

Areca nut and its systemic outcomes

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Abstract: areca nut association with human being is since pre vedica period where it is used as a regular part of meals also it is considered as a token of gift in many cultures. Its deep association with traditions of our country we are not able to completely eradicate its use. Areca nut has its systemic effects on almost every system of our body. Thus its use should be curbed. Apart from its deleterious effects scientists have progressed to utilise its constituents as a treatment modality for cancers.

Key words: catechu, tannins, collagen, arecoline, molecular biology

1. INTRODUCTION:

Betel nut or areca nut has been part of our Indian culture since long time. Even though it provides minor benefits its adverse effects outweighs the benefits on prolong use. Betel nut is not indigenous to India. In Indian sub-continent chewing betel nut can be traced back to pre-vedic period Harappan empire and was described as Tamboola. It is more commonly followed in Hindu religious ceremonies during weddings and presented to visitors as a sign of cordiality. It is presented to deities in adoration in the form of tamboola, it contains two betel leaves and one areca nut.

Areca means cluster of nuts in a primeval Malay language. It was found that the areca nut belonged to Malaysian area where different varieties of nuts were grown, it was then exported to different countries down south and reached India where it is cultivated as a cash crop.

Different countries use areca nut in variety of ways. Here is the list of few countries of South Eastern part of Asia where traditionally areca nut is used.

1. Malay culture:

Malay people are natives of Malay Peninsula of eastern Sumatra of Indonesian country.

Tradition: Areca nut is usually given as a take away in family functions at the end of meal. Since it is considered as auspicious ritual it is followed till date in few religious ceremonies.

2. Solomon Island

(east of Papua New Guinea and northwest of Vanuatu)

One of the mariner long back has observed that the natives of Solomon Island chew the nut and leaf combined with lime in a manner which resulted in red staining of their teeth and mucosa. It is considered as token of friendship.

3. Bhutan

Areca nut is known as doma, here the areca nut is taken in raw form which is more softer and moist.

In other places of Bhutan raw nut with husk is fermented and juice was extracted from it. It has a putrid odour which can be smelt from distance. Use of doma is a part of Bhutanese culture and its use is continued regularly.

4. China

Xiangtan City, Hunan	Areca nut with maltose and calcium hydroxide
“Hainan Island”	Fruit with calcium hydroxide and betel leaves (Pindborget <i>al.</i> , 1984)

5. Taiwan

Three types of quids have been classified:

- a. Laohwa quid
- b. Betel quid
- c. Stem quid

A. Laohwa quid is more prevalent in urban areas and prepared of Piper betle L with lime paste that has calcium hydroxide and flavouring agents to areca nut.

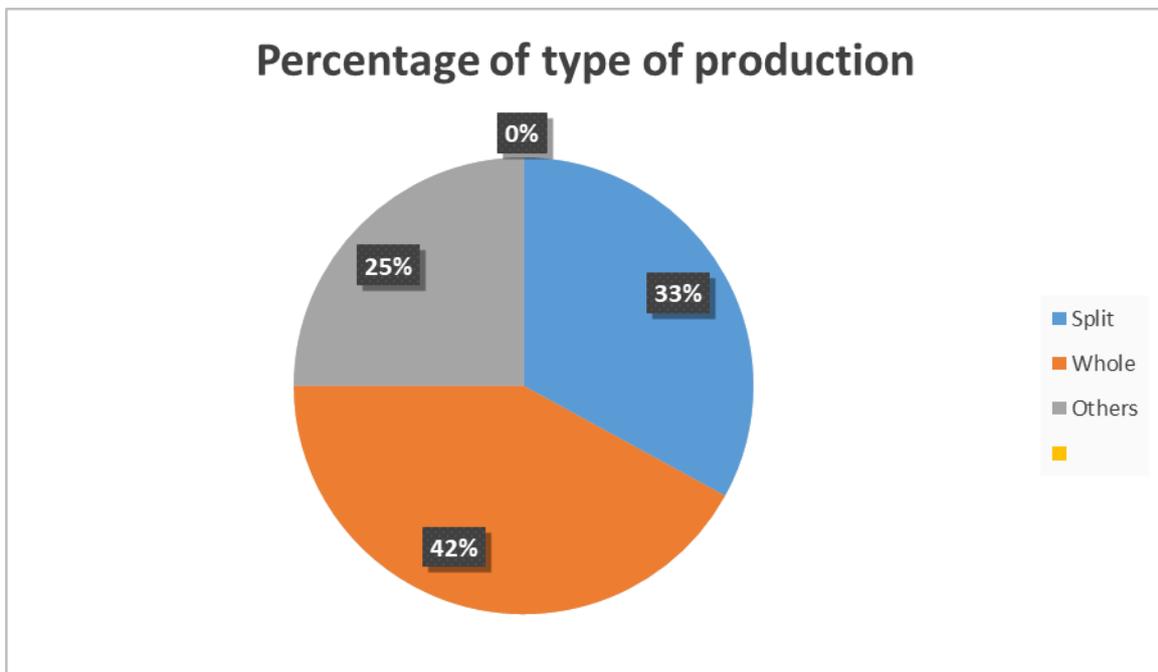
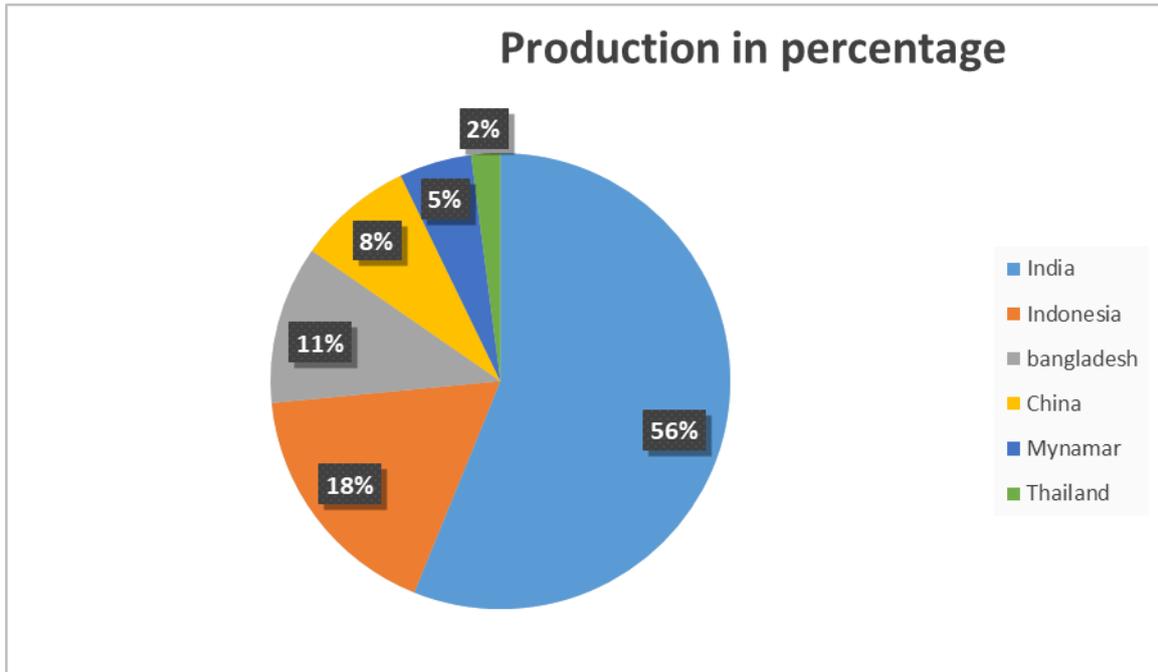
B. Betel quids are prepared by covering a fresh areca nut & white calcium hydroxide paste on a betel leaf. There is no addition of tobacco.

C. Stem quid remains same as laohwa quid but there is no part of inflorescence which is substituted by portion of stem of piper betle L. It is mostly seen in south of Taiwan and in paiwan and yami tribes.

India: areca nut production

Top areca nut producing states in India

1. Karnataka
2. Kerala
3. Assam
4. Meghalaya
5. West Bengal
6. Mizoram
7. Tamil nadu
8. Tripura
9. Andaman and nicobar islands
10. Maharashtra



India

1. Buratamul – developed garden-fresh nuts are conserved in coats of mud, it is moist to chew and those nuts get infected with different types of fungi^{1,2}.

2. Neetadaka- Nuts are well-kept-up by drenching them in rainwater and the nuts turn into discoloured and produce odour due to the decomposition of bacteria. Innermost core is conserved and to eliminate the foul smell we can use sodium benzoate (0.1%) solution and potassium (heated), blanchings are also suggested³.

3. Chali or kottapak- it is a form of a dried whole areca nuts used mostly for trade. Full-grown nuts are dried for 1 and half months under sunlight, later de-husked and advertised as whole nuts. Whereas Chali is available in different sizes and shapes⁴

4. Parcha (pareha) – ripened areca are divided vertically into 2 different splits and dehydrated under sunrays for a week and later dried and dehusked. Kernels are then taken out and dried. It is more prevalent in Kerala & Karnataka. Husk removal can be done manually operated dehusking machine³. Machines can be used to dry the nuts.

5. Kalipak- made from areca nuts that are 7 months old, they are again dehusked, chopped into small parts, cooked and layered with kali later it is desiccated. Kali when applied 3- 4 times more it gives it a glossy appearance.

6. Iylon- raw nut is sliced and dried.⁴

7. Nayampak- immature nut cut transversely and dried.⁴

8. Nuli –unripened form of nuts⁵

9. Supari –Areca nut that is dehydrated is mixed with different flavours and later exported. Necessary oils have been mostly added in grated coconut to evade microorganism growth⁵.

10. Tamol - Fermented areca nut prevalent in east of India⁶

Smokeless tobacco and tropics

Khaini

More popular in north India and with advancing abuse of the product younger population is exposed to the product. Tobacco and calcium hydroxide are carried in double ended metal container independently. Tobacco and slake lime is mixed on palm and placed in buccal or labial vestibule or on dorsal surface of tongue. It is sucked unlike other products which are chewed.^{6,7}

Pattiwala tobacco

Sundried tobacco leaves can be used with lime in it or they can be consumed minus calcium hydroxide.

Manipuri tobacco

It includes tobacco, slaked lime and finely chopped areca nut & camphor, cloves^{8,9}. Manipuri tobacco is more prevalent in Uttar Pradesh's villages and have greater occurrence of head and neck carcinoma as well as leukoplakia¹⁰.

Mishri

Black, cooked crushed tobacco is consumed by taking it out from the packet with finger and applying it on to the teeth and gums. It has been found that 22 villages in Maharashtra use this.

Zarda

The tobacco leaves are stewed in water along with lime and spices till it evaporates. Remaining tobacco is dehydrated and coloured by vegetable dye.

Kiwam

De-stalked tobacco leaves stewed in water along with rose petals water & some flavours this is made into a thick paste or when dried they form pills.¹¹

Gudakhu

It is a sort of paste of tobacco in powder form and molasses with additional ingredients¹².

Shammah

It is a combination of powdered tobacco leaves, lime and undetermined constituents.

Toombak

Tobacco of sudan that is in smokeless form, dried tobacco leaves of nicotinarustica and lime.^{13,14}

Paan and quid

Paan is referred to betel leaf in india, although it refers mainly to a combinationwrap in betel leaf¹⁵.

Paan

Paan in india means a combination of areca nut with some other ingredientcovered in a leaf of piper betle plant¹⁶. Therefore, the practice of eating the quids arefrequentlycalled as paan chewing⁸. Paan is derived from hindi language. It is prolonged tradition in countries like india and its neighbouring countries to chew betel leaf adding areca nuts, lime paste as well as Katha (brown powder/paste) with several local and indigenous disparities¹⁷.

Betel quid is a very specific type of quid, it may or may not contain tobacco as its ingredient and is always wrapped in betel leaf¹⁷. Therefore, betel quid means a blend of ingredients that are consumed with betel leaf.

Paan has countless customs and ingredients.¹⁸

It comprises:

- Tobaccopaan (tambakupaan)- Betel leaves with tobacco powder and flavours
- Areca nut paan also known as paansupari, paan masala, or sadapaan –betel leaves with crudely cut areca nuts.
- Sweet paan (methapaan)- betel leaf without arecanut and tobacco, filled with coconut, fruit, rose petals preserves and spices often given with a cherry on top.
- Trento (colarnopaan)- It is betel nut with a taste of minty flavours, it is consumed with potatoes
- Deshimahoba- it is plain paan with added flavours and is more commonly used in west bengal.
- Maghai and Jagannath – it is a type of banarasipaana
- Chigrayale – more common in south of india where paan is made out of delicate betel leaves
- Ambadi and Kariyele - tobacco in thickened dark paan leaves¹⁹

Three major different type ingredient of betel quid comprises:

- Areca nut
- Some Portions of betel vine
- Calcium hydroxide.

Additionally supplementary components like catechu, antibacterial spice cloves (a spice), tobacco as well as coconut might or might not be used.

Catechu (katha) – It is imitative from soaked wood of tree Acacia carechu. It is resin extract. It is more famously called as gambir in Malaysia which is made ofbranches and foliage of bushUncaria gambiri.⁸

While serving the leaf is taken off from the wrapped cloth , lime paste with kattha is applied on the surface with toppings of cardamom, along with coconut pieces etc

The leaves are folded into triangular shape known as gilouree then is prepared to eat. On some rare circumstance, gilouree can be enveloped in a fragile silver leaf. Before serving it a silver pin is put in it so that it does not unwrap and place in a casket known as khaasdaan..⁷

In India readymade form of betel is also available known as beeda.²⁰

Papua, New Guinea- betel nut is chewed by placing of a part of areca nut in the oral cavity, people with no teeth usually grind the areca nut with the help of mortar and pestle. The nut is masticated for half minute following which betel vine leaf and lime is added to the mixture.⁸

Java and Bali in Indonesia- They usually use shredded tobacco to clean their teeth, it is an age old custom there. They use a large stem which is placed in the sulcus of oral cavity and is left hanging outside the mouth. Betel nut after chewing adds a red colour to saliva and quid, it is because of the high pH of mixture due to the presence of slaked lime

Taiwan- it is raw form of areca nut which is as big as an olive and is over and over again combined with betel leaves¹⁰. Taiwanese quid consists of areca nut with piper betel inflorescence in addition to liquid lime which is enveloped in a piper betel leaf.⁹

Guam- raw areca nuts have been masticated alone or by adding leaves in it.

Pacific islands of Palau- a half of areca nut is masticated at a time which is usually are in a raw form with calcium hydroxide and tobacco that is enveloped in betel leaves.

Cambodia- Quid with tobacco, it is used by gently massaging it over the teeth after putting in mouth betel leaves.

Quid

Quid is, "a matter or combination of substance put in mouth or chew and outstanding in make contact to mucosa frequently sustaining one basic ingredient tobacco as well as areca nut in uncooked or an artificial or process form".^{21,22}

Detailed components of the combinations should be mentioned so as to define its variability²³.

There are following different classes of quid:

Class I (areca nut quid)

Quid without any tobacco ingredient is called as paan masala or supari^{23,24,25}

Paan masala is made of areca nut with catchu cardamom, slaked lime with various natural and artificial flavouring substances.

Supari it is a word used in Indian terrain for the areca nut and is a mix of numerous flavours whose chief base is areca nut which is cut into small pieces.

It is marketed in attractive foil packs and tins.

Class II -- quid + tobacco products with no areca nut.

Class III - quid + areca nut + tobacco. It is also called as gutkha (AQ + T) (Hazarey VK, 2007).

Gutkha is a type of chewable paan masala with flavoured tobacco is added³. Gutkha is amalgamation of betel nuts along with tobacco and perfumed spices with or no lime²⁷.

The different classes of quid are unique to each other and one substance can relate to one kind only. Betel nut quid is a mixture of areca nut, and tobacco leaf with lime paste²⁹. It can be chewed by adding tobacco to it or even without tobacco. When quid is consumed with no tobacco it is categorised as Group 1 carcinogen³⁰

The betel vine leaves comprise eugenol which is a volatile aromatic but unsaturated substance that stimulates CNS and has minor quantities of an alkaloid which has cocaine like characteristics. It does not contain tobacco but still has capabilities of producing mutagenicity and carcinogenicity characteristics. It also raises the oral cavity pH from 5-6 to an acidic pH 3-4 within 60 seconds once consumed³¹.

Betel quid may or may not be composed of tobacco³. Betel leaves is a risk factor for oral pre cancers³² and has a high tendency of OSMF compared to leukoplakia as well as erythroplakia⁵.

It is quite relevant to understand the constituents of the products and also the manner in which it is practiced. Following are the few reasons to why it is necessary to demarcate the importance

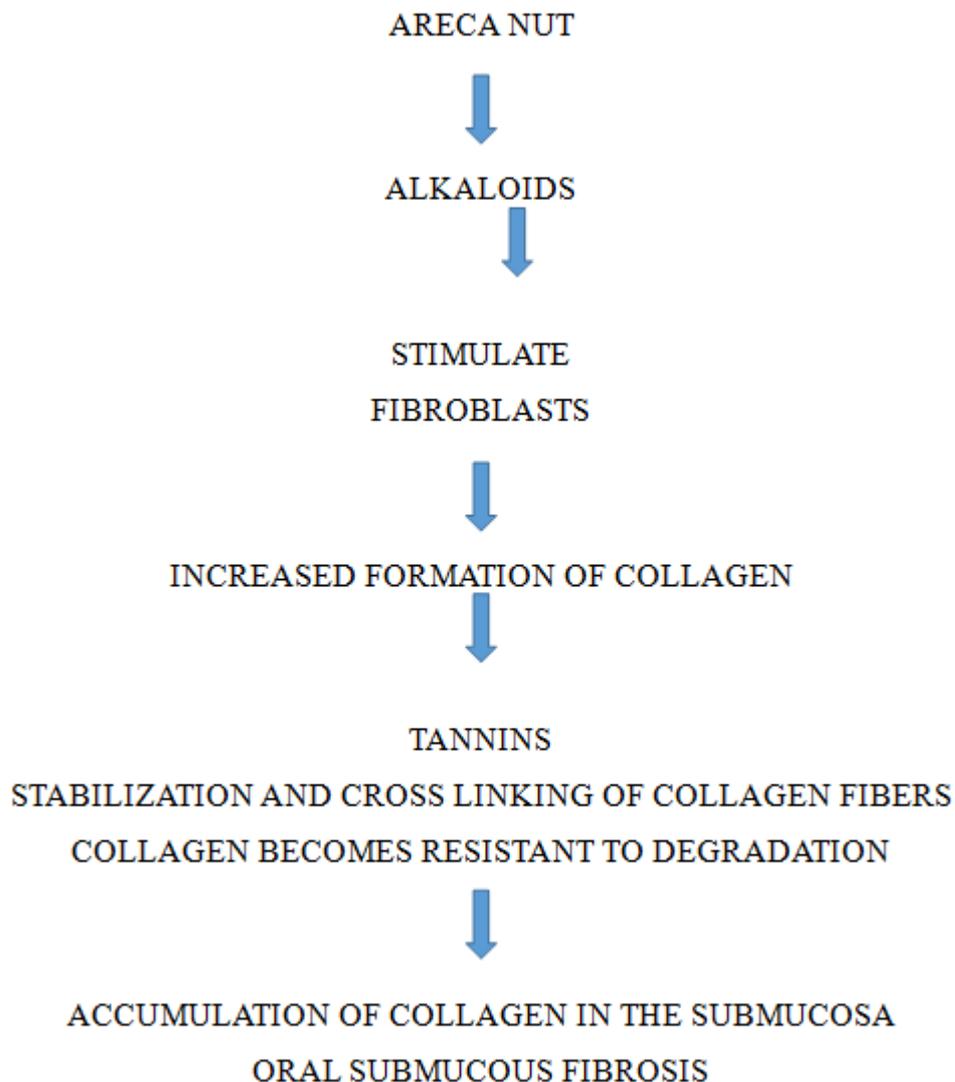
- Areca nut consumers will often demonstrate lesions in oral cavity which are related to the nut.

- Many cases of tobacco induced lichenoid like reactions have been reported that bear a resemblance to lichen planus. There are certain difference with the help of which we can differentiate between lichen planus and lichenoid reaction.
- Tobacco and slaked lime chewers mucositis, snuff induced lesions of oral mucosa, areca quid lesions, etc bear resemblances however they show varied clinical and histopathological appearances⁷.
- Leaving apart the varied clinic pathological picture, with adding or removing ingredients can lead to huge difference in properties of carcinogenesis and mutagenesis. For ex, betel quid with inflorescence piper betle has a greater carcinogenic potential than the normal paan masala⁹.

Detrimental effects of betel quid

A quid is normally consist of a betel leave, areca nut with lime. Its ingredients differed depending on various cultures in different part of the planet. Provisional on the local preferences of additional substances those items are added to the paan. Few chief constituents like tobacco as well as areca nut alone or in different groupings minus using the betel leaves.

Zain et al 1999 “ a consensus workshop held in 1996 recommended that word ‘quid’ would be distinct as ‘ a thing or combination of things, keep in between teeth that usually contain either of the two essential ingredient, tobacco or areca nut.



Chemical ingredients of areca nut

Major chemical ingredients of areca nut is:

- a. carbohydrates,
- b. fat, proteins,
- c. crude fibres,
- d. polyphenols,
- e. Alkaloids, mineral matter.

Polyphenols are the substance responsible for an astringent taste in teeth's oral cavity. Hence, to eradicate the mordancy the brokers often add some lime to the betel quid.

The most relevant chemical constituent among all the ingredients are the alkaloids. The nut was shown to comprise at least six related alkaloids out of which only five have been identified these are arecoline, arecaidine, and guvacoline.

Nitrosamine results in each of the areca alkaloids are formed by nitrosation of the alkaloids in crushed nuts processed in the mouth and in particular under the acidic environments establish in the intestinal, in the existence of nitrous oxide created by microbial activity.

From place to place, more than 600 million betel quid chewers are recorded. Chiefly in South East and South Asia, India, China, Taiwan, Papua New Guinea, and Solomon Islands. Consumers chew betel quid for its sense of well being and euphoric experience that the individual gets after eating it, it also heightens alertness so most of the truck drivers consume it so that they can drive for long durations. It also reduces hunger and improves digestion. Betel quid is not only an addictive substance but also is a carcinogenic ingredient."The International Agency for Research on Cancer (IARC) revealed that the BQ constituents, with and no tobacco condiments, is categorised as a group I carcinogen in individuals, and increased risks be recognised for head and neck cancers ". Additionally, Areca Nut is as well a group I carcinogen for humans. In many trials conducted in animals there has been a durable link observed between the betel quid and occurrence of cancers of head and neck region.

The main chemical constituents causing the carcinogenic effects and how?

Betel quid as we know is categorised as group I hazard by the many international Agency. The effects are not only controlled to oral cavity. The consequence of quid can be seen on various other body systems. Following is the detailed explanation on the theories that were produced that describe the effects caused by the particular chemical constituent present in the betel quid.

Effects involving tooth-

1. Dental Attrition-

Areca nut are quite abrasive in nature, with prolonged chewing of it may wear off the occlusal as well as incisal surface of teeth, enamel is thinned out exposing the dentin below which results in sensitivity. The amount of areca nut, along with occurrence of use and length of habit is directly proportional to the amount of tooth wear and sensitivity.

2. Dental Caries-

Betel quid leads to un-aesthetic stain on the tooth surface and the colour usually depends on the ingredients used. This stain forms a coating on the tooth surface, and acts a physical barrier between the tooth and the oral micro flora. So it acts similar to that of a varnish.

3. Periodontium—

Gingivitis- betel quid chewers are more prevalent to gingivitis due to the lack of oral hygiene by the consumers, and poor oral hygiene will lead to deposition of plaque increasing

the chances of gingivitis. (Amarasena et al.,2003)

4. Oral Submucous Fibrosis—

A pre-cancerous disorder and is chronic, resistant disease. Following are various hypothesis proposed in relation with the constituents of betel quid and occurrence of OSMF.

A. Copper hypothesis-

“When an areca nut is chewed for more than 15 minutes it will increase the amount of soluble copper in oral cavity which increases the movement of enzyme lysyl oxidase, This is a copper-based extracellular enzyme that catalyzes the cross-linking of elastin. Lysyl oxidase is concerned in many fibrotic diseases, including oral submucous fibrosis, being pathogenesised.”

B. Chang, Y.-C, et al., (2002a) theorised that “Any disruption in homeostatic balance between the synthesis as well as degradation of extracellular matrix and/or changed fibrolysis that result in fibrosis throughout quid chewing leading to osmf, and attempts are made to evaluate the role of metalloproteinase tissue entered in pathogenesis of the disease”. TIMP-1 level is found to be more than fibroblasts from buccal mucosa. In the study carried out by Chang they concluded that arecoline increases TIMP-1 expression and inhibits matrix metalloproteinases (MMP) in human buccal mucosal fibroblasts *in vitro*.

5. Effects on nervous system-

Areca nut is composed of psychoactive alkaloids and it moves the nervous system in prejudiced users, can induce excess salivation and perspiring. It can also stimulate sympathoadrenal response (Chu, 2002). The plasma concentrations of adrenaline and noradrenaline have shown significant rise in the areca nut chewers (Chu, 1995a)

Chu (2001) hypothesized that the alkaloids can act both on central and peripheral nervous system. It was noted the arecoline voluntarily moves across the blood brain block (Asthana et al 1996) and causes increase in the acetylcholine levels in the brains of animals by 150-250%. Areca nut has stimulant effect as well as inhibition effect; arecaidine and guvacine have been inhibitors of GABA acceptance (Johnston et al., 1975; Lodge et al., 1977). Therefore, areca nut adds to relaxation over and done with its anxiolytic effects.

Betel quid aggravates the extrapyramidal symptoms like marked stiffness, tremors and distressing akathisia in those patients who are on neuroleptic medication (Dealh, 1989). Meige's syndrome in this syndrome it is a risk factor (Behariet *al.*, 2000). Palpitations, nausea, and facial flushing with feelings of warmth in the skin are early symptoms of areca chewing and 0.5–2°C rise in skin temperature (Chu 1993). Cardiac levels rise with or without habituations, but systolic blood pressure only rises in consumers of novices (Chu, 1993). Low intake of areca-nut can stimulate the sympathetic nervous system and high doses stimulate both the sympathetic as well as parasympathetic nerves *in vivo*.

6. Effect on cardiovascular system- Effect of areca nut on cardiovascular system is mostly due to the increase in TIMP-1 independent of increase related to MMP-9, May contribute to pathogenesis of diseases characterized by increased fibrosis, such as liver cirrhosis. Arecoline itself causes dose-dependent intensifications in the expression of TIMP-1 in human fibroblasts along with an inhibition of MMP-2 secretion, a occurrence pertinent to the risk for oral mucous fibrosis. In the existence of coronary heart ailment, with vasoconstriction cause by areca nut could upsurge the risk of heart attacks.

7. Effects on respiratory system- “Since 1912 it is known that Arecoline induces contraction of bronchial muscles (Trendelenburg, 1912)”. Decreased levels of FEV in one second is seen in patients having custom of eating areca nut and are not asthmatics.

8. Effect on the GI system-Users reported that quid pacifies the absorption and

evades constipation; Colonic soft might is activated by its muscarinic things. Peptic ulceration, though, is enlarged in betel quid chewers. (Ahmed et al. 1993). Areca-nut extracts reduce halitosis, possibly by reducing methyl mercaptan volatility via arecal phenolic derivatives; and calcium hydroxide plays a pivotal role in its utility (Wang *et al.*, 2001).

9. Effect on pregnancy_ in a systematic review conducted on areca nut use and adverse pregnancy outcomes by Manarangi de silva et al concluded that there was a noteworthy correlation among low birth weight of infants and use of betel nut by the mother at the time of pregnancy. However, only few cases were reported showing this relation further studies should be done in order to confirm that areca nut is harmful to use during pregnancy.³⁰

Customary BQ eating has remained specially connected to the manifestation and progression of oral premalignant disorders and oral/pharyngeal carcinomas. In several zones, tobacco-free quid, frequently in aggregation as the practice of tobacco, encourages primary malignancy incidence for definite superior aero digestive tract carcinomas and affects the frequency outline of cancer site. Additionally, epidemiological research have discovered that persistent BQ use results in increased risk of oesophagus, hepatocellular cancers (HCC), cirrhosis of liver, metabolic syndromes, leading to type 2 diabetes mellitus (DM), CVDs, heart ailment in women, long-lasting kidney ailment, and detrimental effects on death from carcinoma & from other reasons. BQ compulsion is connected to anemia, preeclampsia, and acute severe asthma.

Necessary action that is a need of the hour

India has successfully made many policies in order to curb the extensive use of areca nut in day to day life of a common man. Yet these policies are being misused and the effects are diluted as day pass by. India has not able to increase the testing capability for tobacco products. Once these laboratories are established we will be able to control the type of product being used in a particular region. As India is a vast country mixed with several cultures and we know that areca nut is used in different ways in these countries thus, we need a customised action plan for each area.

Awareness is also quite essential. Mainly educating the age group which is more prone to the areca nut abuse should be targeted. Education plays a pivotal role in managing the areca nut abuse control. In India the age group which is being exposed to these products is 10- 18 years old, so a child protection services should be established to monitor the children who have started using tobacco since childhood and they should be taken to rehabilitation centre till they stop the use of tobacco.

Molecular biology of areca nut and oral carcinogenesis

In many studies it has been noticed that the oral tumours are affected by physiological impact by chemicals, which is in contrast to the statement whether the consequences of therapy might summarise the physiological environment of oral cells which are in contact with areca nut substances.

Because of this matter, many studies chose to use a crude extract from areca nut. It can be produced by two different methods, depending on the amount of areca nut husk, by this means it results in ripe areca nut extract and tender areca nut extract which is used for research purposes. We know the extract from areca is tumour inducing in the derma of mouse and it induces sarcoma in the connective muscle of rats. It also causes hepatocellular cancer in rat on gastric intubation which suggests that areca nut extract has the capacity to stimulate the carcinoma. Molecular evidences beneath the areca nut extract induced carcinogenesis are comparable to the aspects that are responsible for carcinogenesis. However the amount of dose administered for the treatment of oral carcinoma cell lines is much higher than the routinely administered concentration of areca nut.²⁹

2. DISCUSSION:

Areca nut induced lesion in oral cavity are more commonly reported at the places where the quid is placed. In a long time abusers there can be chewer's mucositis that is areca nut colour encrusted change at the place where quid is placed. More prevalent diseases occurring in relation to areca nut are oral leukoplakia and osmf, together are potentially malignant disorders. Oral carcinomas arise from such lesions. In 1985, IARC concluded that areca nut solely cannot be responsible for causing cancer. However there are some studies that link oral cancer with pan chewing without tobacco. More awareness should be instilled in the people's mindset concerning the detrimental results of areca nut chewing and the long tradition of having areca regularly after dinner should be stopped without any hindrance in traditional values. This article is an effort is made to accumulate entire detrimental effects of areca nut and implication is specified on how it effects various systems of our body. Also, we have stated the ingredients of areca nut accountable for the carcinogenic effects.

3. CONCLUSION:

The present article mainly focuses on the history of areca nut to know the origin of the nut into the daily life of human being, the chemical constituents of it that are mainly responsible for causing harmful effects on various systems of the body. It is always considered better to have complete knowledge before providing any treatment to the patient. As there is always a key to the treatment and complete cure of the disease if we know the exact substance that is responsible in causing the pathology.

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