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# How Areca Nut Chewing Was Made the Cause for Oral Submucous Fibrosis and Oral Cancer: An Analysis

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## ABSTRACT

Areca nut is the nut or seed of *Areca catechu* palm. This nut is mostly used for chewing because of its immense beneficial effects. The antiquity of its chewing goes back to more than thousand years. Of late, several researchers claimed areca nut chewing as the cause for oral submucous fibrosis and oral cancer. But in most of such research papers it was observed that the chewing substance was not authenticated by any experts in plant science leading to wrong identification of the chewing material. Consequently, the chewing mixtures such as betel quid, pan masala, gutkha, etc were wrongly quoted as areca nut and the researchers tagged the ill effects of chewing such mixtures to areca nut. Certain reviewers, without noticing such lacunae, published several review papers under the heading areca nut chewing. Some of such research and review papers are cited and analysed in this article.

***Keywords:*** Oral cancer, OSF, Areca nut, *Areca catechu*, misidentification, chewing substance

## INTRODUCTION

Commercially, areca nut is the endosperm of the fruit of an oriental palm, *Areca catechu* L. of Arecaceae family. In several parts of the world areca nut is misnamed as 'betel nut' as this nut is commonly chewed along with the leaf of *Piper betle* L., a tropical, evergreen, perennial vine of Piperaceae family [1].

Areca nut is mainly used for chewing and the antiquity of its chewing goes back to thousands of years [2]. This nut is chewed either alone or mixed with the leaf of betel vine, slaked lime (calcium hydroxide) and certain condiments as it is believed to contain lots of medicinal values [3]. This chewing mixture is commonly called betel quid (BQ). While chewing BQ some people also add a small piece of tobacco (*Nicotiana tabacum*) leaf to this mixture. In certain parts of the world such as Papua New Guinea, Taiwan, etc., instead of using mature endosperm of areca nut, immature areca nut along with its husk and instead of the leaf of *P. betle*, its inflorescence along with slaked lime are used to prepare BQ [1]. All the ingredients of such mixtures are generally in wet forms.

Of late, most probably during 1970's, a novel idea of preparing dry chewing mixtures with long shelf life and making them readily available in small sachets came into practice for easy chewing. Such chewing mixtures are now marketed in many forms in various names such as gutkha, paan masala, kainy, mawa, etc. by different companies. Invariably, most of such chewing mixtures

contain tobacco along with areca nut and several other ingredients [1].

In ancient systems of medicines such as Ayurveda, Unani, etc., areca nut is used to cure different ailments in several countries such as India, China, Bangladesh, Philippines, etc [4-7]. The World Health Organization has already listed out as many as 25 beneficial effects of *A. catechu* [8]. Most of these folklore medicinal properties of *A. catechu* are now validated with proper scientific data [9-12].

In spite of all these medicinal uses of areca nut, several researchers and reviewers highlighted areca nut chewing as the cause for oral submucous fibrosis (OSF) and oral cancer [1,13-43]. While scrutinizing such research and review papers it is noticed that in most of such papers the chewing substances were not at all authenticated by any experts in plant science and wrongly quoted as areca nut, putting the entire blame on areca nut chewing. Hence, an attempt has been made to discuss and project such research and review articles where areca nut is misidentified as the culprit.

## LITERATURE REVIEW

A study was conducted at Bhavnagar, Gujarat with the objective to elucidate the etiology of oral submucous fibrosis wherein the publication was titled as "A case-control study of oral submucous fibrosis with special reference to the etiological role of areca" [13]. In the abstract column of that publication, it was written 'The work was carried out on 60 oral submucous fibrosis patients at a dental clinic. Among them 98% chewed areca nut regularly in one form or the other. Areca nut chewing was practiced most commonly in the form of mawa: a mixture containing mainly areca nut, some tobacco, and a few drops of lime. Mawa chewers and those who chewed mawa along with other chewing habits showed very high relative risks'. From these statements it is clear that the authors wrongly treated mawa as areca nut and tagged this nut as the most important etiologic factor in oral submucous fibrosis without any data on sole areca nut chewers.

In a South African study entitled "The areca nut chewing habit and oral squamous cell carcinoma in South African Indians", though the objective was to find out the effect of chewing areca nut on the incidence of oral cell carcinoma, exclusive figure for chewing sole areca nut was not given in the paper [14]. While describing Table No IV on the occurrence of oral habits in relation to oral cancers, it is mentioned '(Note that the figures shown are not mutually exclusive)'. This shows that, there is no exclusive data for sole areca nut chewing. Still, the paper is titled as areca nut chewing habit.

In the paper entitled "Oral submucous fibrosis, areca nut and pan masala use: A case-control study" data were collected from people who chewed pan masala, kharra, betel quid, etc, but not a single instance on chewer of only areca nut [15]. The paper says 'A wide variety of areca nut and tobacco chewing habits were reported; the most common (50%) being the use of pan masala which literally means betel quid mixture, is a commercially manufactured product almost always containing tobacco and areca nut. The next most popular habit among patients was the use of kharra, a local preparation containing pieces of areca nut (7-8 g), a small amount of tobacco flakes, and drops of slaked lime, mixed, homogenized and wrapped in a cellophane paper ball. Other chewing habits were tobacco-lime and betel quid in different combinations'. Though there is no data on sole areca nut chewers, the word areca nut is prominently highlighted in the title as well as in several other places. This shows that the authors wrongly identified such chewing products as areca nuts.

There is a paper entitled "Risk of betel chewing for oesophageal cancer in Taiwan" wherein the authors summarised by saying 'Among 104 cases of squamous-cell oesophageal carcinoma patients and 277 controls in Taiwan, after adjusting for cigarette smoking, alcohol consumption, and other confounders, we found that subjects who chewed from 1 to 495 betel-year and more than 495 betel years (about 20 betel

quids per day for 20 years) had 3.6-fold (95% Cl = 1.3-10.1) and 9.2-fold risk (95% Cl = 1.8–46.7), respectively, of developing oesophageal cancer, compared to those who did not chew betel' [16]. From the definition of betel years given above, it is understood that the authors mistook betel (areca nut) chewing as betel quid chewing and wrongly highlighted betel chewing as the risk factor for oesophageal cancer.

"Betel nut and tobacco chewing; potential risk factors of cancer of oesophagus in Assam" is a paper wherein there was no data on sole areca nut chewers [17]. The data were given on the chewing substances such as: chadha; betel leaf + betel nut; betel leaf + betel nut + dhapat and betel leaf + betel nut + zarda. Still in the results column of that paper the first sentence is 'The adjusted risks associated with the chewing of betel nut were higher than those for tobacco smoking and alcohol consumption at all levels of consumption'.

"Relationship between site of oesophageal cancer and areca chewing and smoking in Taiwan" is the title of another paper wherein in the materials and methods column areca chewing was defined as 'Those who had regularly chewed betel quid for at least 6 months'[18]. This shows that the authors wrongly considered betel quid chewing as areca chewing!

In a letter addressed to the editor of European Academy of Dermatology and Venereology during 2004 with the heading "Oral disease caused by the chewing of betel nut and concoctions containing betel nut" the discussions were concentrated on the problems associated with chewing of concoctions containing betel nut such as betel quid, pan masala, gutkha, mawa, etc but not on sole betel nut [19]. The letter further says 'Betel is composed of the betel nut (*Areca catechu*), the fresh leaf of betel pepper (*Piper betle*) and calcium hydroxide (lime); Pan or paan masala is a quid of piper betel leaf that contains areca nut (AN), lime, condiments, sweeteners and sometimes tobacco; Pan masala containing tobacco is a mixture of AN, tobacco, lime, kattha (catechu) and spices; Mawa is a mixture of tobacco, lime and AN.' Ironically, there was no reference on sole betel nut chewing. Still, the authors concluded by saying 'Betel nut chewing is a major risk factor for health leading to benign, precancerous and malignant diseases of the gastrointestinal tract with the highest frequency in the oral mucosa'.

The paper entitled "Oral submucous fibrosis: a case-control study in Chennai, South India" wherein the authors concluded by saying 'The study confirms the strong association between areca nut use and OSF' [20]. However, in Table 2 on 'Habits and OR' no significant risk (p= 0.078) was reported with sole areca nut (AN) use. On the other hand significant risks were reported with other habits. Still the authors misled people by concluding with a statement 'The present study confirms the strong association between areca nut use and OSF'!

The title of the paper "Cytogenetic alterations in buccal mucosa cells of chewers of areca nut and tobacco" gives an impression that the authors had studied the effects of areca nut and tobacco on the cells of buccal mucosa [21]. However, in the materials and methods part of the abstract it is mentioned 'The assay was applied to exfoliated buccal mucosa cells of 262 subjects (nonchewers – 161 and chewers – 101) and 1000 cells per individual were examined microscopically. Nuclear anomalies were compared among chewers, non-chewers and OSMF subjects and correlated with consumption of quids per day and duration of chewing in years'. This shows that the entire study was carried out on betel quid chewers and not on sole areca nut or tobacco chewers though the title highlights 'chewers of areca nut and tobacco'.

"Association between grading of Oral Submucous Fibrosis with frequency and consumption of areca nut and its derivatives-----" is the title of a paper from Karachi [22].The authors reported that majority of the sample 54.5% (n = 417) ate only plain or packaged areca nut, followed by 26.1% (n = 200) who consumed betel quid (paan) with

tobacco and 14.6% (n = 112) consumed betel quid (paan) without tobacco, while 2.2% (n = 17) used naswar and only a few 0.4% (n = 3) consumed other chew types. Among the 417 people who ate only areca nut, 318 people ate packaged brand A of areca nut, 64 people ate brand B, 21 ate brand C of packaged areca nut and rest no preference. Hence, the data were mainly on chewers of different packaged forms of areca nut and not on plain areca nut chewers. Further, the actual contents in the packaged products were not at all disclosed.

In another paper, though the title was "Prevalence of oral submucous fibrosis among betel nut chewers dental patients of Patna" the subjects were not on sole betel nut chewers, but mostly on chewers of gutkha and other related chewing products [23]. In the Methods and materials column, the inclusion criteria for subjects in betel nut chewers group was mentioned as those chewing areca nut/pan/gutkha for more than 3 year. That means, the authors did not project any data on sole betel nut though the title is on betel nut chewers. Further, it was mentioned 'In the present study males were found to be more dominantly affected, as they were using gutkha and other related products more frequently because of easy availability of gutka at all the working places. This further shows that the study focused mainly on gutkha rather than on betel nut. But the authors wrongly titled the paper as betel nut chewers!

The aim of a study on "Correlation between areca/betel nut chewing habit with facial and dental characteristics in school going children - A prospective cross-sectional survey" was to evaluate the prevalence of areca/betel nut chewing and establish correlation with facial and dental characteristics in school going children [24]. But, nowhere in the paper the actual chewing substance was defined, but vaguely mentioned as Areca / Betel nut chewing habit!

**Review Articles and Pamphlets**

"A case-control study of oral submucous fibrosis with special reference to the etiological role of areca nut" is the title of a paper published during 1990 on a study conducted in Bhavnagar, Gujarat wherein among 60 cases, 1 person was without any chewing habit; 5 people were chewing betel quid with or without tobacco + lime; 4 people were chewing betel quid without tobacco; 30 people were chewing mawa and 20 were chewing mawa with others [25]. In that paper mawa is described as a mixture containing areca nut tobacco and lime. Strangely, there is no data on sole areca nut chewers. Still the last sentence of the abstract reads 'The present findings confirm areca nut as the most important etiologic factor in oral submucous fibrosis'!

"Etiology of oral submucous fibrosis with special reference to the role of areca nut chewing" is the title of another review [26]. In the 3rd page of that article, it is written 'In Bhavnagar town, Gujarat, India, there was a sudden upsurge of this condition (OSF) with 275 cases being recorded in a recent 5-yr period as compared to very few cases observed earlier. This trend corresponded with the increase in an areca nut (mawa) chewing habit in that area'. This shows that the authors mistook mawa as areca nut and wrongly titled the paper as areca nut chewing.

In the paper entitled "Areca nut use: an independent risk factor for oral cancer" authored by Warnakulasuriya et al the areca nut was highlighted as an independent risk factor for oral cancer, but reviewed mostly the papers on mixtures of chewing substances and not on sole areca nut [27]. In that paper it is mentioned 'An increased risk for the development of oral malignancy in areca nut only users is reported' by citing two reference papers in which the one cited in Sl no 6 was titled as 'Paan without tobacco: an independent risk factor for oral cancer' where the word paan was described as 'a quid of *Piper betel* leaf that contains areca nut, lime, condiment, sweeteners, and sometimes tobacco, which is also used extensively'.

That means, in that review paper of Warnakulasuriya et al (*op cit*) the authors mostly referred the papers on betel quid as if both betel quid and areca nut are same.

In an authoritative report on "The evaluation of carcinogenic risks to humans: betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines" it is noticed that there was no reference of any research paper to show that chewing of areca nut alone caused cancer in humans [1]. In that report there is a chapter on 'Studies of Cancer in Humans' (Chpter no 2; page 80-142) wherein more than 60 research papers were cited, but none of them, except one (Wasnik et al 1998; page 92) gave any data on sole areca nut chewers. Even in the data provided by Wasnik et al (*op cit*), the number of sole areca nut chewers in cases was 4% but in control it was 6%. This clearly shows that there is no enough data on sole areca nut chewers in humans to substantiate the statement 'Areca nut chewing is carcinogenic to humans'. In spite of that, in the overall evaluation part of the report it is said 'Areca nut is carcinogenic to humans (Group 1)!

There is a paper entitled "Areca nut or betel nut control is mandatory if India wants to reduce the burden of cancer especially cancer of the oral cavity" wherein the author highlighted areca nut chewing as highly dangerous to humans [28]. Again, it may be noted that in that review there is no solid evidence on sole areca nut chewers to substantiate that statement. The figures from 1-3 show the photographs of several commercial chewing mixtures in sachets. In the figure no 4 there is a photograph of a patient with mouth cancer. The citation is like this 'A young lady having mouth cancer due to areca nut chewing. She was consuming gutkha for 6 years and got this cancer at the age of 18 years'. That means the author mistook gutkha and other chewing mixtures as areca nut and titled the paper accordingly.

Another paper is titled as "Association of betel nut with carcinogenesis; revisit with a clinical perspective" [29]. As per the title the review should have been concentrated on the research papers on sole betel nut. But the abstract says 'The PUBMED database was searched to retrieve all relevant published studies in English on BN and BQ and its association with oral and oropharyngeal cancers. This systematic review attempts to put in perspective the consequences of this widespread habit of BN/BQ mastication. BN/BQ mastication seems to be significantly associated with susceptibility to oral and oropharyngeal cancers. Despite the widespread usage of BN/BQ and its strong association with human susceptibility to cancer, no serious strategy seems to exist to control this habit'. Thus, the authors mixed up both betel nut and betel quid but titled as only betel nut!

The primary objective of the review paper entitled "Areca nut as an emerging etiology of oral cancers in India" was to review the literature on areca nut as an etiological factor for oral cancer [30]. While going through the paper it is seen that in table no 3 on Epidemiologic studies, 18 papers were cited, most of them were on betel quid and not a single one was there on sole areca nut. This shows that these authors also mistook betel quid as areca nut.

Similarly, in a review paper entitled "Betel nut chewing and its deleterious effects on oral cavity" the reference papers were mainly on chewing betel quid rather than sole betel nut [31]. It looks as if both betel nut and betel quid are same for reviewing authors.

Another paper is titled as "Areca nut and its role in oral submucous fibrosis" [32]. The aim of this study, as mentioned in the abstract, was to discuss in detail the effects of the components of areca nut on pathogenesis of oral submucous fibrosis. But, instead of concentrating on the components of arecanut, the authors mainly concentrated on chewing mixtures such as paan masala, gutkha, etc. In the 2nd page of the article it is mentioned 'The reason for the continuous rise in the incidence of OSF could be attributed to increased popularity of commercially available areca nut preparations, i.e., paan masala/gutkha in India and an increased uptake of this habit by young people due to

easy access, effective price ranges, and marketing strategies'. This shows that all these chewing mixtures were considered as areca nut by the authors!

In the paper entitled "A review of the systemic adverse effects of areca nut or betel nut" the abstract column says 'There is substantial evidence for carcinogenicity of areca nut in cancers of the mouth and esophagus. Areca nut is not a harmless substance as often perceived and proclaimed by the manufacturers of areca nut products such as Pan Masala, Supari Mix, Betel quid, etc'[33]. This shows that the authors, instead of collecting data on sole areca nut, treated Pan Masala, Supari Mix, Betel quid, etc. as areca nut and titled the paper as adverse effects of areca nut!.

There is a review paper entitled "Areca nut use and cancer in India" [34]. The abstract says 'relative risks for precancer or cancer with use of areca nut without inclusion of tobacco is the focus of the review'. But in that paper the authors wrote 'Six case-control studies on head and neck cancers, primarily oral cancer reported elevated ORs for chewing of betel quid without tobacco, eight case control studies on oral cancer have reported elevated and significant ORs for betel quid with tobacco, a significant risk in oral cancer was noted in gutkha users'. There was no mention of sole areca nut users but the title is 'Arecanut use'!

"Multifaceted mechanisms of areca nuts in oral carcinogenesis: the molecular pathology from precancerous condition to malignant transformation" is a review paper wherein the authors reported in the abstract 'In this review, we comprehensively discuss and concisely summarize the up-to-date molecular and cellular mechanisms by which areca nuts contribute to malignant transformation' [35]. In the 2nd page of the article it is mentioned 'Areca nut chewers have a much greater risk of developing oral cancer than non chewers and 5-year survival rate of oral cancer patients who chew areca nuts is much lower than that of those who do not chew these nuts' by citing the studies carried out mostly on betel quid chewers.

"Effect of areca nut on oral health: A review" is a paper prepared by searching the Google Scholar, PubMed, Scopus, Science Direct, and Web of Science databases (about 35 articles) with the keywords: areca nut, habits, and oral health, from 1990 to 2020 [36]. However, in the results column it is mentioned 'By reviewing the studies, it was found that areca nut products cause periodontal disease as well as oral lesions, which can become malignant with ongoing use'. That means, according to these authors there is no difference between areca nut and areca nut products.

The first sentence in the abstract column of the review paper "Areca nut and its products: A culprit for many cancers" reads 'This article is to give a comprehensive review about the areca nut, different products made from it, and the important cancers associated with the use of different products of areca nut'[37]. But the photo cited as areca palm in Fig 1 is not of areca palm but of calappa (*Actinorhytis calapparia*) palm. This shows that the authors are even ignorant of areca palm!

In a review paper entitled "Areca nut an ignored carcinogen of Asian continent in a nutshell" the authors cited six papers in the reference column, but all of them are again review papers and not a single one on original research on sole areca nut [38]. Further, all the six review papers cited in that article reviewed the effects of chewing betel quid and other chewing mixtures and were wrongly titled as areca nut. For example the paper cited in Sl no 5 in that paper was titled as 'Areca nut use: An independent risk factor for oral cancer' but that paper was mainly on betel quid or paan chewers and not on sole areca nut. This shows that the authors did not read the cited papers critically but titled their review paper as areca nut.

The objective of the review paper entitled "Do betel quid and areca nut chewing deteriorate prognosis of oral cancer? A systematic review, meta-analysis, and research agenda" was to explore the correlations between the habit of betel quid and areca nut (BQ-AN) chewing and the

prognosis of oral cancer (OC) [39]. It is the known fact that BQ is a mixture of AN, betel leaf or betel inflorescence and slaked lime, with or without catechu and tobacco [1]. As BQ contains AN as one of the ingredients, the necessity of mentioning AN separately in the heading was irrelevant unless separate study on sole AN chewing was made. But the above paper did not give any reference on sole AN chewers.

There is an exhaustive review by Warnakulasuriya and Chen entitled "Areca nut and oral cancer: Evidence from studies conducted in humans" [40]. In the abstract of the paper the authors wrote 'The risk of oral cancer increases in a dose-response manner with the daily number of quids consumed and the number of years chewing. In the Indian subcontinent and in Taiwan, approximately half of oral cancers reported are attributed to betel quid chewing'. Further, in the sub title on the Evidence for carcinogenicity of areca nut in humans (page no 1140) it is mentioned 'A meta-analysis of 26 observational studies published between 1933 and 2013 assessed the relationship between chewing BQ and the risk of cancers of the oral cavity'. There is no mention of sole areca nut users in the entire paper. However, in Table 2 (page 1144) several papers were cited with the exposure criteria 'areca nut chewers vs never'. If one goes through the original papers cited in that, most were on betel quid chewers and not on sole areca nut. For example the reference paper by Lee et al 2012 (Population burden of betel quid abuse and its relation to oral premalignant disorders in South, Southeast, and East Asia: an Asian betel-quid consortium study) was categorised in the paper of Warnakulasuriya and Chen (*op cit*) under the exposure criteria of areca nut chewers vs never! Still, the authors claimed that they had reviewed systematically on the carcinogenicity of areca nut in humans.

"Global burden of oral cancer in 2022 attributable to smokeless tobacco and areca nut consumption: a population attributable fraction analysis" is a review paper authored by 18 people wherein the chewing substance was not clearly defined but mentioned as 'smokeless tobacco and/ or areca nut consumption'[41]. There is no clarity whether the data provided were for smokeless tobacco or for areca nut or for both together. For example, in the Methods column of the abstract it is mentioned 'We calculated population attributable fractions (PAFs) using prevalence of current use of smokeless tobacco or areca nut products from national surveys and corresponding risks of oral cancer from the literature. We applied PAFs to national estimates of oral cancer incidence in 2022 from the Global Cancer Observatory's Cancer Today database to obtain cases attributable to smokeless tobacco or areca nut consumption' and in the Findings column 'Globally, an estimated 120 200 (95% UI 115 300–124 300) cases of oral cancer diagnosed in 2022 were attributable to smokeless tobacco or areca nut consumption'. More clarity is needed on the chewing substance, whether it is for smokeless tobacco or for arecanut or for both.

'Areca Nut Chewing is strongly associated with oral cancer' is the sentence highlighted in the public awareness pamphlet entitled "Beware of areca nut" without citing any research work on lone areca nut chewing [42]. The authors mostly relayed data on chewing of betel quid and other forms of chewing mixtures but not on sole areca nut. The front cover page of the pamphlet emphatically projects 'Beware of Areca nut' but shows the photographs of Gutkha, Mawa, Pan Masala, Sweet Supari and Sugandhi Supari but not the photograph of pure areca nut. This shows that the authors mistook all such chewing mixtures as areca nut!

## CONCLUSION

In the IARC Monographs on the evaluation of carcinogenic risks to humans: Betel quid and areca nut chewing and some areca nut derived nitrosamines Vol 85, 2004, areca nut was defined as 'the seed of the fruit of the oriental palm *Areca catechu*'[1]. There is no ambiguity in that explanation. Still, with the aim of establishing the relation between

areca nut chewing and incidence of OSF and oral cancer several researchers, without authenticating the chewing substance as areca nut by experts in plant science, wrongly identified the chewing substances such as betel quid, paan masala, gutkha, etc., as areca nut. It is strange to note that even several reviewers of such research papers did not comment on such glaring mistakes.

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