tobacco and areca nut usage (Welding et al., 2022).

## **2. ETHNOMEDICAL BACKGROUND**

### **2.1 Areca Nut**

Charaka and Sushruta spread the custom of chewing areca nut after meals between 75 and 300 AD. Areca nut wrapped in a leaves chewed with a little bit of fragrant spices were believed to aid digestion, clean the throat and freshen the mouth odor between 300 and 750 AD. Around 500 AD, the therapeutic value of it was known to the renowned Indian scholar Vagbhata.

Ancient historians record that it was also in use in the eighth and ninth centuries in Ceylon and Persia about 600 AD. The nut was introduced to Europe by Marco Polo in about 1300 AD and thrived as a high-priced areca nut in western Pacific (Rashid et al., 2015).

Areca catechu plays an important role in Ayurvedic medical system. It is a pitta and Kapha mitigating. It acts as a proficient laxative and also as a stimulant. Ayurveda has been using it to treat mental confusion, ocular swelling, muco-purulent secretion and chronic urinary pain. It is applied as nervine tonic and aphrodisiac. Chewing of areca nut strengthens the gums, control sweating and produces a good breath and curbs bad oral taste. It is employed as

carminative, diuretic, digestive, antiulcer, antidiarrheal, anthelmintic, anti-heartburn, laxative drug (Grover & Areca, 2021).

Modern Chinese medicine incorporates areca nut (*Areca catechu* L.) for various purposes with main use as an anthelmintic agent against intestinal worms. areca nuts were probably brought to China for the first time during the Ming era between A.D. 1368–1644. The practice of areca nut chewing has reached its highest levels in southern Chinese provinces including Yunnan and Hainan provinces along with Hunan province. The area of Hunan does not produce Areca palms so residents import these nuts from Thailand or Hainan.

The process of drying both husk and areca nuts results in industrial products. Manufacturing techniques involve treating cut fruits with different flavoring substances. The final chewing product consists of half fruits combined with dried husks. Chewing barbecue is common in most cities across China. People in all the main cities throughout Hunan province have established a Areca nut chewing habit including Xiangtan, Changsha, Hengyang, Yiyang, and Loudi (Tang & He, 2021). Many pharmacological and biological properties of areca nut have sustained the extensive medical plant usage throughout Chinese history. Medical practitioners have utilized areca nut as a treatment for digestion and parasite removal for extensive historical periods.

The seed of areca nut constitutes the main medicinal component and manufacturers prepare it through stir-frying and subsequent carbonization that results in dark brown or yellowish hues. Both raw and burnt areca nuts serve as principal types utilized during clinical practices. TCM medical records show this herb as having been in use in the past 1700 years when Yaolu listed it in its recognized TCM monograph during China's Jin period. The areca nut received its first mention as a medicinal herb in Mingyi Bielu due to its anti-parasitic and digestive as well as diuretic properties. A traditional treatment using areca nuts exists for both abdominal distension and the common remedies of constipation and dysentery and abdominal distension per the Compendium of Materia Medica Bencao Gangmu and Xinxu Bencao. Chinese materia medica monographs Yaoxinglun, Haiyao Bencao, Yixue Qiyuan, Rihuazi Bencao, and Bencao Huiyan discussed how areca nut could treat constipation alongside diarrhea, parasitic illnesses, abdominal distension and various other medical conditions (Peng et al., 2015).

## 2.2 Tobacco

The history of Tobacco consumption in China radically changed because of tobacco's discovery alongside its distribution throughout the region. Chinese society received tobacco transported through Southeast Asian trade by Portuguese and Spanish merchants during the late 16th century. During the Qing Dynasty (1644 - 1912) tobacco spread through all Chinese social classes because it initially used conventional pipes to smoke. The practice was commonly used for hospitality purposes while medical works from ancient China made reference to it because people claimed to gain health benefits (Barnett & Peng, 2021).

The American-Indians apparently became the first who used tobacco in different forms. They chewed, smoked, sniffed it up their nostrils. The pipes were used to smoke tobacco during ceremonial and medicinal purposes and also as a symbol of goodwill that is the peace pipe. They used tobacco to ease toothache, to heal ulcers and skin sores, lung diseases, spleen and womb diseases, bug bites and as an antifatigue product and also to clean teeth thus making them white. It was the main cause of introduction of tobacco in Europe due to these medicinal properties (Chaly, 2007).

China includes tobacco plants within their exclusive category of medicinal resources. Traditional Chinese Materia Medica states tobacco provides medicinal advantages by energizing vital energy while also relieving pain and removing moisture and swelling and detoxifying the body and acting as an insect killer. Tobacco serves medical purposes for treating arthralgia, carbuncles, furuncles, scabies, eczema, snakebite, sprains, contusions, fullness with food stagnation and pain related to Qi stagnation. The Compilation of National Chinese Herbal Medicine describes tobacco as a thermal substance with sweetness and toxicity that possesses both insecticide properties and detoxification benefits and detumescence feature (Table 1).

The primary use of tobacco exists in the treatment of furuncles, tinea capitis, psoriasis, alopecia, snakebites along with neck and back carbuncles and wind phlegm and crane knee (Zhang et al., 2024).

### Table 1: Comparative Overview of Areca Nut (*Areca Catechu*) and Tobacco

#### (*Nicotiana Tabacum*) in TCM

(Bensky et al., 2020; Wang et al., 2024; Liu and Chang, 2023; Chen et al., 2025).

Category	Areca Nut (Areca Catechu)	Tobacco (Nicotiana Tabacum)
Plant parts used	Areca nut Seed (nut, kernel), Husk (pericarp), Flower (rarely in decoction)	Mature leaves, stalks (rarely), Flowers (rare in folk remedies)
Traditional Forms / Preparation	Raw nut slices: chewed with betel leaf and slaked lime as a stimulant. Dried nut: sun dried or oven dried, chewed or powdered. Carbonized nut: stir or fried until black used in decoction for diarrhoea. Powdered husk: applied topically for skin disorders.	Cured / dried leaves: smoked in pipes, cigar, or rolled leaves. Burnt leaf ash: Mixed with oils and applied on wounds or ulcers. Steeped leaves: The leaves are soaked in water and used as a poultice for skin infections or bites. Leaves powdered: sprinkled on the skin against lice/scabies; added to ointment.
Ethnomedical / TCM uses	Expel intestinal parasites (anthelmintic), Remove indigestion, bloating and constipation, Reduce edema (diuretic), Treat dysentery, obstinate abdominal pain and Qi stagnation, Oral, topical application of ulcers and gum disease.	It is traditionally used to relieve arthralgia and pain caused by trauma, decongest and detoxify snake and insect bites, and to treat conditions such as carbuncles, furuncles, scabies, and psoriasis. It also exhibits insecticidal properties, helping to eliminate parasites and lice, and is believed in TCM to dry dampness and remove stagnation.
Addiction Potential	Moderate Arecoline act on muscarinic receptor – mild euphoria and habit forming	High nicotine stimulates nicotine receptor and dopamine release, strong reinforcement and dependency
Toxicological Profile	Oral submucous fibrosis, oral cancer (Group 1 carcinogen). Fibrosis of mucosa & organs (via collagen). Genotoxic and reproductive toxicity. Hepatotoxicity and nephrotoxicity at high doses.	Oral, lung and other cancer (group 1 carcinogen). Cardiovascular and neurotoxicity. Oxidative stress related damage. Reproductive and development toxicity
Pharmacological Profile	Arecoline: partial agonist at muscarinic receptors - stimulates parasympathetic activity (salivation, peristalsis, pupil constriction), CNS stimulation (alertness, mild euphoria).	Nicotine: full agonist at nicotinic receptors - stimulates both sympathetic and parasympathetic pathways, increases dopamine, elevates heart rate, blood pressure and cognitive focus.
Cultural Notes in China	Chewing as a social ritual, particularly in Hunan and Yunnan provinces. Seen as invigorating & warming in cold climates. Gifted during weddings & festivals.	Smoking became widespread during Ming and Qing dynasties. Used for hospitality and rituals. Associated with masculinity and social status.

### 3. CHEMICAL COMPOSITION

#### 3.1 Areca Nut

The chemical composition of areca nuts is complicated, with many components which are found in various regions of the nut. Areca nuts are primarily composed of polyphenols (10-30%), polysaccharides (18-25%), alkaloids, fibres and fatty acids (Guo et al., 2024). While areca nut husk may be a great source of wood fibre, its greater cellulose content and higher lignin content give it a harder texture and more mechanical friction on the mouth mucosa when chewed. In addition, areca nuts contain a number of beneficial compounds (Sun et al., 2024). Each component of the areca nut has variable properties, where the primary alkaloids, polyphenols, and certain amounts of elements are the active components of the areca nut, which produces the unfavourable effects (Dangore-Khasbage et al., 2023).

### 3.1.1 Alkaloids: [Arecoline]

The group of higher plants contains the nitrogen-containing organic compounds known as alkaloids, which are mainly cyclic nitrogenous compounds and psychoactive drugs that occur in nature. The total alkaloid content of areca nut ranges between 0.3% and 0.7%, and the four main alkaloids present in the areca nut are arecoline (C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub>), arecaidine, guvacoline, and guvacine. Among these, arecoline is the most abundant and pharmacologically active compound, playing a major role in the psychoactive and toxic effects of areca nut. The chemical structure of arecoline are shown in the (Figure 1).

### 3.1.2 Alkaloid: [Guvacine, Guvacoline and Arecaidine]

The guvacine component is nearly three times more abundant than arecoline in mature areca nuts, even though arecoline is consistently the richest alkaloid in immature green areca nut extracts. This shows the amounts of various alkaloids in areca nuts, which fluctuate with maturity (Dangore-Khasbage et al., 2023).

Unexpectedly, the maturity period of the areca nut will influence the amount of guvacine, where guvacine levels were 6 times greater in mature areca nut extracts than in younger ones (1871.4 µg/g vs 302.9 µg/g). Multiple areca nut products contained trace amounts of arecaidine together with guvacoline at levels below the arecoline content (0.64-2.22 mg/g) and the guvacine content (0.17-0.99 mg/g) per dry weight. Analysis of saliva after chewing three formulations detected arecaidine and guvacoline while guvacoline exhibited low concentrations when compared to arecoline and nicotine across the pan masala formulation (Zhang et al., 2022; Jain et al., 2017).



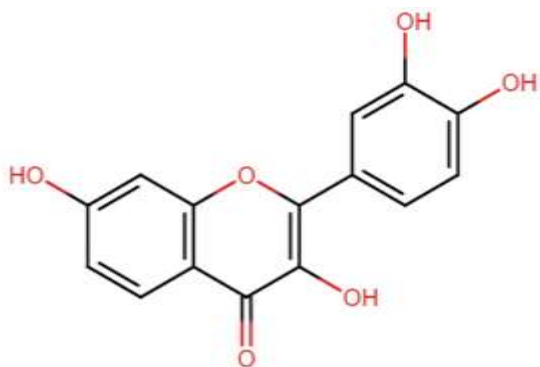
**Figure 1: Chemical structure of arecoline, the primary psychoactive alkaloid responsible for the addiction and toxic effects associated with areca nut consumption.**

### 3.1.3 Polyphenols

The secondary metabolites of the plant, known as phenolic compounds or polyphenols, are the most common phytochemicals that act as antioxidants. Flavonoids, tannins, and other phenolic compounds are abundant in areca nuts. areca nuts have a substantially larger number of total phenols and flavonoids than areca husks and flowers. Additionally, the total phenolic content of areca nuts varies according to their length, maturity, and provenance (Fan et al., 2022).

### 3.1.4 Flavonoids

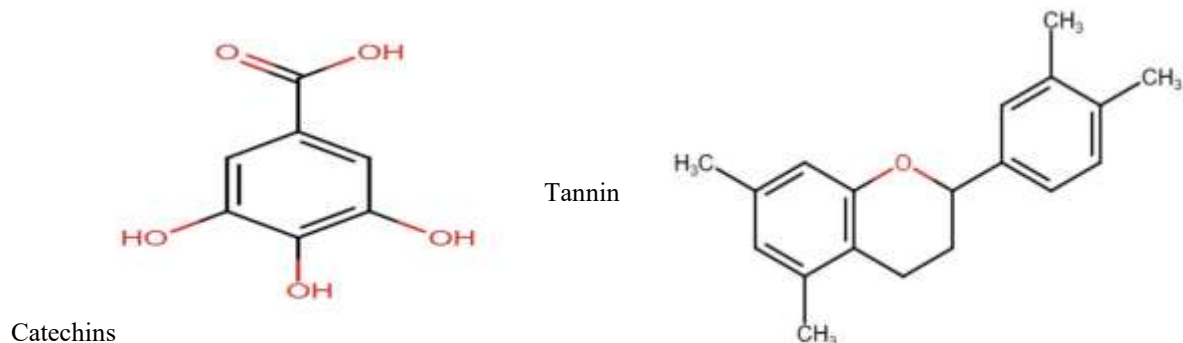
The areca nut also contains flavonoids (Figure 2), which also have a variety of biological properties, such as antibacterial and anticancer properties. Isorhamnetin, luteolin, chrysoeriol, glycyrrhizin, jacareubin, quercetin, flavan-3-ol, flavan-3,4-diols, 4',5'-dihydroxy-3',5',7'-trimethoxyflavone, and 5,7,4'-trihydroxy-3',5'-dimethoxydihydroflavone are the primary families of flavonoids found in areca nut (Singh et al., 2023).



**Figure 2: Chemical structure of a flavonoid, a plant polyphenol with potent antioxidant and anti-inflammatory properties, shown in contrast to the toxic alkaloids present in areca nut.**

### 3.1.5 Tannins

Tannin is primarily responsible for the bitter as well as astringent flavour of areca nuts, and proanthocyanidins, catechins, arecatannin, proanthocyanidins A and B are the major tannins extracted from the areca nut (Grover & Areca, 2021).



**Figure 3: (3a) Chemical structure of tannin, a natural polyphenol exhibiting antioxidant and protective effects, contrasting the toxic alkaloids found in areca nut. (3b) Chemical structure of catechin, a flavan-3-ol type polyphenol exhibiting antioxidant and protective effects, shown in contrast to the toxic alkaloids present in areca nut.**

### 3.1.6 Polysaccharides, Lipids, and Other Components

Polysaccharides, triterpenes, steroids and fatty acids are the substances which are also present in areca nuts. areca nuts are rich in polysaccharides (Rashid et al., 2015). About 18.7% of the areca nut is made up of polysaccharides, mostly galactose and sucrose, which are important antioxidants. Mannose, galactose, arabinose, and xylose make up the majority of PAP1b, a new neutral polysaccharide that was isolated from areca nuts. It has a strong scavenging capacity on DPPH and hydroxyl radicals, which shows that it may have antioxidant properties (Sun et al., 2024). Some trace elements have also been identified in areca nut, such as ferrous, zinc, chromium, aluminium, cobalt, manganese and so on (Zhang et al., 2023). It contains a lot of copper in nuts, which will cause fibrotic conditions and improve Lysyl oxidase function. One of the trace elements presents in areca nuts is copper, which is said to be consumed in excess of what chronic areca nut chewers actually need. This raises fibroblastic activity, which involves collagen synthesis and degradation inhibition (Prasannakumaran et al., 2024).

### 3.2 Tobacco

Tobacco is known to contain a complex mixture of naturally formed and low process-derived compounds. The most dominating of them is nicotine which is the chiefly alkaloid and its addictiveness is prominently given by it. Tobacco leaves also contain traces of alkaloids such as normicotine and anabasine besides the carbohydrates and polyphenol found along with nicotine. The smoke that arises after burning tobacco or even after a process of curing a tobacco smoke contains toxic chemicals volatile aldehydes, polycyclic aromatic hydrocarbons (PAHs), and tobacco-specific nitrosamines (TSNAs).

Such metabolites have been directly linked with chronic inflammation, oxidative damage as well as increased cancer risk. Also, use of fertilizers in the production process and its disposal to the environment can cause presence of harmful metals such as lead and cadmium (Cheng et al., 2022).

### 3.2.1. Nicotine

Nicotine occurs naturally in the leaves of plants of the genus *Nicotiana* (Lewis, 2020). It is a unique alkaloid which contains two nitrogen-containing heterocycles, pyridine and pyrrolidine. Whereas this component is what makes smoking so addicting, resulting in long-term cancer. It is a dinitrogen alkaloid that is found in dried tobacco plant leaves (*Nicotiana tabacum*), and its quantity is up to 3%. Nicotine makes up over 90% of tobacco alkaloid content, the chemical structure of nicotine is illustrated in (Figure 4), highlighting this dual-ring system, which facilitates its rapid absorption and potent biological activity. This structure plays a crucial role in its contribution to tobacco dependence and toxicity. In *Nicotiana rustica* (commonly referred to as Aztec tobacco), nicotine is present in significantly higher concentrations, reaching up to 14% (Popova et al., 2020).



**Figure 4: Chemical structure of nicotine, the primary psychoactive alkaloid responsible for the addiction and toxic effects associated with tobacco consumption**

Nicotine is a colourless, photosensitive alkaloid and one of the few substances existing in liquid form. It becomes brown when exposed to light or air and is rapidly oxidised. Another similar alkaloid is cotinine (Lewis, 2020). The active component of tobacco is nicotine. It acts on the receptor nicotinic acetylcholine (nAChRs) in the brain and affects the neurotransmitter release and leads to its stimulant and psychoactive effects (Hoffman & Evans, 2013).

### 3.2.2 Other Harmful Constituents of Tobacco

In addition to nicotine, tobacco contains an immense number of toxins and cancer-causing chemicals, which are a primary reason behind the adverse health effects. The International Agency for Research on Cancer categorises tobacco-specific nitrosamines like N-nitrosamino nor nicotine (NNN) and 4-(methylnitrosamino)-n-butanone (NNK), human carcinogens with high correlation to oral and lung cancer (Cheng et al., 2022). Included among the products of combustion are the generation of polycyclic aromatic hydrocarbons (PAHs) like benzo[a]pyrene, which is also a potent mutagen. Volatile aldehydes such as acetaldehyde, acrolein and formaldehyde induce cytotoxic effects, including oxidative stress, DNA damage and chronic inflammation.

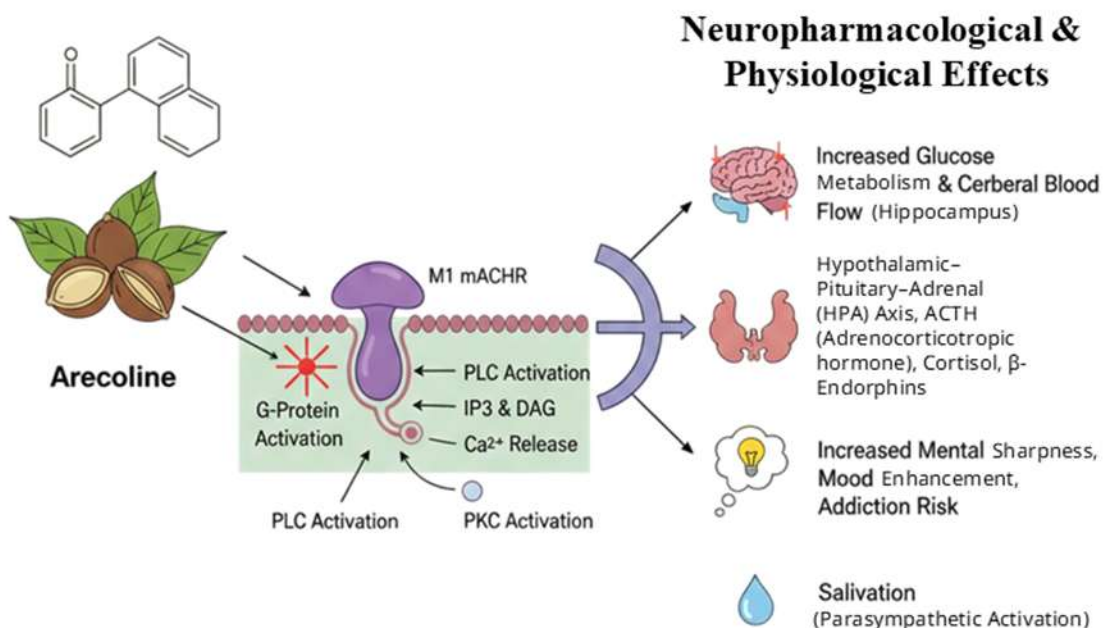
In addition, tobacco plants also absorb heavy metals such as cadmium, lead and arsenic, from the soil which accumulate in the human body and cause systemic toxicity through bioaccumulation. Smoking releases carbon monoxide, which decreases oxygen availability to tissues and increases the risk of cardiovascular disease. It is the combination of these compounds with nicotine which makes them closely linked with the occurrence of numerous diseases like malignancies, cardio vascular disease and reproductive disorders (Zhang et al., 2024).

## 4. BIOLOGICAL EFFECT

### 4.1 Areca Nut

Research conducted in recent times shows that arecoline, arecaidine and guvaine in the areca nut have a hand in its effects on the central nervous system (CNS). When they bond with cholinergic receptors in the brain, especially the M1 muscarinic receptors, these chemicals stimulate or depress certain processes. As an illustration (Figure 5), arecoline has been shown to boost glucose metabolism and cerebral blood flow in the brain, mainly in the hippocampus

and it even activates the hypothalamic - pituitary - adrenal axis and leads to increases in ACTH, cortisol and  $\beta$ -endorphins. Both mental sharpness, a better mood and the risk of addiction are the result of these neuropharmacological effects. Combining areca nut and tobacco in the traditional way greatly helps both the central nervous system and general health. Because of this, there is a greater possibility of developing drug-related brain damage, addiction and health problems in the long run. To judge the dangers of using tobacco and areca nut in combination, it is important to know how these substances impact our body (Islam et al., 2025).



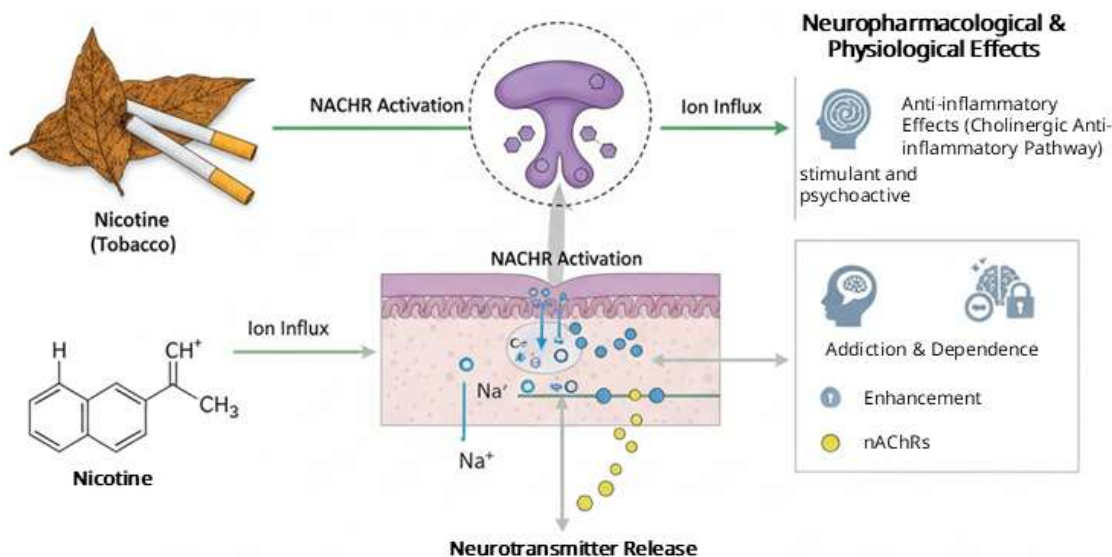
**Figure 5: Mechanism of arecoline-induced neuropharmacological and physiological effects. Arecoline activates M1 muscarinic acetylcholine receptors, triggering G-protein and PLC pathways that increase intracellular Ca<sup>2+</sup>. This leads to enhanced glucose metabolism, increased cerebral blood flow, and activation of the HPA axis. The downstream effects include improved mental alertness, mood elevation, and increased salivation via parasympathetic stimulation.**

#### 4.2 Tobacco

The cholinergic anti-inflammatory pathway serves as the main operational component of the inflammatory reflex neural network to control inflammatory reactions. Endogenous acetylcholine operates as a neurotransmitter by using receptors generated on neural circuit target immune cells to alter cell behaviour. The integral membrane protein shows binding affinity for two receptor groups known as nicotinic acetylcholine receptors (nAChR) and muscarinic acetylcholine receptors (mAChR).

Nicotine activates the nicotinic acetylcholine receptor signaling anti-inflammatory pathway to produce anti-inflammatory effects while simultaneously reducing depression symptoms and attention deficit hyperactivity disorder manifestations as well as schizophrenia cognitive deficits and Alzheimer's disease symptoms along with pain symptoms. Nicotine is able to affect the brain by binding to nAChRs which sets off a series of changes linked with addiction and reward systems. The receptor protein nAChR found across various systems of both central and peripheral nervous systems along with muscle tissue and additional tissues in numerous organisms gets activated by agonist nicotine. Shown in (Figure 6), nicotine is able to affect the brain by binding to nAChRs which sets off a series of changes linked with addiction and reward systems (Zhang et al., 2022).

## Nicotine's Action Through Nicotinic Acetylcholine Receptors (nAChRs)



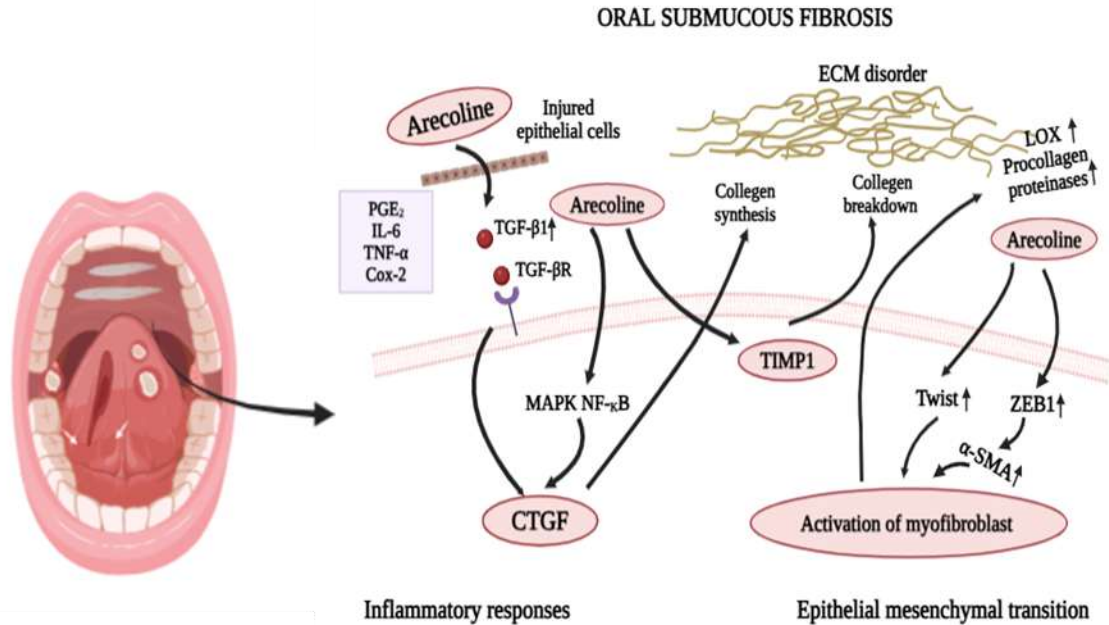
**Figure 6: Mechanism of nicotine action via nicotinic acetylcholine receptors (nAChRs). Nicotine from tobacco activates nAChRs, inducing  $\text{Na}^+$  and  $\text{Ca}^{2+}$  influx and subsequent neurotransmitter release. This results in stimulant and psychoactive effects, as well as anti-inflammatory responses. Prolonged receptor activation contributes to addiction and dependence.**

### 5. HARMFUL EFFECTS

The use of areca nut and tobacco is associated with multiple harmful effects, including cardiovascular, reproductive, and oral health consequences, as well as systemic complications. Their active constituents, particularly arecoline and tobacco-specific nitrosamines (TSNAs), exert toxic, mutagenic, and carcinogenic effects, contributing to a wide range of public health problems (Ezhilarasan & Kumar, 2025; Satapathy et al., 2025).

#### 5.1 Oral and Dental health

The use of areca nut and tobacco is closely associated with precancerous and malignant conditions of the mouth. The most prevalent oral cancer is squamous cell carcinoma, which occurs on the lips, tongue, and the mucous membranes of the mouth. Chewers often develop leukoplakia, erythroplakia and oral mucosal stiffness, oral submucous fibrosis (OSMF), which is a potentially malignant condition, is common among habitual chewers. Research has estimated that 4.2 per cent of precancerous lesions of the mouth develop into malignancy (Yuwanati et al., 2023). The main alkaloid in areca nut, arecoline, helps in tissue damage and cancer formation in a number of ways. It may result in chromosomal abnormalities and cellular mutations which are conducive to mutagenesis. Moreover, nitrosation of areca nut components including guvacine results in the N-nitrosamines, which are very strong carcinogens with the ability to damage oral mucosa. At a molecular level, arecoline triggers inflammation and oxidative stress, leading to upregulation of pro-inflammatory and pro-fibrotic cytokines (IL-6, TNF- $\alpha$ , TGF- $\beta$ , COX-2, PGE<sub>2</sub>) via MAPK and NF- $\kappa$ B pathways (Figure 7).



**Figure 7: Arecoline-Mediated Activation of Fibrotic Signalling in Oral Submucous Fibrosis.** This diagram illustrates how arecoline induces the production of pro-inflammatory and pro-fibrotic cytokines, including prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), transforming growth factor- $\beta$  (TGF- $\beta$ ), and cyclooxygenase-2 (COX-2). These cytokines contribute to the upregulation of connective tissue growth factor (CTGF), primarily through the activation of mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF- $\kappa$ B) signalling pathways, ultimately leading to tissue fibrosis and chronic inflammation.

On a molecular level, arecoline induces inflammation and oxidative stress, which destabilize collagen metabolism, stimulates fibrosis, and provides a microenvironment that supports the formation of oral submucous fibrosis (OSMF) and leads to oral squamous cell carcinoma (Rumgay et al., 2024). Over 90% of individuals who used both areca nut and tobacco presented with visible oral lesions characterized by abnormal tissue growth (Sumithrarachchi et al., 2024). Several individual studies have explored the relationship between areca nut use and oral health risks in different populations. Table 2 summarizes key findings from original observational studies.

**Table 2. Health Effects of Areca Nut in Different Populations, including Associations with Oral Cancer and Oral Submucous Fibrosis - OSMF**

(Guha et al., 2014; Hashmi et al., 2024; Pengpid and Peltzer, 2023; Auluck et al., 2009; Kaliyaperumal et al., 2025).

Study Population	Geographic Location	Substance Used	Observed Health Effects	Statistical Measure (OR / CI / PAF)
General population (areca nut users)	Taiwan	Areca nut (no tobacco)	High prevalence of oral cancer oral lesions including leukoplakia and OSF	PAF=53.7%
Women with oral cancer	Natal, South Africa	Areca nut only	High proportion of habitual chewing among oral cancer patients; mostly affecting oral cavity tissues	OR = 43.9
General population	India	Areca nut + Tobacco	Increased risk of oral cancer; dose-dependent increase in oral premalignant lesions	PAF=49.5%

General areca nut chewers (multiple studies)	India, Taiwan	Areca nut (±Tobacco)	Dose- and frequency-dependent increase in oral cancer and oral precancerous lesions (OSF, leukoplakia)	OR = 7.9 (95% CI: 7.1–8.7)
General population (OPMD cases)	Asia	Areca nut (no tobacco)	Strong association with OSF and leukoplakia; potential progression to oral cancer	OR for OSF = 25.7 (up to 153.3); OR for leukoplakia = 2.8–48.6
Immigrant populations (South Asians)	USA, UK, Europe	Areca nut (±Tobacco)	Higher prevalence of oral lesions and OPMDs and early signs of OSCC	Not reported
Genetic susceptibility studies	Taiwan, India	Areca nut (no tobacco)	Genetic polymorphisms associated with higher risk of oral lesions, including oral submucous fibrosis (OSF) and leukoplakia, and progression to oral cancer	Mechanistic data; no OR reported
Education intervention cohort	India	Areca nut (no tobacco)	Reduction in leukoplakia with cessation programs	Not reported

Note: OR = Odds Ratio; CI = Confidence Interval; PAF = Population Attributable Fraction; OSMF = Oral Submucous Fibrosis; OPMDs = Oral Potentially Malignant Disorders.

Odds ratios indicate the relative risk of developing disease in exposed individuals compared to non-users. For instance, an OR of 7.9 suggests that areca nut chewers are nearly eight times more likely to develop oral cancer than non-chewers. Wider CIs suggest more variability or smaller sample size. PAF reflects the percentage of disease in the population that can be attributed to the exposure.

## 5.2 Reproductive Impairments

### 5.2.1 Male Reproductive Health Hazards

The use of tobacco and areca nuts has adverse effects on male reproductive health by causing genotoxicity, oxidative stress, and spermatogenesis disruption. In human studies, tobacco chewers have been found to have reduced sperm counts and motility, but smokers and individual with multiple substance addiction had a higher proportion of abnormal sperm morphology. These results are also supported by experimental evidence; long-term feeding of mice on areca nuts has been linked to malformation of sperm, reduced motility, and lowered concentration. It is believed that these effects are due to the potential of areca nut components to penetrate the barrier of the testes and disrupt the spermatogenic processes, which eventually affect male fertility (Kumar, 2013).

### 5.2.2 Female Reproductive Health Hazards

Use of tobacco and areca nuts has serious negative effects on the female reproductive system, including hormonal imbalance, ovarian performance, and oocyte quality (Shrestha et al., 2010).

Studies in premature female mice have shown that administration of 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanol (NNA), a tobacco-specific nitrosamine, led to a decrease in ovarian follicles and ovary weight and super ovulated oocyte survival.

Research also suggests that the increase in oxidative stress caused by tobacco use and exposure has resulted in numerous negative effects on oocyte quality, quantity, and reproductive success in women. Nicotine is also an endocrine-disrupting chemical that affects ovarian steroidogenesis and promotes oxidative stress, all of which adversely affect oocyte quality and reproductive fitness. Research in Syrian golden hamsters and rodents also suggests

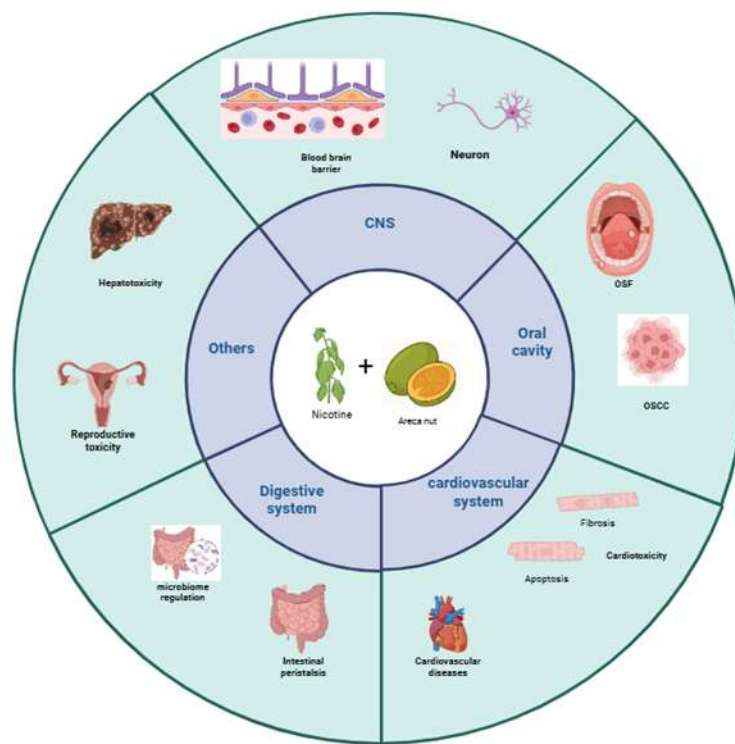
that chronic nicotine treatment triggers the apoptotic death of ovarian follicles, thereby decreasing ovarian follicular growth and fertility potential. Altogether, human and experimental data show that the use of tobacco and areca nuts negatively affects the female reproductive system under the influence of genotoxic, endocrine, and oxidative stress effects (Kumaravelu et al., 2025).

### 5.3 Cardiovascular Problems

Areca nut chewing has been associated with a variety of cardiovascular and metabolic ailments. Frequent use is linked with diabetes mellitus, hypertension, ischemic heart disease, obesity, metabolic syndrome, and arrhythmias. Areca nut may result in a transient increase in heart rate (tachycardia), although its potential therapeutic effects have not been well determined. Laboratory analyses indicate that the acetylcholine-deactivating enzymes acetylcholinesterase and carboxylesterase may be able to degrade arecoline, the major alkaloid in areca nut (Figure 8).

A review of 19 studies has shown that regularly chewing on areca nuts can lead to systemic inflammation, atherosclerosis, and increased cardiovascular risks (Table 3). Not only is long-term use more likely to cause arrhythmias and heart disease, but it also contributes to general mortality.

Areca nut and tobacco are also combination products, which also increase the health risks, such as cardiovascular issues, metabolic imbalances, immune suppression, and cancer (Itaki & Taufa, 2024).



**Figure 8: Multi-systemic toxic effects of nicotine and areca nut. Nicotine and areca nut induce systemic toxicity, affecting multiple organs. They impair neuronal function, disrupt oral and gut health, contribute to cardiovascular damage, and cause liver and reproductive toxicity, thereby increasing the risk of chronic diseases.**

**Table 3: Tobacco Use and its Associated Health Risks such as Cardiovascular Disease and Low Quit Rates in Various Populations** (Reynolds et al., 2021; Tasdighi et al., 2023)

Study Population	Geographic Location	Substance Used	Observed Health Effects
Adults with Cardiovascular disease (PATH Study)	USA (national survey)	Tobacco (Cigarette, E-cigarette, Cigar)	28.9% were current users; most used product: cigarettes (82.8%); only 10% attempted formal cessation

Large pooled cohorts (~322,000 participants)	USA + Brazil	Cigarette, E-cigarette, Pipe, Snus, etc.	Strong associations with subclinical and clinical CVD markers; inclusive of underrepresented populations
Multi-racial cohorts (e.g., MESA, JHS)	USA (multi-state)	Traditional & non-traditional tobacco	Sub-clinical inflammation, atherosclerosis indicators elevated in current tobacco users

## 6. ADDICTION AND DEPENDENCE

Nicotine is involved in producing tobacco dependence, which in turn is a major cause of premature deaths and disability. Thus, through interaction with nicotinic cholinergic receptors, nicotine, activating the processes of release neurotransmitters, implements all the activities of nicotine in tobacco smokers. Tobacco dependence is mediated by dopamine, glutamate and gamma-aminobutyric acid, while nicotine withdrawal may involve corticotropin-releasing factor (Athukorala et al., 2021). Both nicotine and carbon monoxide are in cigarette smoke, and nicotine is absorbed in the lungs via smoke particles and then transported fast in the pulmonary veins.

Tobacco, after being inhaled, reaches the lungs and other subsidiary respiratory tracts, then quickly and almost directly reaches the brain. In the case of the delivery method, blood nicotine concentrations can increase to the maximum after 5-20 min (Benowitz, 2009). Areca nut, like tobacco, is habit-forming. Users of areca nut in most of the preparations are addicted, especially those with tobacco.

The addition of slaked lime enhances dependence. Central nervous system and autonomic nervous system effects have been observed, including increased pulse rate, blood pressure, profuse sweating and fevered body temperature, in users of these products (Mehrtash et al., 2017). Areca nuts have arecoline, an alkaloid that acts on the entire centre, including the brain sites, leading to the development of physical dependency (Ezhilarasan & Kumar, 2025). This activation of the receptor might explain why areca nuts and tobacco can be both mind-altering and addictive, and it could also increase the effectiveness of quitting aids like varenicline or cytosine (Papke et al., 2015).

**Table 4: Comparison of Arecoline and Nicotine in Addiction via Neurotransmitter and Receptor Pathway**

Topic	Arecoline	Nicotine	Significance
Receptors involved in addiction	Partial agonist at $\alpha 4\beta 2$ , $\alpha 6\beta 3$ , and silent agonist at $\alpha 7$ nAChRs	Full agonist at $\alpha 4\beta 2$ , $\alpha 6\beta 3$ , and $\alpha 7$ nAChRs	Both act on same receptor classes involved in addiction
Mechanism	Weak/partial efficacy (6–10%)	Strong activation and dopamine release	Explains habitual use of areca nut despite lower potency
Inflammation modulation	Silent agonist action at $\alpha 7$ → potential anti-inflammatory effects	$\alpha 7$ agonism also linked with neuroinflammation regulation	Adds dimension to both substances as modulators of CNS
Implication for cessation	Similarity to nicotine suggests cytosine/varenicline might help	Nicotine dependence treated with varenicline	Opens pharmacological options for areca nut addiction

## 7. SOCIO-ECONOMIC IMPACT

This mixture of tobacco and areca nut is best known for integration into social practices and cultures within the regions where the substance is used. Such substances are so significant culturally that they might not be easy to quit since they are linked with hospitality, customs, and even religious ceremonies (Gupte et al., 2020). It loads both the single person and the public health facilities with these steep costs of treatment since the health implications of its usage are cancer, cardiovascular diseases, and dental problems. Further, it is alarming to note that these chemicals continue to be widely used, and this is a big issue for human health. The only way to solve this and change the current societal perceptions would be to establish specific measures such as community mobilisation, culturally relevant cessation initiatives as well as the promotion of awareness (Peres et al., 2019). Based on the findings of the Global Adult Tobacco Survey, that there were significant geographical and socioeconomic variations in the usage of areca nut in India. Groups that

were socioeconomically poor such as daily wage labourers, Scheduled Castes, Scheduled Tribes, and individuals with low levels of formal education used a lot more areca nuts with or without tobacco.

In addition, the prevalence showed substantial geographical differences, with some states in the northeast having usage prevalence exceeding 60 percent of the adult population. This high consumption is caused by social norms, normalization within certain cultures, and even ignorance towards the health risks in certain populations. These findings point to the fact that health literacy and socioeconomic change initiatives are inseparably associated with areca nut control. Without focused treatments to address these discrepancies, smoking cessation programs are not likely to be successful (Singh et al., 2021). Cigarettes become popular gifts across both smoking and non-smoking groups because they easily exchange for cash or be redistributed.

People from every social background throughout the country regularly use cigarette packets to make gifts which follows the same customs as single cigarette gifting. Chinese households with limited incomes face greater pressure when receiving expensive cigarettes during gift exchanges because they normally make buying choices based on social status. Families who purchase cigarettes for themselves and gifts suffer related financial decline which results in reduced availability of resources for food expenses, utility costs and educational expenses (Rich & Xiao, 2012).

## **8. BEHAVIOURAL AND PHARMACOLOGICAL APPROACHES TO ARECA NUT CESSATION**

the experiences of various areca nut cessation interventions applied in high-burden areas and noted the behavioral and pharmacological approaches (Muralidhar & Madhivanan, 2023). The structured model of counselling, 3A3R (Ask, Advise, Assess, Relevance, Risk, Rewards), was reported to be effective in Taiwan, where more than half of the pre-contemplation or contemplation stage individuals became ready to quit, and 36 percent showed positive behavioral transformation.

A group-based cognitive behavioral therapy (CBT) program comprising of five, one-hour sessions delivered over 22 days had a quit rate of 18% in the intervention group versus 8% in controls in Guam. In Pakistan, a school-based behavioral change intervention carried out among adolescents in Karachi got a quit rate of 29 percent in the intervention arm, which was significantly higher than 8 percent in the control group. To add, a national media campaign in Myanmar dubbed “Avoid Areca Nu Chewing So You Don’t Regret Your Life Choices” resulted in more than half of the viewers trying to quit the habit. Most recently, a randomized controlled trial in Taiwan compared the efficacy of pharmacologic cessation aid, escitalopram and moclobemide, with quit rates exceeding 33 percent, compared to only 5.4 percent in the placebo group (Muralidhar & Madhivanan, 2023).

A nationwide intervention study in Sri Lanka to train dental surgeons on areca nut (AN) and smokeless tobacco (SLT) cessation. A total of 663 dental surgeons were trained and evaluated in half-day workshops organized by the Centre for Research in Oral Cancer with national health authorities’ involvement with pre-and post-intervention questionnaires. There was a great increase in knowledge and attitudes ( $p < 0.001$ ) because of the program. The knowledge of the understanding the cancer-causing potential of areca nut increased significantly (52.5 to 83.9 percent) and so did the knowledge of counseling approach such as the Five R model (33.2 to 74.4 percent). The SLT/AN cessation attitude was also improved with 66.3% of the participants displaying positive attitudes towards the cessation after training. Though some barriers such as unavailability of materials (39.7%) and knowledge (30.8%) still persisted, the research proved that capacity-building workshops could be applied as an effective intervention to reinforce cessation practice among dental practitioners (Jayasinghe et al., 2021).

## **9. CULTURAL ASPECT**

### **9.1 Cultural and Ritual Practices**

Areca nut chewing has cultural importance; its mild psychic and euphorogenic effect has some relevance in negotiation procedures among the tribes. It is also used in healing or during celebrations, such as when making gestures of gifts when expressing friendship or when welcoming someone. areca nut holds significant cultural value in many societies; it is commonly chewed to show honour during courtships, betrothals, marriages, and funerals (Muralidhar & Madhivanan, 2023; Herzog et al., 2023).

### **9.2. Youth Exposure and Public Health Concern**

Previous literature on the use of tobacco by youth in the Southeast Asian countries was collected for a review. Findings estimated that out-of-school youth, with limited education and residing in rural areas use tobacco and begin during preteen ages.

Youth who are relatively better educated know the effects of smoking have an impact on human health. But there is rather very little awareness of the effects of passive smoking; they do not care about the present and the future adverse impacts of tobacco use on health. Children and youth also respond more positively to tobacco education than adults. In India, one of what some people call smokeless tobacco products, known as gutkha, has also been marketed towards

the young and has gained popularity. A changing vector of oral submucous fibrosis due to gutkha consumption has been well reported, especially in the young generations, and consequently, there has been a rise in the incidence of oral cancer in the younger population. In India, many children involved in tobacco manufacturing have higher chances of using tobacco (Pratt, 2015).

### **9.3. Traditional and Ritual Use of Areca Nut and Tobacco in Asian Societies**

In many Asian countries, areca nut and tobacco products, participate in the social and cultural profile. The use of a mixture containing areca nut, betel leaf, slaked lime, and often tobacco is deeply rooted in cultural practices across many countries such as India, Bangladesh, Sri Lanka, Papua New Guinea, Taiwan, and Myanmar. It is most often offered as a gesture of hospitality or respect during the religious offerings, rituals, and marriages. Among Indigenous and tribal peoples also have a spiritual and metaphorical importance, with regard to areca nut it is often a part of either ancestor rituals or figures in negotiations (Tamí-Maury et al., 2019).

### **9.4. Barrier to Cessation**

Similar culture-driven programs are in use in South Asia. Awareness programs conducted in schools in India with support of the community (local panchayats) have given encouraging evidence of how the gutkha use by adolescents can be decreased. Despite these cultural challenges, successful community-based interventions have been developed. The areca nut Intervention Trial (BENIT), conducted in Guam and Micronesia, successfully incorporated local cultural values, community leaders, and peer support in its behavioral intervention model. These cultural practices offer a formidable force against quitting. In communities where the elderly or religious societies engage in the chewing habits, youth often begin to chew at an early age because to them it is part of their culture. According to the research that was done in Taiwan and Papua New Guinea, peer pressure, family norms, and the role of areca nut in social relationships affect both initiation and persistence of use. Just like this, smokeless types of tobacco such as gutkha and khaini are not only highly available but also accepted in India, especially among low-income and rural citizens (Herzog et al., 2023).

## **10. HEALTH CARE COST**

The consumption of smokeless tobacco products, such as areca nut and combined tobacco products, does carry an enormous socioeconomic cost. It is associated with critical diseases and diseases of the mouth relative to oral cancers, oral submucous fibrosis, cardiovascular diseases and other dental diseases. Direct healthcare costs refer to the costs of treating, operating, and rehabilitating as well as providing end-of-life care, especially to patients with stages three and four cancers. It has a heavy indirect impact on productivity, annual premature deaths and the cost borne by the carers. Low- and middle-income countries are most impacted due to both high utilisation and scarce available health care. Through loss of income and high costs of treatment out of pocket, families get into poverty cycles, thus deepening poverty. At the societal level, pressure is placed on the health sector, taking away resources and other amenities from other important fronts (Mounier-Jack et al., 2017).

## **11. POLICY MEASURE AND REGULATORY OUTCOMES**

The Food Safety and Standards Act (FSSA), 2006, prohibits the production, distribution and sale of gutkha, a form of flavoured smokeless tobacco in India due to its well-documented association with oral cancer and other serious health risks. The policy has not acted consistently irrespective of its being a dramatic step of regulation. In West Bengal, 68.5 percent of the sellers believed that gutkha was still easily accessible and 75 percent of the sellers admitted to selling to children despite the ban (Mukherjee et al., 2022). Moreover, only one-fifth of the merchants was aware of the legal consequences thereof, which suggests that the process of effective policy communication and actual enforcement on the grassroots level has failed. Similarly, vendors often used to sell two separate packets, one containing tobacco and the other one pan masala to circumvent the gutkha ban (Welding et al., 2022).

This will allow customers to mix the ingredients with each other and consume the output in a way similar with gutkha. Regulatory attempts were compromised by the awareness that most of these packs did not contain health warnings and proper labelling as required by law. The study noted that there was a need to have more community-based information initiatives, tighter observation of the supply chain, and stricter enforcement to enhance the success of government action made against smokeless tobacco in India (Welding et al., 2022; Mukherjee et al., 2022).

## **11. CONCLUSION**

Use of tobacco and areca nuts may result in severe oral and systemic disease, such as cardiovascular disease, complications in pregnancy, oral submucous fibrosis and oral cancer. Arecoline worsens injury to oral tissues as well by enhancing inflammation and collagen regulation disturbances.

The epidemiology of oral lesions among habitual users highlights a major issue of public health concern. Such risks can only be mitigated with the help of particular awareness campaigns, culturally specific cessation treatments, stricter regulations, and further research into preventive and effective treatment.

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There are no conflicts of interest.

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#### **ABBREVIATIONS**

AN: Areca Nut; ANP: Areca Nut Products; BQ: Betel Quid; CNS: Central Nervous System; CVD: Cardiovascular Disease; DNA: Deoxyribonucleic Acid; FSSA: Food Safety and Standards Act; GABA: Gamma-Aminobutyric Acid; GPFDD: Global Polyherbal Formulation Database; HPLC: High-Performance Liquid Chromatography; IARC: International Agency for Research on Cancer; LC-MS/MS: Liquid Chromatography–Tandem Mass Spectrometry; NFHS: National Family Health Survey; NNK: Nicotine-Derived Nitrosamine Ketone; OSCC: Oral Squamous Cell Carcinoma; OSMF: Oral Submucous Fibrosis; PFAS: Per- and Polyfluoroalkyl Substances; PM: Pan Masala; ROS: Reactive Oxygen Species; ST: Smokeless Tobacco; TCM: Traditional Chinese Medicine; TSNAs: Tobacco-Specific Nitrosamines; WHO: World Health Organization.

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