BOHR International Journal of Current research in Dentistry
2023, Vol. 2, No. 1, pp. 1–12
DOI: 10.54646/bijcrid.2023.11
www.bohrpub.com

REVIEW

An account of areca nut uses and oral health damages from an Indian perspective

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Received: 05 January 2023; **Accepted:** 07 January 2023; **Published:** 30 January 2023

There is a perception in India that packaged *paan masala* and betel quid (BQ) with areca nut loosely called *paan supari* both being devoid of tobacco are not carcinogenic. This article intends to be an awareness initiative against this notion. It focuses on the use of areca nuts in various forms. An understanding is necessary for the identification of components of *gutka*, various forms of BQ, and *paan* masala wherein areca nut is used. Areca nut consumption damages oral health and leads to the development of oral submucous fibrosis (OSF). OSF is used as an umbrella term for depicting all potentially malignant lesions. *Gutka* is a product popular in India that uses areca nuts and a form of flavored tobacco (*zarda*) as the main component. Although oral tobacco is implicated as a grade I carcinogen, areca nuts and BQ-containing areca nuts belong to the same grade. Areca nuts are the fourth largest addictive substance in the world. Deleterious effects of areca nuts in various forms are a grossly underreported area of research. Initiatives against areca nut uses are required.

Keywords: areca nuts, betel quid (BQ), *Paan masala*, arecoline, *gutka*, oral health, oral submucous fibrosis (OSF)

Introduction

India fourth in the world in incidence of oral cancer with 9.1 per 100,000 people, after Papua New Guinea (20.4), Pakistan (12.2), and Bangladesh (9.5) (1). According to the report of the National Institute of Health and Family Welfare (NIHFW), the country had 86% of the world's oral cancer cases. The rising curve of oral cancer is a major health hazard in India (2). One-fourth of Indian adults (23.9%) consume areca and among that 10% of the users consume it along with tobacco. With 223.79 million users, India tops globally both in the production and consumption of areca nuts (3). India protects the cultivation, and the areca nut production saw a rise from 2.5 lakh metric tons, of annual production in the 1990s, to 9 lakh metric tons in 2020. These earnings from areca nuts are much order than other cash crops (4). Areca nuts are cultivated in almost every individual house along the boundary walls (**Figure 1**) and areca is considered sacred according to cultural and religious beliefs (5). In states like Assam, Manipur, Meghalaya, Mizoram, and Uttar Pradesh, 40% of men consume areca nut in different forms. Northeastern states have a relatively higher prevalence of tobacco use along with areca nuts, whereas southern states consume betel quid (BQ) without tobacco (6). Uttar Pradesh reported 22% of all areca consumers followed by Maharashtra (12%), Karnataka (9%), and Tamil Nadu (8%). A demographic divide exists in the uses; education levels affected the usage and statistic shows that daily wage earners have the highest (30%) level of consumption; usage in the population belonging to the scheduled tribe was 25.8%, and in Muslims, 30.8% usage was noted (3). Areca nut is seldom used in pure form. Various combinations, additions, preparations, and processing are made (e.g., in *gutka* and *paan masalas*) and consumed alone or along with a BQ.

Despite its rampant use as a psychoactive agent, the areca nut and *gutka* chewing habit and addiction remain a gross under-researched area compared to the endemicity of its use. The western world cannot recognize the complexity and use of numerous components in these oral habits (7). This may be attributed to underreporting, linguistics, and social and cultural gaps (8, 9). This necessitates compiling the usage and forms in distinguishable groups while reporting

FIGURE 1 | (A) Arrow points at the Areca fruits have the kernel inside which is consumed. **(B)** Both ripe (orange color) and unripe (green colour) varieties are seen on the same tree.

or reviewing. Recent global reviews call for more research on areca consumption, which is the world's fourth largest addicting agent (10). In this review, the misconception which assumes that areca nut/BQ are not carcinogenic without tobacco addition is dealt with.

Areca nut consumption: The variability quotients

Raw nuts may be consumed dried (sun-dried or freeze-dried) or fresh, mature or immature, or processed (soaked, boiled, or prepared with numerous additives) (11). Similarly, there are numerous variations in tobacco that are used in conjunction with areca nuts. It may be either dried mature leaves or boiled fermented leaves, or differently flavored processed leaves (e.g., in *zarda)*; variations exist in the relative number and contents of different components, while they are prepared in *paan* shops (11, 12). Furthermore, the amount of chewing/grinding (time of oral exposure), consumption versus rejection (through spitting the oral contents), and extractions vary and so do the methods of consumption that affect the severity of afflictions (13).

Cocktail of a variety of mixtures in BQ and *Paan Masala* deterrent for definitive study

In low- and middle-income countries and in a heterogeneous population like ours, the multiplexity and variety of use of the chemicals and components (lacking labels), unregulated local manufacturing, and consumption make the whole thing virtually indistinguishable and confusing (**Figures 2–4**) (12). There is specificity in uses and damage. Damages created by the variety of individual components with numerous combinations make it more complex to report specifically (9). Here, it is worth mentioning that the addiction item preferences and habits are specific for an individual and are relatively constant and an attempt at generalization is a gross mistake. For reviewers, the problem for reporting and relating becomes manifold (14), with alterations of the pharmacology, variety of bio-availability of extracted phytochemicals, variations in mutual interactions of the chemical cocktails, and the extent of phytochemical extraction all being a deterrent in definitive reporting of damages created (15–18).

This article will be accounting for the various forms of areca consumption in *paan masala*, BQ (variations in preparations), and *gutka*, all of which contain areca nuts as the principal ingredient. The different uses of oral tobacco/smokeless tobacco forms such as in *zarda* and *khaini* which are used along with areca nuts or separately consumed are mentioned.

Paan masala

According to the Food Safety and Standards Authority of India (FSSAI), *Paan masala* means the food commonly consumed alone or with *paan*; common ingredients are lime, areca nut, catechu, coconut, saffron, cardamom, dry fruits with aromatic herbs, and spices with permitted natural colour and non-prohibited flavors; it must not have any other harmful ingredients or coal tar as coloring agent. It must also meet the following criteria: total ash not more than 8% by weight and ash insoluble in dilute hydrochloric acid not more than 0.5% (both on a dry basis).

FIGURE 2 | Different individual components are displayed in the *paan* shop. Metal-coated cardamom seeds (1), colored fennels (2) with original spices of cardamom (3A), cloves (3B), and fennel seeds (3C) are seen. Various colored vegetables (4) and locally made components are added.

The *paan masala* packs shown in **Figure 4** are devoid of the original ingredients mentioned in the norms of FSSAI. Out of the eight *paan masala* packs, three packs were found to have mentioned their ingredients; the labels of ingredients are presented in **Figure 2** (local variations) and **Figure 4** (packaged *paan masala*). None of them used original spices and condiments for flavors.

Zarda

Flavored tobacco itself is termed *zarda* (**Figures 3**, **4**). Both tinned packs and sachets are available readily in any roadside stalls. Bright shiny packs of sachets forming ribbons are a very common site in India. Picture shows sachets of *zarda* being sold along with *paan masala* packs.

Betel quid (BQ)

Primary components of a BQ (**Figure 3**) are the betel leaf, slaked lime, and catechu smeared on it, areca nuts, and optional tobacco in the form of *zarda*. Readers are directed towards a review by Islam et al. (19) for a more or less extensive reporting of the combinations added in India. In BQ, the variety, flavors, and mixtures added are according to taste, tradition, and regional variations. A BQ (pictures of various preparations with or without tobacco are referred to for the reader) makes it an elaborate process made by *paan* shop owners. A huge number of combinations and variations of locally made flavoring substances are serially added to the leaf; the leaf is smeared primarily with catechu and lime, then spreading a woody powder (menthol/*paan masala*/rose-flavored) known as *chaman bahar* (**Figure 3**) on the leaf, then adding areca nuts, (**Figure 3** depicts components with arrows), condiments like fennel seeds (sugar and colour coated or non-coated), cardamom/clove, saffron, anise seeds, turmeric, coconut (dried/fresh or soaked in saccharine), various sweeteners (brightly colored pieces of vegetables soaked in saccharine) (**Figure 3**) and flavoring substances, sweetened rose leaf paste (*gulkand*) (**Figure 3**), and sweetened flavored paste *gulab chatni* (*gulab* refers to rose-flavor) (**Figure 3**) (12). All these are consumed together in a wrapped betel leaf made by the vendor according to the directions and taste of the consumer. While *paan* alone with areca nuts and other ingredients without tobacco is considered an independent risk of oral cancer, tobacco/*zarda* addition increases the risk even further (20). BQ users exhibit BQ-induced lichenoid oral lesions which are seen solely in this user group (21). It resembles lichen planus with some characteristic differences.

Various combinations where areca nuts are consumed are given as follows:

I. Betel leaf + lime + catechu + *chaman bahar* + with various combinations of sweetened vegetables and condiments (coated and colored), the combination locally called ***meetha paan***, although another nomenclature exists (**Figure 3**).

II. Betel leaf + lime + *zarda* + *chaman bahar* (locally called ***zarda paan***; **Figure 3**).

III. Betel leaf + areca + lime + fennel seeds + *chaman bahar* is used in common conception as a mouth freshener (locally called ***sada paan****; sada* implies tobacco devoid version).

FIGURE 3 | The making of betel quid (BQ1, BQ2, and BQ3) are shown here. The components are labeled in the figures. The names of individual components of BQ are as follows:A – Betel leaf, B – Areca nuts, C – Slaked lime, D – Catechu, E – *Zarda,* F – *Chaman Bahar*, G – Colored vegetables, H – *Gulkand, and* I – Coated condiments of *paan masala.* Various *zarda* (E1-E4) are added as per preferences (anyone, E1-E4) and quantity is shown.

All other components are used in various combinations and vary widely according to preferences. A few more variations are there in the methods of consumption as well.

Gutka

Gutka is a generic name for a banned product in India (**Figure 4**). Principally, it is a mixture of artificially flavored (saffron/rose/*kewra*/*paan masala* flavors) chewing tobacco and freeze-dried areca nut with menthol, catechu, and lime (**Figure 4**) (12, 22). Mostly, roasted areca nuts are used to form a dry granular powdery mix packed in sachets (**Figure 4**). *Gutka* is mostly banned in India (till May 2013, 26 states banned *gutka*). *Gutka* and tobacco industry evaded the *gutka* ban by selling two separate pouches instead of one sachet. One is labeled as *paan masala* (the larger one labeled in "A" columns in **Figure 4**), and the other one is *zarda* ("B" columns in **Figure 4**). *Gutka* is commercially available in different brand names with variations in its composition. Every company has both these consecutive products (kept side by side for reference **Figure 4**). The numerous chemicals used to make the concoction of *gutka* are reviewed by Bhisey et al. (23).

Lack of awareness leads to early exposure to the psychoactive agent

Gutka, *zarda*, and BQ all are separately intended as mouth freshening agents initially introduced in a young population after which it turns out to become an addiction. Chewers begin using areca nuts as a mouth freshener in adolescence, mostly unaware of the damaging effects of oral cancer (24). A cross-sectional study on the prevalence of areca nut uses in the Khasi region of Meghalaya reports a 43.9% use in an age group of 15 years. Almost 30% of respondents in the study were not aware of the ill effects of areca

FIGURE 4 | (A) *Paan masala* sachets are sold together (8 larger packs) containing 3–4 g of mixture with *zarda*. **(B)** (similar 8 smaller packs) of the same companies to make a combinatorial *gutka* mixture (*zarda* sachets are to the right of the *paan masala* packs). Labels are obfuscated. **(C)** Only 3 of them listed their ingredients where synthetic flavors are used as opposed to FSSAI guidelines. **(D)** All the *paan masala* packs and corresponding *zarda* packs are evacuated and the contents were displayed (inner ring is of *zarda*). In the center is shown dried areca nut (in raw pure form) of a particular cut as consumed or used to make BQ.

nuts in causing oral cancer (25). As high as 49.5% of the population in India is under oral habits, the cessation of BQ consumption may prevent half of the oral cancers in India (26). Very low concern exists in the Indian psyche about the use of areca nut, areca with *paan* (BQ called *paan*), and *paan masala* (packaged products of commercially produced flavored, mentholated, and saccharinate processed versions of areca nuts) as against oral tobacco uses in forms of *zarda* and *khaini* (**Figure 5**). Through *paan masala*, *BQ*, and areca nut use, a hidden and disguised entry takes place for future *gutka* or oral tobacco use (27). Extensive use of areca nuts in different forms by children, and adolescents, is mostly because of their affordability, pleasant taste, and easy accessibility. In Mumbai, regular consumption of gutka among school students (40%) and college students (70%) is prevalent. About 20% of women and 46.4% of men in Wardha, Maharashtra, consume *gutka* (8). In this context, it would be worth mentioning that smokeless tobacco is preferred by women because Indian society reprimands smoking and due to this social disapproval, women acquire oral habits of *paan masala* and subsequently get addicted to *gutka*. Not only the people from the Indian sub-continent but the immigrants living in the United States and Europe are also habitual users of *paan* and *gutka* (28, 29).

Areca and its derivative compounds

Areca nuts have a wide variety of chemical compounds including alkaloids, polyphenols, tannins, carbohydrates,

fats, proteins, fibre, and various trace elements (30). Alkaloids present mainly are arecoline (principal active ingredient), arecaidine, guvacine, and guvacoline (31, 32). Eugenol or betel oil (a volatile oil) is the key component of the betel leaf. It contains two psychoactive phenols (betel-phenol and chavicol) and cadinene (an alkaloid stimulant) having cocaine-like properties (33).

Arecoline is classified as a Group IIB carcinogenic agent. In the oral cavity, it undergoes nitrosation producing more potent areca-specific N-nitrosamines (22, 34, 35). Four major N-Nitroso compounds, namely, N-Nitrosoguvacoline, N-Nitrosoguvacine, N-(Methylnitrosamino)propionitrile, and N-(Methylnitrosamino)propionaldehyde are produced via nitrosation of arecoline (36, 37).

A few steps towards restriction and banning in India

There had been few interventions specific to BQ use in teenagers, the age group unaware of the dangerous consequences of BQ use and lacking the motivation for cessation (38). Ban on *gutka* consumption has mostly taken place in India after Supreme Court orders (8). Such bans focus principally on tobacco components specifically and form a warning for tobacco addiction in the *zarda* pouches but no such warning is present in the *paan masala* pouches (**Figure 4**). A very low awareness exists about the carcinogenic effects of areca nuts consumed by the way of *paan masala* consumption (areca nut is the principal component of *paan masala and* BQ). Areca nuts and BQ (containing areca) consumed in various ways and combinations fall under Group 1 carcinogen (39). Specifically stated tobacco-devoid-versions of BQ and the *paan masalas* are carcinogenic by themselves. This carcinogenicity has been the subject of several studies as found in meta-analyses and systematic reviews by Guha et al. (26), Gupta and Johnson (40), Yang et al. (11), and Warnakulasuriya and Chen (41). Areca nut is linked to cancers of the oral cavity, pharynx, larynx, esophagus, gastrointestinal system, and liver.

Areca nut addiction: A neurological perspective

Arecoline, an alkaloid and a potentially addictive component of areca nut, is a cognition enhancer, a psychic stimulant, an anxiolytic, and a sedative (9). Chewing areca nuts brings about positive subjective outcomes, like higher concentration, relaxation, and euphoria. Arecoline has psychoactive effects, as it binds to α4/β2 and α6/β3 subunits of muscarinic and nicotinic acetylcholine receptors (42, 43). Guvacine and arecaidine (other alkaloids present in the areca nut) act as GABA uptake inhibitors and increase the synaptic availability of the neurotransmitter, thereby acting as anxiolytics (9). Arecoline discontinuation results in withdrawal effects with reports of anxiety, mood swings, irritability, and insomnia (44). EEG changes in cortical desynchronization are seen with arecoline exposure (45, 46).

Areca nut related to oral health

'*Gutka* Syndrome', a terminology offered by Chaturvedi (47), aptly described it as a combination of well-known oral disabilities, directly related to *gutka* consumption. Patients are seen with fibrotic lesions termed OSF in the oral mucus lining. These lesions also affect the muscles of mastication and tongue movements. Gingival recession is seen with enamel loss and razor-sharp discolored teeth (gaps appear between teeth) (48). Reduction in salivary outflow and impediments in speech is noted. The person becomes extremely temperature sensitive, avoids eating spices, and cannot open his mouth fully with typical facial characteristics like loss of facial, buccal fat, and stiffening of soft tissue in the cheek (appearing in chronic users) (49). The inner lining of the cheek appears pale with progressive fibrosis and a kind of stiff mouth-like features develop; lips get inverted with a reduction in the ability to open the mouth (from a loss of gingivobuccal sulcus due to fibrosis) (50). Skinfolds appear in the perioral area, while they try to open their mouth fully, unable to do so. Lower tongue movements and stiffened lips lead to a distinct characteristic in speech, with difficulty in moving the jaw (51, 52). A typical sucking of saliva by a peculiar movement is seen. Fibrosis around the eustachian tube opening leads to hearing loss (47). For *khaini* and *gutka* users who dump the contents in the cheek pouch, OSF appears there, whereas in BQ chewers, the fibrosis is located posteriorly in the buccal cavity and extends into the upper and lower sulcus (53). Buccal mucosal cancers are seen frequently in Southeast Asian countries with the habit of chewing BQ.

Severe wear and tear of tooth surface particularly in the incisors and occlusal teeth are noted. Loss of enamel with staining of teeth is noted. Increases in exposed dentin surfaces lead to sensitivity in teeth (54). Root fractures take place from mastication efforts of areca nut chewing. Dentinal surfaces often become sclerosed and such sclerosis may be protective against microbial attack and cavity pain. Areca nuts are reported to be protective against caries (cariostatic) (55, 56). The stained teeth act like a varnish (57). Loss of stagnation areas by a breakdown of tooth edges may lead to lesser observed cavities. Bleeding gums, halitosis, problems in swallowing solid and spicy foods, ulcers on the oral mucosa, and burning sensation of soft tissues are characteristic features of oral health deterioration (48).

Higher salivary secretions may lead to more washing in chewers that inhibits plaque formation; further pH

FIGURE 5 | (A) Tobacco leaves with the cutting machine; **(B)** *Khaini* is made by hand-rubbing finely cut tobacco leaves **(C)** with a pinch of slaked lime; **(D)** The prepared *khaini* is dumped in the cheek pouch.

changes due to slaked lime may lead to lower acidity in plaques and thereby lower cavitations (58). Loss of attachment to periodontal tissues with deposition of calculi is seen in areca chewers. Pockets of periodontal tissues were higher in chewers when compared to non-chewers (59). Periodontal-cultured fibroblasts are seen to produce less amount of extracellular matrix proteins indicative of loosened dental attachments.

Brownish red discoloration (Betel chewer's mucosa) of oral mucosa appears at the sites of placement of the BQ in the buccal cavity (mostly found in older women with chronic and extended uses of BQ) (60). Epithelial hyperplasia with encrustation is seen at the sites where the BQ is placed (58). Microscopic examinations of the area having a wrinkled appearance reveal BQ particles (lime and areca) inside the cells and intracellularly. Oral keratinocytes show a ballooning characteristic. High-risk human papillomavirus subtypes with keratinization and leukoplakia in the mucosa are seen as characteristic features (61). Temporomandibular joint arthrosis and trismus may develop in chronic users (47).

Histopathology of OSF

Hematoxylin and eosin staining is used as a control in various histochemical staining in OSF specimens (Mallory stains are used for identifying stratified layers of keratin; other stains include Masson and Van Gieson stains). Epithelioid alterations in shape, depositions of collagen, infiltration of inflammatory cells, and hyalinization characteristic patterns of fibrillar versus homogenous collagen are routinely used in pathology labs for the detection of OSF grades (62). Lower keratinization, lower number of intercellular bridges, more nuclear and cellular pleomorphism, and more mitotic figures are used as features in subjective histological differentiations in grading squamous cell carcinomas. With higher multinucleated cells and lower intracellular bridges, lower keratinization is associated with higher disease grades (58, 63).

Areca nuts and an analysis of OSF risks

Chewing of areca nut is a major contributing element to OSF development as suggested by epidemiological studies (64, 65). OSF mainly occurs in the buccal mucosa, the mucosal area of the retromolar region, and the soft palate (66, 67). Oral leukoplakia and erythroplakia develop along with OSF.

The clinical features of OSF include taste disorders, dry mouth, dysphagia, changed tone, pain, and restricted opening of mouth and tongue movements. The soft pink oral mucosa hardens and gets whitish, opaque, and tough; the cheeks and the lips get tightly held with fibrotic inelastic

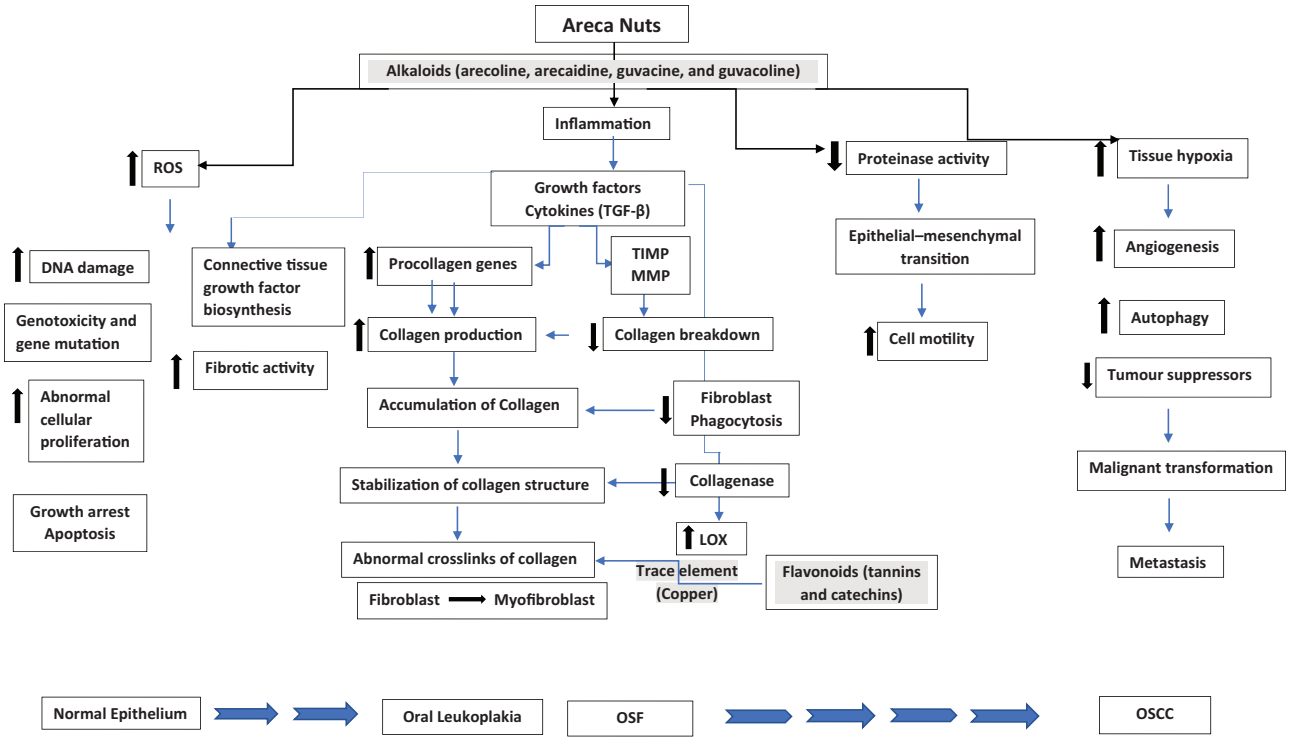

FIGURE 6 | Mechanism of development of OSF and transformation to OSCC. This flowchart is made based on the data compiled in reviews of (62, 70, 102).

bands (palpable from outside) with inabilities to open their mouth (used for staging the disease) (68). Pharynx and esophagus also get fibrotic. The malignant transformation rate is 1.5–15% (69) and the prevalence is high in Southeast Asian countries and India (prevalence of 0.6–6.42) (70).

A recent review by Warnakulasuriya and Chen (41) evaluated the sole implications of areca nut and BQ as an agent for oral carcinoma and estimated the aggregated relative risk (RR) factor for such to be 7.9 (through this meta-meta-analysis for all studies up to 2022). Earlier IARC in 2004 re-evaluated the carcinogenicity of areca nuts to humans with past reports from South Africa (OR 43.9) (71) and Taiwan (OR 13.56). In these countries, BQ preparations are mostly consumed without tobacco and these studies were instrumental in framing the carcinogenic risks associated with areca nut consumption. Before Warnakulasuriya and Chen (41), two systematic reviews and meta-analyses also confirmed the carcinogenicity of BQ without tobacco (40, 72). IARC implicated areca as an independent carcinogen with an RR of 3.22 when consumed alone and an RR of 7.03 when consumed along with tobacco (26, 39).

OSF is considered a precancerous state, a potential condition for the development of oral submucous cancer (73). In a cohort study, it is seen that tobacco users without any precancerous lesions were at a lesser risk of malignant transformation than tobacco consumers with reported OSF (8). The incidence of oral cancer is high in North India due to excessive consumption of *gutka* in this region (8, 74). The overall harmful effects are oral cancers, cancer of the lip, mouth, tongue, throat, and esophagus, poor oral health, lower immunity, and a range of benign conditions and oral infections, caries, mucositis, gingivitis, sores, and stains. In an Indian scenario, the variety in damage must be categorized for the different forms of areca nut chewers, for example, the only areca nut user-induced OSF or the *pan masala*-induced OSF, snuff-induced lesions, areca with quid lesions (devoid of tobacco), areca with BQ lesion with tobacco, tobacco-lime (*khaini*) user's lesion, *gutka* chewers mucosa, and likewise. Although the damage looks similar, it shows diversity in clinical and histopathological features (12, 75). In India, while reporting, a mention of the name of a packaged product in the case of *paan masala* users may be beneficial in categorization. Consumers mostly stay loyal to these brands. The products vary in their quality and labeling (**Figure 4**). Some of them use synthetic ingredients and flavors, while some have actual formulations of condiments and spices. This may help in the identification of adulterants that should be recorded for inspections and bans. The categorization in research and reporting would definitely narrow down the ambiguity spectrum, focus on the particular characteristics in lesions, and target implications of use.

In a recent review, Cirillo et al. (14) showed that with different BQ components, the risk of development of OSF differed. Chewing of BQ inflorescence increases the risk of OSF and so does the tobacco addiction. The areca leaf alone seemed protective. The studies that calculated the

relative risk (RR) of OSF with associations of areca nut chewing were that of Hazare et al. (76) and Ranganathan et al. (77). They calculated the risk of OSF to be most for *paan masala* chewers and relatively lower values of relative risks were reported for BQ chewers. Mehrotra et al. (78) reported an odds ratio (OR) for OSF to be 3.01 (95% CI: 1.23–7.36) for OSF development in users of *paan masala*. Both studies significantly reported a positive association of pan masala with the disease. Mehrotra et al. (78) and Khan et al. (79) both reported a higher OR for *gutka*. Khan et al. (79) reported an OR of 18 + for *gutka* use to develop OSF with respect to smoking. A total of 33.3% of BQ and *gutka* chewers presented with tobacco pouch keratosis (79). Maher et al. (80) reported a higher risk with lime and tobacco additions when compared to areca and betel leaf alone. Sari et al. (81) reported that slaked lime increased the damage by higher production of reactive oxygen species (ROS) and they showed that the permeability barrier and damage due to chemical exposure of the alkaloids increase the risk. Lee et al. (82) stated lime induces chromosomal damage with increased mucosal turnover. Lime converts the arecoline and guvacoline into more potent arecaidine and guvacine, increasing further risks (14, 83). Contradicting reports have been seen evaluating whether mature areca or ripe one is more toxic. Sari et al. (84) reported unripe to be more toxic, whilst Jayalakshmi and Mathew (83) reported mature nuts to contain more alkaloids and therefore contribute more towards the development of OSF. Alteration of ingredients changes the property of carcinogenicity and mutagenicity in these mixtures widely (85).

OSF may develop due to a genetic predisposition for damages created by the variety of chemical challenges from any of the pan masala and BQ components. The polymorphic genes mostly implicated to be a factor in OSF development are those that lead to disease pathogenesis.

Molecular mechanism of OSF development

Genes for collagen, matrix metalloproteinases (MMPs) responsible for degradation of heavy metal-activated enzymes, lowering activity of tissue inhibitor of matrix metalloproteinase (TIMP), and transforming growth factor-β (TGF-β) are implicated in the etiology of OSF. Modification of these genes and promoters associated with the expression of transcription is proposed. The polymorphisms in genes making a person more susceptible to OSF are likely to reside in the DNA of these proteins and in a plethora of others proposed in recent studies of proteome, transcriptome, and metagenomic alterations (86). Specific molecular features develop in fibrotic tissues. Epigenetic alterations like hypermethylation in promoters and genes are seen in several genes in OSF patients (87, 88). There is a growing body of evidence that arecoline present in areca nuts is responsible for the development of OSF.

TGF-β and a variety of other pro-inflammatory and profibrotic cytokines are secreted by macrophages and other immune cells recruited by damages created by inflammation. Further ROS-mediated activation and formation of nitrosoamines lead to the induction of various pathways that leads to secretions of numerous cytokines and growth factors (89). Collagen formation by induction of procollagen genes, defective collagen clearance by inhibition of collagenases and metalloproteinases, and stabilization of collagen fibrils by cross-linkages formed by enzymatic activation of cross-linking enzymes are the processes involved with fibrotic changes in the submucosa (62). There is also a deficiency in phagocytosis of crosslinked collagens by fibroblast. Alkaloids in areca nuts stimulate fibroblast cells to produce more collagen. The ratio of collagen chains is altered (90, 91). Induction of genes like Cystatin C, TIMP, and plasminogen activator inhibitor (PAI) by TGF-β leads to the inhibition of collagen degradation (92, 93). Arecoline elevates proinflammatory and profibrotic cytokines and growth factors, in turn, promotes collagen synthesis. Proteinases like MMP- 9 and MMP-2 are inhibited by the areca alkaloids to create a disequilibrium in ECM dynamics (65, 94). A higher concentration of copper in areca nut leads to increased salivary and serum copper concentrations. Lysyl oxidase, an enzyme that cross-links collagen and elastin proteins, is induced by copper. Increased cross-linked collagen in fibrotic tissues renders them resistant to collagenases and thereby phagocytosis is inhibited (65, 93–98).

OSF development in betel nut users is due to the presence of arecoline, the major alkaloid present in areca nuts (99, 100). Approximately, 7.6% of OSF patients develop oral cancer in India (101). The promotion stage from a premalignant lesion, OSF to a malignant form, oral squamous cell carcinoma (OSCC) is a lengthy and irreversible process. Once OSF is diagnosed and the patient seeks medical help interventions and cessation of habit lead to interruption in the process of carcinogenesis and malignancy. This leads to a decrease in the malignant transformation rate of OSF (**Figure 6**).

Conclusion

The traditional uses of BQ called the *paan supari* include uses in hospitality, religious offerings, depiction as a social and ethnic symbol and as a medicinal ingredient makes the task of controlling and restriction of its use a daunting one in India. Aggressive commercialization, economic benefits through cultivation, lack of education, and awareness in India had turned this *paan masala* addiction into a situation where drastic steps are needed to be taken by the government. In a country of 1.3 billion, a huge heterogeneity in demography and a predominance in oral habits due to its cultural identity

will be a challenge to target populations and devise selective restrictions for *paan masala* (an item recognized as food in Indian law). Imposing selective bans and restrictions on a huge number of adulterations, sold under the name of *paan masala*, are necessary. Initiatives for mandatory categorization of items, declaration of their contents, and level of use of ingredients will further elucidate the toxicity that is hidden and sold under the name of an oral freshening and aromatic agent.

Author contributions

The manuscript is solely and fully conceived, developed, interpreted, analyzed, and drafted by SB. All pictures are taken by SB. SB is accountable for the content of the work.

Funding

No grant was received from any funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We thank all the scientists and working groups for their effort to elucidate the harmful effects of areca nut in betel quid and *paan masala* preparation.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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