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ARECA NUT SYMPOSIUM

The oral health consequences of chewing areca nut

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Abstract

Deleterious effects of areca nut on oral soft tissues are published extensively in the dental literature. Its effects on dental caries and periodontal tissues, two major oral diseases, are less well researched. Areca-induced lichenoid lesions mainly on buccal mucosa or tongue are reported at quid retained sites. In chronic chewers a condition known as betel chewer's mucosa, a discoloured areca nut-encrusted change, is often found where the quid particles are retained. Areca nut chewing is implicated in oral leukoplakia and submucous fibrosis, both of which are potentially malignant in the oral cavity. Oral cancer often arises from such precancerous changes in Asian populations. In 1985 the International Agency for Research on Cancer concluded that there is limited evidence to conclude that areca chewing may directly lead to oral cancer. There is, however, new information linking oral cancer to pan chewing without tobacco, suggesting a strong cancer risk associated with this habit. Public health measures to quit areca use are recommended to control disabling conditions such as submucous fibrosis and oral cancer among Asian populations.

Introduction

Areca nut may be consumed either on its own or more commonly in association with other ingredients such as tobacco, lime, catechu and other spices wrapped in a betel leaf and referred to as a betel quid or pan.[1] Recently the trend has been to chew processed areca products known as pan masalas. These contain a mixture of areca, catechu and slaked lime and may also on occasion contain tobacco.

Chewing areca nut on a habitual basis is known to be deleterious to human health.[2] A growing body of evidence over the last 40 years, mainly in the form of large-scale epidemiological and experimental studies, has shown that even when consumed in the absence of tobacco or lime areca may have potentially harmful effects on the oral cavity. These effects can be divided into two broad categories: those affecting the dental hard tissues, which include teeth, their supporting periodontium and the temporomandibular joint and the soft tissues, which make up the mucosa that lines the oral cavity.

Effects on hard tissues

Dental attrition

The main effects of areca on the hard tissues are on the teeth. The habitual chewing of areca may result in severe wear of incisal and occlusal tooth

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surfaces, particularly the enamel covering. The loss of enamel may also expose the underlying dentine and as this is softer than enamel wears at an increased rate. The exposure of dentine may also result in dentinal sensitivity. The degree of attrition is dependent upon several factors, which include the consistency (hardness) of the areca, the frequency of chewing and the duration of the habit. Root fractures have also been demonstrated in chronic areca chewers and this is likely to be a consequence of the increased masticatory load that is placed upon the teeth and is not direct effect of areca.[3]

Areca staining

Among areca chewers, extrinsic staining of teeth due to areca deposits is often observed particularly when good oral hygiene prophylaxis is lacking and where regular dental care is minimal.

Dental caries

It has been suggested that areca chewing may confer protection against dental caries. Epidemiological studies carried out in South East Asia suggest that the prevalence of dental caries in areca chewers is lower than in non-chewers.[4–6] Some investigators, however, have shown that there is no difference in the prevalence of dental caries between areca chewers and non-chewers in other Asian populations.[7,8] Although little is known about the cariostatic properties of areca it has been suggested that the betel stain, which often coats the surface of the teeth, may act as a protective varnish.[9] There is also *in vitro* evidence that suggests that the tannin content of areca may have antimicrobial properties and this may contribute to the cariostatic role of areca.[10] In addition, chronic chewers also have marked attrition of cusps of teeth leading to loss of occlusal pits and fissures, which may reduce the risk of pit and fissure caries by eliminating potential stagnation areas. The increased production of sclerosed dentine in response to attrition may confer protection against microbial invasion. Furthermore, the process of chewing itself brings copious amounts of saliva to the mouth and in the presence of added slaked lime may increase the pH in the oral environment; this may act as a buffer against acid formed in plaque on teeth.

Temporomandibular joint (TMJ) pathology

The masticatory forces generated during chewing areca may be transmitted to the TMJ and subsequently may give rise to joint arthrosis. However, there is no reliable data to substantiate an increased prevalence in areca users and further studies are required. Furthermore, symptoms such as trismus are common to both TMJ pathology and to other oral disorders associated with areca chewing such as oral submucous fibrosis. It is difficult to distinguish a direct effect on the TMJ from the fibrotic involvement of the oral musculature that may contribute to limitation of mouth opening in chronic chewers.

Effects on soft tissues

Periodontal disease

In vitro studies have demonstrated that areca extracts containing arecoline inhibit growth and attachment of, and protein synthesis in, human cultured periodontal fibroblasts.[11,12] On the basis of these findings the investigators proposed that areca may be cytotoxic to periodontal fibroblasts and may exacerbate pre-existing periodontal disease as well as impair periodontal reattachment. Some investigators have shown that loss of periodontal attachment and calculus formation is greater in areca chewers.[13] However, it is difficult to interpret such studies, as there are several confounding variables such as the level of oral hygiene, dietary factors, general health and dental status, not to mention tobacco smoking, which may have a significant influence on periodontal status. Furthermore, as the majority of chewers are in the Indian subcontinent, where oral health education is limited, periodontal health may be compromised even in non-areca chewers. It is therefore difficult to ascertain the biological effects of areca on periodontal health but in view of the recent *in vitro* evidence further clinical and experimental studies are necessary.

Lichenoid lesions

Areca-induced lichenoid lesions, mainly on buccal mucosa or tongue, have been reported at sites of quid application.[14] This is considered to be a type IV contact hypersensitivity-type lesion but resembles oral lichen planus clinically. The main detectable features are that it is found at the site of quid placement in areca chewers and may be unilateral in nature. Fine wavy keratotic lines are

Table 1. *Prevalence of betel chewer's mucosa in different populations*

Reference	Country	Year	Number	Prevalence %
16	Cambodia	1996	102	60.8
17	Malaysia	1995	850	21.9
18	Cambodia	1995	1319	< 1
19	Thailand	1987	1866	13.1

seen to radiate from a central red/atrophic area and, interestingly, the keratotic striae do not criss-cross and are parallel to each other. The histology is suggestive of a lichenoid reaction and the lesion is noted to resolve following cessation of areca use.

Betel chewer's mucosa (BCM)

This condition was first described by Mehta *et al.*[15] and is characterized by a brownish-red discolouration of the oral mucosa. This discolouration is often accompanied by encrustation of the affected mucosa with quid particles, which are not easily removed, and with a tendency for desquamation and peeling. The underlying area assumes a wrinkled appearance. The lesion is usually localized and associated with the site of quid placement in the buccal cavity. The lesion is associated strongly with the habit of betel quid chewing, particularly in elderly women who have been chronic chewers for long durations.[16] Several epidemiological studies have shown that the prevalence of betel chewer's mucosa may vary between 0.2% and 60.8% in different South East Asian populations (Table 1). Histologically, betel chewer's mucosa shows epithelial hyperplasia, which is encrusted with an amorphous deposit. This reacts positively to von Kossa staining suggesting that these granules, which are located both intra- and intercellularly, may contain calcium from the calcium hydroxide in slaked lime.[20] A ballooning effect of oral keratinocytes is noted. The presence of the human papilloma virus (HPV) subtypes 11, 16 and 18 has also been demonstrated in BCM but the significance of this is not fully understood. [21]

Although the exact mechanisms underlying the development of this condition are not fully understood it is thought that the chemical and traumatic effects of the betel quid on the oral mucosa may be significant factors. Furthermore, there is also evidence that the presence of tobacco in the quid is not essential for the development of BCM.[22] At present BCM is not considered to be potentially malignant, although the condition often co-exists with other mucosal lesions such as leukoplakia and oral submucous fibrosis, which are well known for their potential for malignant change.

Oral leukoplakia

Leukoplakia can be defined as a predominantly white patch or plaque on the oral mucosa that cannot be characterized clinically or pathologically as any other disease and is not associated with any other physical or chemical agent except tobacco.[23] Based on clinical appearance, leukoplakia can be divided into several subtypes: homogeneous (white), speckled (red/white), nodular or verrucous leukoplakia.

This condition is well known for its potential for malignant change and transformation rates between 0.1 and 17.5% have been quoted in the literature.[24]The figures for malignant transformation based on population studies reported from India[25] are much lower than those reported from Europe and the United States based on hospital series, but this may be due to a selection bias. There is also evidence that the clinical presentation (site and type) may influence the risk potential for malignant change. The speckled lesions carry a greater risk for malignant change in comparison to the homogeneous white plaques.[26]

In biopsies in addition to the presence of an amorphous brown-staining von Kossa positive layer on the surface, parakeratosis and atrophy of the covering oral epithelium are reported in areca chewers.[27] In another study, 14% of leukoplakia biopsies obtained from areca chewers demonstrated cellular atypia amounting to epithelial dysplasia.[28] Histopathology of an areca nut-associated oral mucosal lesion presenting clinically as a white/red patch and demonstrating severe epithelial dysplasia is shown in Fig 1.

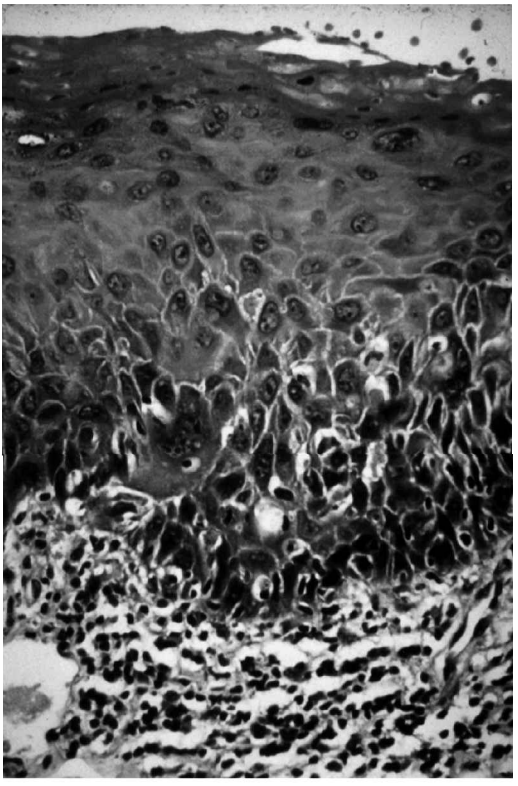

Figure 1. *Severe epithelial dysplasia in a 'speckled leukoplakia' arising in the lateral border of tongue mucosa in a long-term tobacco and areca nut user; male aged 47 years; H&E ×100.*

Although there is considerable controversy and debate about how to define oral leukoplakia there is little doubt that both tobacco, in any form, and areca nut use are major risk factors for developing this condition.[29,30] In Ernakulum, India a 10-year follow-up study recorded that the incidence of leukoplakia in a group of chewers, which consisted mainly of pan chewing, was 2.5 per 1000 people.[25] Warnakulasuriya[31] reviewed four case–control studies that examined relative risk of oral leukoplakia in betel quid chewers. In one of the studies, chewing areca (in betel quid without tobacco) raised the odds ratio (OR) to 5 compared with non-chewers (OR = 1); adding tobacco to the quid further raised the relative risk by at least threefold compared with non-tobacco users.[32] More recently, the results of a case–control study conducted in Taiwan, where areca is chewed without tobacco, found the odds ratio for developing leukoplakia was 17.43 (95% CI 1.94–156.27) for areca nut chewers.[33] Furthermore, the authors demonstrated that the cessation of areca chewing resulted in resolution of 62% of leukoplakias, suggesting that areca on its own is a significant aetiological factor in the development of leukoplakia. Further evidence of its relationship with areca chewing has come from the increased prevalence of this condition in subjects who suffer from oral submucous fibrosis, which is associated strongly with the habit of areca chewing.[34]

Oral submucous fibrosis (OSF)

This is a chronic disorder characterized by fibrosis of the lining mucosa of the upper digestive tract involving the oral cavity, oro- and hypopharynx and the upper third of the oesophagus.[35] The fibrosis involves the lamina propria and the submucosa and may often extend into the underlying musculature resulting in the deposition of dense fibrous bands, which give rise to the limited mouth opening which is a hallmark of this disorder. Warnakulasuriya[36] defined a series of symptoms and subjective signs which are characteristic of OSF to be employed as the clinical criteria required to make a diagnosis of OSF (Table 2). This symptomatology of OSF was adopted at a consensus workshop held to clarify the nomenclature of areca quid-associated lesions and conditions.[1] Histopathology of OSF is illustrated in Figs 2 and 3 in long-standing areca chewers, with underlying fibrosis of lamina propria being the pathognomic feature. Epithelial atrophy often associated with OSF is seen in Fig. 2 and accompanied epithelial dysplasia in Fig. 3.

The potentially malignant nature of this condition has been well documented. A malignant transformation rate of 7.6% over a period of 10

Table 2. *Clinical features of OSF*

Early	Late
Blanching of mucosa	Fibrous bands
Intolerance to spicy food	Trismus
Petechiae	Flattening of palate
Depapillation of tongue	Hockey-stick uvula
Oral ulceration	Reduced tongue mobility
Leathery mucosa	Xerostomia
Taste disturbance	Keratosis

Source: Refs 1 & 36.

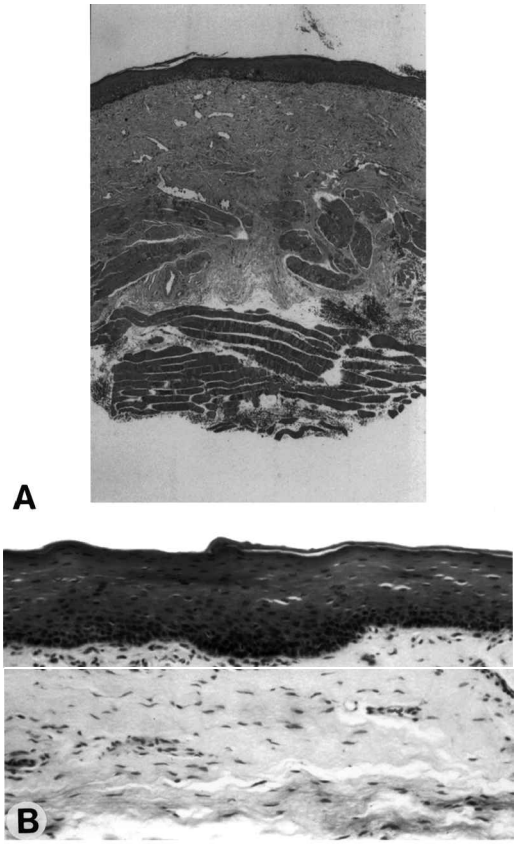

Figure 2. *(A) Epithelial atrophy and subepithelial fibrosis extending into the underlying voluntary muscle fibres in the buccal mucosa of 49 year-old male with a long history of oral submucous fibrosis; H&E ×10 (B) Epithelial atrophy and subepithelial fibrosis in the floor of mouth mucosa from a 43 year-old female with extensive oral submucous fibrosis and a long history of both tobacco and areca nut usage; H&E ×50.*

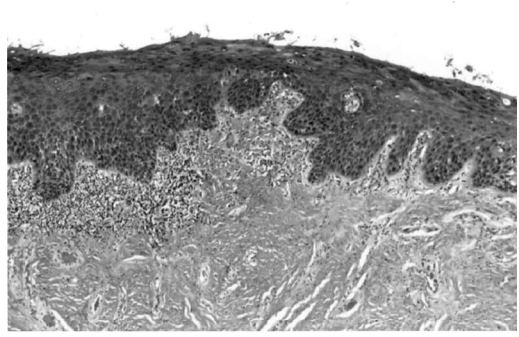

Figure 3. *Severe epithelial dysplasia in the retromolar mucosa of a 59 year-old female with oral submucous fibrosis and a long history of both tobacco and areca nut usage; same patient as shown in Fig. 2B but 16 years later; H&E ×20.*

years was described in an Indian cohort[37] and the relative risk for malignant transformation may be as high as 397.3.[38]

Although OSF was first described by Schwartz[39] in a series of Indian women living in East Africa there are descriptions of a similar condition occurring in betel chewers in early texts dating back to 1908.[40] Since Schwartz's publication, OSF has been detected in several epidemiological studies conducted mainly in India, among Indians living in south Africa, among Chinese or in other south Asian populations (Table 3). At present there are few data on the prevalence of OSF among Asians living in Europe and the United States but there have been several case reports, describing OSF in some habitues who continue to chew areca following migration.[50–52]

It is now accepted that chewing areca is the single most important aetiological factor for developing OSF.[53,54] Other causes which have been proposed in the past but have not been substantiated include excessive consumption of chilies, autoimmune reaction and nutritional factors, particularly iron deficiency.

Much of the evidence implicating areca has been derived from epidemiological data arising largely from India, Pakistan and South Africa. Many observational studies on OSF patients have recorded a high frequency of the areca chewing habit in the OSF subjects (close to 100%) compared to that of the general popula-

Table 3. *The global epidemiology of OSF*

Country/Ref.	Sample no.	Prevalence %
India		
41	10 000	0.51
42	5000	1.22
43	10 071	0.16
44	35 000	0.59
45	101 761	0.07–0.4
46	5018	3.2
South Africa		
47	1000	0.5
48	2058	3.4
China		
49	11 046	3.03

Table 4. *Relative risk (RR) of developing of OSF in areca chewers*

Reference	Country	Cases	Controls	Relative risk (RR)
46	India	164	5018	60.6 (areca) 75.6 (Mawa)
56	India	200	200	489.1 (pan masala) 136.5 (areca)
57	Pakistan	157	157	154.0 (areca only) 64.0 (betel quid + tobacco) 32.0 (betel quid)
58	India	60	60	29.9 (areca) 106.4 (Mawa)
59	Taiwan	35	100	43.8 (betel quid)

tion.[48,49,55] Several case–control studies have also shown that there is an increased risk of developing OSF in subjects consuming areca products (Table 4). The relative risk was noted to rise with an increasing frequency of the areca chewing habit, suggesting a dose–response relationship.[57,58] An interventional study conducted over a 10-year follow-up period in India showed a decrease in the incidence of OSF in the trial cohort compared with a control population as a result of cessation of areca use.[60] However, the authors point out that OSF is emerging as an new epidemic in India due to rising trends in per capita areca consumption.[46]

Although there is good evidence to support the role of areca as the major risk factor in the development of OSF, the mechanisms by which this occurs are not fully understood. *In vitro* studies have shown that areca nut alkaloids such as arecoline and its hydrolysed product arecaidine may stimulate cultured fibroblasts to proliferate and synthesize collagen.[61,62] In addition flavonoids within the nut have also been shown to increase the stabilization of collagen by enhancing the cross-linking of collagen, thereby increasing the resistance to degradation by collagenases.[63] However, subsequent *in vitro* studies have failed to show similar effects of arecoline on cultured OSF fibroblasts.[64,65] Furthermore, recent studies have shown that arecoline inhibits collagen synthesis and fibroblast proliferation *in vitro*, suggesting that arecoline may have cytotoxic properties.[12,66,67] The disparity of results from *in vitro* studies suggests that the areca may contain other agents in addition to arecoline which are important in the pathogenesis of OSF; the role of arecoline, therefore, needs further evaluation.

There has been recent interest in the role of copper in the pathogenesis of this disorder and raised copper concentrations have been shown in products containing areca nut in comparison to other nut-based snacks.[68] Chewing areca for up to 20 minutes releases significant amounts of soluble copper to the whole mouth fluid.[69] Furthermore, there is evidence to show that mucosal biopsies taken from OSF subjects contain a higher copper concentration than those taken from controls.[70] This has led to the hypothesis that the increased tissue copper may increase the activity of the enzyme lysyl oxidase, which is a copper-dependent enzyme that has been implicated in the pathogenesis of several fibrotic disorders, including OSF.[71,72] Further support for this theory comes from studies which demonstrate that inorganic copper salts *in vitro* significantly increase the production of collagen by oral fibroblasts.[73]

Very few animal models of OSF have been described. Khrime *et al.*[74] demonstrated histopathological changes consistent with OSF in albino rats whose skin was subjected to repeated exposure to commercially available areca products. Earlier studies, however, found that the application of arecoline to the palates of B_{12}-deficient rats did not give rise to any features which were suggestive of OSF.[75] Application of arecaidine to hamster cheek pouch also failed to show any microscopic changes suggestive of fibrosis.[76]

The fact that only a small proportion of subjects who chew areca actually develop OSF raises the possibility that there may be a genetic predisposition for this disorder. There is limited evidence in the literature to support that people

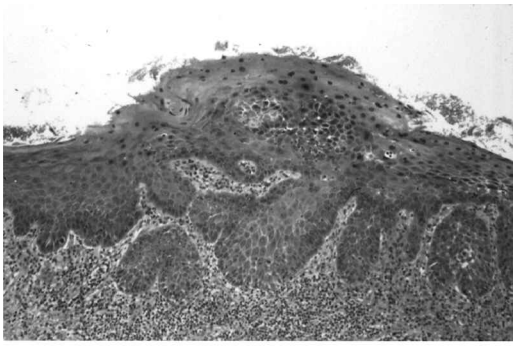

Figure 4. *Micro-invasive, well-differentiated squamous cell carcinoma arising in the ventral tongue mucosa of the patient shown in Fig's 2b and 3; now aged 63 years and still using both tobacco and areca nut; H&E ×25.*

of Bangladeshi origin develop OSF although they indulge in areca habits. HLA studies conducted on OSF have shown divergent results and a study of a cohort of UK-based OSF patients found an increased frequency of DR3, A10 and B7,[77] whereas a study conducted on a Pakistani population found an increased frequency of CW2 and DR1.[78] In contrast, studies conducted in Asians living in South Africa found no HLA-associated susceptibility in OSF.[79] The evidence from the literature strongly implicates areca in the aetiopathogenesis of OSF although further studies are warranted to uncover the mechanisms underlying the pathological processes in relation to the development of the fibrosis and transformation to squamous cell carcinoma, which can be considered as the most serious oral health sequence of this disorder. Figure 4 illustrates a case of squamous cell carcinoma arising in a case of OSF.

Oral squamous cell carcinoma (OSCC)

There is historical evidence dating back nearly a century that suggests that the areca nut may be involved in the development of OSCC.[40,80,81] Although it is widely accepted that the presence of tobacco in betel quid plays an important role in the pathogenesis of oral squamous cell carcinoma the carcinogenic potential of areca in the absence of other ingredients is less clear.[82]There are epidemiological data from several case–control studies that confirm that the habit of betel quid chewing increases the relative risk of developing OSCC.[83] The description of the chewing habit has not been explicit in some of these studies. Some of the relevant studies with estimated relative risk are listed in Table 5. The bulk of the data in the literature suggests that the addition of tobacco to the quid increases its carcinogenic potential.[88–90] Areca (pan) chewing without tobacco causing oral cancer has been highlighted in a few recent studies. In one South African study, 68% of cheek cancers and 84% of tongue cancers were found in subjects consuming areca without tobacco.[87] Furthermore, there is new evidence which suggest that areca in the absence of tobacco may be an independent risk factor for the development of oral SCC.[84]

In addition to human data there are also a large number of experimental studies, which have attempted to evaluate the carcinogenic potential

Table 5. *Relative risk of developing oral squamous cell carcinoma (SCC) in relation to chewing habits*

Reference	Country	Cases	Controls	Habit	RR for SCC
33	Taiwan	60	100	Areca nut	3.79 (95% CI 1.20–12.24)
84	Pakistan	79	149	Pan with tobacco	8.42
				Pan without tobacco	9.9
85	Taiwan	40	160	Betel quid*	58.4 (95% CI 7.6–447.6)
				Duration (years): 1–20	17.1 (95% CI 1.8–161.9)
				21–40	108.4 (95% CI 11.9–987.9)
				40 +	403.5 (95%CI 20.8–7843.0)
				Frequency (/day) 1–9	28.3 (95% CI 3.3–240.7)
				10–20	61.9 (95% CI 7.9–487.2)
				> 20	294.1(95%CI 16.5–5233.6
86	Taiwan	107	200	Betel quid*	123
87	South Africa	143	735	Areca nut	43.9 (95% CI 18.6–103.6)
				Areca nut + tobacco	47.4 (95% CI 20.3–110.5)

*The betel quid used in Taiwan is predominantly areca nut based.

of areca and its derivatives both *in vivo* and *in vitro.* Jeng *et al.*[91] in a recent review examined the mutagenecity and genotoxicity of areca alkaloids to target cells in the oral mucosa.

In vivo *studies*

Several animal studies have confirmed that areca products and derivatives such as arecoline- and areca- derived nitrosamines have the ability to induce neoplastic changes in experimental models. Early studies found that the application of arecaidine to the oral mucosa of experimental animals failed to have any carcinogenic effects, but when supplemented with a known promoter such as croton oil resulted in cellular damage,[76] whereas other studies have shown that the application of areca products to the oral mucosa of animals results in histological changes which may be indicative of DNA damage.[92,93] In addition to the local effects of areca on the oral mucosa there is also evidence that suggests that areca, when applied to the skin of animal models or included in the feed, may cause neoplastic changes in sites distant from the oral cavity such as the foregut, liver, kidneys and lung.[94–97]

In vitro *studies*

There are also data in the form of *in vitro* studies which have been conducted on Chinese hamster ovary (CHO) cells and mammalian cell lines that suggest that areca extract may possess cytotoxic and genotoxic effects.[67,98–100] There are also limited data from mutagenicity assays conducted on bacteria (*Staphyllococcus typhi*) which suggest that commercially available products containing areca (pan masalas) have mutagenic properties.[101,102]

Human studies

Among areca chewers possible genomic damage caused by areca nut (without tobacco) was confirmed in cytogentic studies.[103]

Conclusion

It is clear from the literature that areca may have significant effects upon the hard and soft tissues of the oral cavity. Its alleged beneficial effects on dental caries and the possible damage to the periodontium need further evaluation.

Based on many population studies conducted in Asia the role of areca in the pathogenesis of betel chewer's mucosa, oral leukoplakia and oral submucous fibrosus is well established. Both leukoplakia and submucous fibrosis are potentially malignant conditions in the oral cavity. At the time of the last review by the International Agency for Research on Cancer in 1985 information available on the carcinogenic role of areca was limited. New information from several population studies, however, suggest that areca on its own may play an aetiological role in the causation of oral cancer. Public health education against areca nut use is essential to control oral cancer in emerging market economies and among Asian migrant communities in other parts of the globe.

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