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Review Article

Areca nut and betel quid without tobacco are neither harmful nor carcinogenic: scientific evidences

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ABSTRACT

Arecanut, the seed of *Areca catechu* palm, is the most popular chewing substance in most parts of the world. This nut is also called betel nut in several countries as it is invariably chewed along with the leaf of betel (*Piper betle*) vine and lime (calcium hydroxide). This chewing mixture is popularly called betel quid. Lots of scientific papers and reports highlight arecanut chewing as carcinogenic to humans. If such observations are really true, the results should be repeatable and consistent in other identical studies. Strangely, several researchers could not arrive at that conclusion in similar studies. Such research papers are retrieved and presented in this review. While going through several reports which highlighted arecanut chewing as dangerous or carcinogenic, it was observed that in most of such papers the conclusions were drawn hastily and lots of lacunae observed in the methodology. Most important one is that in several such studies, data were collected on mixtures of chewing substances such as betel quid, pan masala, gutkha, etc but the authors wrongly titled the paper as arecanut or betel nut chewing as if all such chewing mixtures contain only arecanut. Contamination and adulteration of arecanut, the dosage of arecanut extract used in such experiments were some of the other factors for this ambiguity. These findings underscore the need for specific interventions to address the issue more scientifically.

Keywords: Arecanut, Betel nut, *Areca catechu*, Betel quid, Non carcinogenic activity

INTRODUCTION

Arecanut, also called betel nut in some countries, is the seed of the palm *Areca catechu* L. of Arecacea family. This palm is mainly grown as an agricultural crop in India and several other south and south eastern countries such as Sri Lanka, Bangladesh, Myanmar, Indonesia, Philippines, China, etc. Arecanut is invariably used for chewing either alone or in combination with several other materials such as the leaf, inflorescence or stem of betel vine (*Piper betle* L.) and lime (calcium hydroxide). Such mixtures are generally in wet, perishable forms and called betel quid (BQ). Some people also add a piece of tobacco (*Nicotiana tabacum*) leaf, a smear of catechu extracted either from *Acacia catechu* Willd. or *Uncaria gambier* Roxb., certain spices, sweeteners, essences, etc., to this BQ as per the preferences of individuals.[1] In early 1970's variety of packaged dry, relatively non-perishable forms of commercial preparations of chewing products, containing arecanut, slaked lime, catechu, condiments, powdered tobacco, etc., entered the market by different trade names such as gutkha, pan masala, mawa, zarda, khaini, etc.[2]

Chewing of arecanut is not of recent origin. There are reports showing the evidences of arecanut chewing in the fossil remains of human skeletons dated back to about

3000 BC from Duyong Caves in the Philippines.[3] In Vietnam also, the fossil remains of humans of Bronze Age (1200-3300 BC) with stains of arecanut in their teeth were reported.[4] In India and several other countries such as China, Bangladesh, Philippines, etc., arecanut is used in different ancient system of medicines.[5-8] Even WHO, in its book entitled "Medicinal Plants of Papua New Guinea" cited *Areca catechu* palm as a medicinal plant having as many as 25 different medicinal values.[9] All such medicinal properties, including anticancer activity of arecanut are now well validated with proper scientific evidences.[10-12]

In spite of such vast medicinal values of arecanut, there are certain reports which categorised arecanut as carcinogenic and its chewing lead to oral cancer in humans. However, several other researchers could not reproduce the same results in their identical experiments. Some of such reports are retrieved, cited and discussed here.

STUDIES ON ANIMALS

In a paper published during 1974 it was reported that the evidences for the carcinogenicity of arecanut and betel quid (BQ) are equivocal.[13] In their study, application of acetone as well as dimethyl sulphoxide extracts of either arecanut or BQ (mixture of 50 g of arecanut, 100 g of betel leaf and 4 g of lime) on the bare skin of mice for nearly two years did not exhibit any carcinogenic activity both in normal as well as in immune suppressed conditions, and were not found either to initiate or to promote tumour growth. Strangely, in their experiments, all 10 animals treated with 5 µg of the chemical carcinogen 3-4, Benzpyrene (BP), developed skin tumours within 39 weeks of treatment, whereas those mice treated with 5 µg of BP along with arecanut extract at 0.1 ml of 2% solution were free of tumours during that period. This showed that arecanut even suppressed the development and growth of tumours induced by BP.

Even direct feeding of arecanut did not induce any carcinogenic activity both in rats and mice. When individual components of BQ (20% dry arecanut powder, 20% dry betel leaf powder, and 20% dry arecanut powder mixed with 1% calcium hydroxide) was fed orally to ACI strain of rats for more than 300 days, no malignant tumour was noticed in any of the experimental as well as in control group with normal diet.[14] Further, it was noticed that the amount of food consumption and rate of weight increase in all experimental groups were almost similar to those of the control group.

In a study conducted on Swiss albino mice by oral feeding of arecanut powder daily for 12 months, it was reported that feeding of such powders at a dose up to 1.0 g/ kg bw/ day failed to induce any tumours.[15] The visceral organs, including liver and lungs, from arecanut-treated mice also did not exhibit any tumours. According to the same authors, on an average, an adult human being masticate up to 0.5 g of arecanut/ kg bw/ day. This human dose is much on the lower side than the maximum safe dose of 1.0 g/ kg bw/ day reported for mice.

In another study, when mice were fed daily by saccharin coated betel nut (arecanut) powder at 10% concentration for 40 weeks, neither it induced any cancer nor potentiated the carcinogenicity of the chemical carcinogen, 1,4-dinitrosopiperazine.[16]

In Taiwan, BQ generally contains a bisected fresh green arecanut (with husk) sandwiched with a spike of betel wine and a brown paste containing slaked lime and catechu. Even such BQs were found safe for animals. In a study conducted with such BQ on hamsters it was noticed that painting of chemical carcinogen, DMBA (7,12-dimethylbenz(a) anthracene) on the cheek pouches of hamsters for 6 weeks developed 70% carcinoma, whereas, insertion of BQ (1.5 g) alone in the cheek pouch of hamsters during the entire period of experiment for 52 weeks or treatment of DMBA for 10 weeks after keeping betel quid for 52 weeks did not lead to any tumor growth.[17] This proves that Taiwan BQ is not carcinogenic but even reduces the effects of the chemical carcinogen.

Arecanut extract was also reported to suppress the growth of certain tumors in xenograft animal models. Studies conducted on hepatocellular carcinoma (HCC) xenograft mice, the arecanut extract (ANE) reduced cell viability, increased cell apoptosis and suppressed tumour progression in HCC (HepG2, HepJ5, and Mahlavu cells) xenograft mice in dose-dependent manner. Tumor sizes and their growth rates in the ANE-treated group significantly decreased by > 50% compared to the vehicle-treated group. Tumor weights in the ANE-treated group dramatically decreased to 30% compared to the vehicle control.[18] Furthermore, the histopathological examination of vital organs such as liver, heart, lung and kidney of healthy mice subjected to intraperitoneal injection of water (control) or ANE (40 mg/kg) twice per week for 30 days did not show any significant difference between mock and ANE group. This demonstrated that the arecanut extract may be a new potential compound for HCC therapy.

The chemotherapeutic effect of ANE on other cancers such as oral squamous cell carcinoma (OSCC) was also reported. In a study conducted on rats, the incidence of OSCC at the end of 23 weeks of observation in animals treated with 30 ppm of cancer inducing chemical, 4-nutriquinoline-1-oxide (4NQO) in drinking water for 12 weeks was 71.43%, whereas when the aqueous extract of arecanut was provided in drinking water at doses of 500 and 1000 mg/kg BW to such 4NQO treated animals subsequently for 10 weeks the incidence of OSCC was nil. Further, in animals treated with 4NQO there was a significant reduction ($p \leq 0.05$) in body weight at the end of the experimental period but there was no such reduction in body weight in those rats treated with ANE following 4NQO treatment.[19]

The silver nanoparticles (AgNPs) of arecanut extract showed even better antitumor activity. In a study conducted on Dalton's Ascites Lymphoma (DAL) induced mice, treating with biosynthesized AgNPs of arecanut extract, a significant decrease in tumor volume was reported. At the same time there was significant increase in life span of such AgNPs treated mice when compared to non-treated animals. Acridine orange staining and DNA fragmentation studies on harvested tumor cells showed higher level of cytotoxicity in AgNPs treated group when compared to ANE treated group.[20]

Arecoline, the most active chemical component of arecanut, was also reported to be anticancerous in mice up to a maximum dose of 50 mg/kg/day.[21] In that study conducted on H1299 and K5612 xenograft mice, intraperitoneal injection of Arecoline hydrobromide for 20 days, very clear dose dependent reductions were reported in the size and weight of tumors with significant inhibition of tumor growth at the maximum tolerated dose of 50 mg/kg/day of the arecoline without any obvious off-target effects.

STUDIES ON HUMANS

In a case-control study conducted at the Cancer Institute, Madras (now Chennai), India to find out the aetiological factors responsible for oral squamous cell carcinoma it was reported that pure betel and nut chewing did not show any significance.[22] In that study it was reported that as much as 85% of cheek carcinoma patients were tobacco, betel and nut chewers against 12.5% in the control group. On the other hand, only 8.7% of cheek cancer patients were pure betel and nut chewers as against 51.8% in the control. In another paper published by the same authors during 1963 on the aetiological factors responsible for the carcinomas of the upper alimentary tract (such as lip, buccal mucosa, tongue, pharynx and oesophagus) in the human population (882 cases and 400 controls) of three South Indian States of Madras (now Tamil Nadu), Andhra Pradesh and Kerala, it was reported that pure betel and nut chewing was not a significant factor in the aetiology for such cancers in both male and female population.[23] The number of betel and nut chewers was reported to be less in the study group than in the control group for all sites in both sexes.

Almost similar observations were made in a case-control study conducted at Bangalore, India.[24] The study was conducted on cancers of the oral cavity by utilising data from the population-based cancer registry with 348 cases of cancers of the oral cavity and matched with same number of controls. The authors clearly mentioned "chewing of pan (consisting of betel leaf, areca nut and lime) without tobacco did not increase the risk of oral cancer". There were no significant variations for cancer incidences (p=0.36 for males, 0. 17 for females and 0.114 for both sexes together) between chewers of pan without tobacco and non-chewers.

While analysing the risk factors for the incidence of oro-pharyngeal cancers, chewing of sole betel nut was not reported to be the cause for such problem (p=0.0842).[25] In that case-control study conducted in Nagpur, India it was noticed that the number of people chewing betel nut alone was 5 in cases and 7 in controls (mean of two groups). Chewing BQ without tobacco was 7 in cases and 9 in controls. On the other hand, number of people chewing BQ with tobacco was 52 in cases and 20 in controls.

Chewing of arecanut and betel leaf without tobacco did not produce any tumours even in the oesophagus of humans.[26] Regional Medical Research Centre (ICMR), Dibrugarh, Assam, India reported cancer of the oesophagus as the most commonly diagnosed cancers in males and ranks second in females in Assam, north-eastern India. Chewing of betel nut, with or without tobacco and prepared in various ways, is a common practice in that region. In a case–control study conducted by them to estimate the risk of different habits of betel nut chewing with additives for the incidence of oesophagus cancer, the authors reported that the ORs associated with taking just green or red betel nut with betel leaf but without tobacco are 1.9 (p=0.089) for males and 0.5 (p=0.422) for females, neither differed significantly from the risk in non-chewers.

Studies conducted in certain other countries also reported similar results. In a case-control study conducted at Papua New Guinea using 143 cases and 477 controls, the adjusted odds ratio for the incidence of oral cancer between non chewers and chewers of betel quid without tobacco was reported to be 1.0:1.1.[27] In ex chewers the ratio was 1.0:0.57; for current occasional chewers 1.0:0.98 and for current daily chewers it was 1.0:1.29. All differed insignificantly.

In Taiwan where people generally chew betel quid without tobacco a cohort study conducted jointly by the Department of Health, Taiwan and the Population Studies Centre, University of Michigan on 6,503 participants reported no significant variation in cancer deaths between non chewers and chewers of betel quid.[28] The overall adjusted hazard ratio for cancer deaths was 1.0:1.03 (p=0.86) between non chewers and chewers of betel quid. For cancers in oral cavity and oesophagus the hazard ratio was 1.0:1.6 (p=0.24); for stomach 1.0:0.78 (p=0.59); for liver 1.0:0.61 (p=0.19); for lung 1.0:1.15 (p=0.60) and others 1.0:1.10 (p=0.673); none differed significantly.

Chewing BQ without tobacco was also reported to be safe for pregnant women. In a largest cohort study conducted to find out the effects of BQ chewing on pregnant women at Thai-Myanmar border no adverse pregnancy outcomes were reported.[29] The study was conducted on 7,685 pregnant women during 1997 to 2006. Of them 2,284 (29.7%) were free from BQ chewing or smoking habits, 2,484 (32.3%) chewed only BQ and no smoking, 438 (5.7%) were not chewing but only smoking and 2,479 (32.3%) were habituated both BQ chewing and smoking. For chewing, pieces of ripe arecanut along with a leaf of

betel and lime were used without tobacco. No adverse pregnancy effects were observed in BQ chewers compared with non-chewers, further supporting lack of effect of BQ chewing. Average birth weights of babies born for chewers and non-chewers of BQ were 2,991 g and 2,940 g, respectively. Such figures for other parameters such as miscarriage were 7.5% and 7.7%; for stillborn 1.1% and 1.0%; for neonatal death 1.4% and 1.4% and for the incidence of malaria 13.7% and 18.0%, respectively. Smoking without BQ chewing had a dose related effect on miscarriage. On the other hand, BQ chewing along with smoking reduced the adverse effects of smoking on birth weight, exhibiting the beneficial effect of chewing BQ without tobacco. Such larger population cohort studies have more power to reflect the actual situation as they are less prone to selection bias.

Chewing of sole arecanut was not found to be the cause for Oral submucous fibrosis (OSF). In a hospital-based cross-sectional study conducted on 1000 OSF patients in Nagpur, India over a period of five years, it was noticed that exclusive arecanut chewing habit was significantly more in females than in males (p=0.0001). Majority of males (97.59%) were chewing mixed products such as kharra, gutkha, etc. Further, the data revealed that the prevalence of OSF was significantly less (p=0.0001) in females than in males.[30] This shows that the incidence of OSF is directly proportional to the mixed chewing habits rather than to sole arecanut chewing.

In a field study conducted on arecanut chewers in Dakshina Kannada District of Karnataka, India during 2005, though sole arecanut chewers were rare, oral examination of 59 sole arecanut chewers, not even a pre-cancerous lesion was reported in them.[31]

Almost similar observation was made in a study carried out in Pune, India.[32] In that study, sole arecanut chewers were only 34 in numbers. Among them OSF was noticed only in two (5.88%) cases. These authors further hypothesised that sole arecanut chewing cannot be a factor for OSF. Instead, some other ingredients in the chewing mixture might be responsible for that.

In order to find out the effect of arecanut chewing on human health, a house to house survey was conducted in certain major arecanut chewing areas of Kasaragod District in Kerala and Dakshina Kannada, Shivamogga and Uttara Kannada Districts in Karnataka, India.[33] Only the traditional chewers who chewed fresh arecanut or betel quid without tobacco (BQ) or with tobacco (BQT) were included in this study. Those who chewed products where the actual ingredients are not disclosed fully (such as pan masala, gutkha, etc) and those indulged in smoking tobacco and drinking alcohol were excluded. The non-chewers were treated as control. Data were collected from 917 people. Among them, 232 were non chewers, 288 were BQ chewers and 393 were BQT chewers. People chewing sole arecanut were very rare with only four persons indulged in that habit. Hence, such people were included in the group of BQ chewers, making the total figure as 292. When the health status of different groups observed, it was seen that among the 232 people in non-chewing group 72 (31.03%) persons reported certain health problems, whereas, in BQ chewing group, only 40 (13.70%) and in BQT chewing group 71 (18.07%) people reported such problems. No significant difference was noticed between non-chewers and chewers of BQ or BQT groups with regard to various health issues except for tooth problem which was significantly more in non-chewers when compared to BQ and BQT chewers. No cancer patient was reported in BQ chewers, but there were 0.25% cases in BQT chewers and 0.86% cases in non-chewers. This clearly shows that BQ chewing is not harmful but good for health.

Almost similar results were reported in another study where chewing of farm fresh betel quid was reported to be a healthy practice.[34] Among the 522 people surveyed, there was a marked reduction in health problems reported by both BQ and BQT chewers when compared to non-chewers. Of the 197 people surveyed in non-chewers, 61 (30.96%) reported one or the other health problems, whereas, in BQ chewers, out of 120 people 22 (18.33%) and in BQT chewers out of 205 people 40 (19.51%) reported such problems. Multiple (more than one type) health problems were also more in non-chewers when compared to either BQ or BQT chewers. Of the 61 people who reported health problems in non-chewers 17 people (27.87%) suffered from more than one health problems, whereas only 22.73% of BQ chewers and 17.50% of BQT chewers suffered from multiple health complications. Not a single instance of cancer was reported in chewers of farm fresh BQ or BQT, but there were three such reports (one liver, one breast and one colon cancer) in non-chewers.

DISCUSSION

Arecanut is already used in certain ancient system of medicines in several countries such as India, China, Bangladesh, Philippines, etc.[5-8] Further, the present observations also reflect that arecanut and BQ without tobacco are neither harmful nor carcinogenic. However, several recent reports are contrary to this.[1] Scientific observations if they are really true and authentic the results should be repeatable. If arecanut chewing is really dangerous or carcinogenic, it should have been, unambiguously, reflected in the studies cited in this paper. When the results are antithetical, something is wrong in the methodology and hence, it may be addressed more scientifically.

On close examination of several reports which highlighted arecanut chewing as dangerous, it looks as if in most of them the conclusions were drawn hastily and several pitfalls or lacunae were observed in such studies.[35-37] Most important one is that in several research papers the title itself was erroneous. The studies were carried out mostly on mixtures of chewing substances such as betel quid, pan masala, gutkha, etc but the authors titled the paper as

arecanut or betel nut chewing as if all such chewing mixtures contain only arecanut.[38] It is also observed that several review papers and reports which highlighted arecanut chewing as carcinogenic to humans, did not notice such glaring mistakes.[37]

Some of the research papers with erroneous titles are: 'Etiology of oral submucous fibrosis with special reference to the role of arecanut chewing' is a research paper wherein the authors wrote "In Bhavnagar town, there was a sudden upsurge of OSF condition 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 arecanut (mawa) chewing habit in that area".[39] That means the authors wrongly interpreted 'mawa' as arecanut! 'Relationship between site of oesophageal cancer and areca chewing and smoking in Taiwan' is the title of another research paper wherein in the materials and methods column the authors wrote "Those who had regularly chewed betel quid for at least 6 months were defined as betel chewers".[40] This shows that the authors mistook betel quid as arecanut and titled the paper as areca chewing. 'Prevalence of oral submucous fibrosis among betel nut chewers dental patients of Patna' is the title of another research paper wherein the authors gave the inclusion criteria for betel nut chewers group as those chewing areca nut/pan/gutkha for more than 3 years. From this it becomes clear that the authors failed to differentiate between arecanut, pan and gutkha.[41]

Even several review papers repeated the same. 'Areca nut use: an independent risk factor for oral cancer' is the title of a review paper wherein the authors highlighted arecanut as an independent risk factor for oral cancer, but reviewed mostly the papers on chewing mixtures and not on sole arecanut.[42] 'The oral health consequences of chewing arecanut' is the title of another review paper wherein it is mentioned "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". This shows that the authors mistook quid as arecanut.[43] 'Areca nut an ignored carcinogen of Asian continent in a nutshell' is a mini review paper wherein the authors cited only six papers in the reference column and none of them was on sole arecanut.[44] There is an exhaustive review entitled 'Areca nut and oral cancer: Evidence from studies conducted in humans' wherein the abstract says "The risk of oral cancer increases in a dose-response manner with the daily number of quids consumed and the number of years chewing".[45] That means these authors considered quids as arecanuts!. Ample number of research and review papers can be seen in the literature with such misleading titles. The irony is that in none of such studies the chewing substance was authenticated as arecanut by a plant scientist!

Certain reports even declared arecanut as carcinogenic to humans without any valid data on sole arecanut chewers. The IARC, in association with WHO published a monograph entitled "IARC monographs on the evaluation of carcinogenic risks to humans' volume 85 betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines" wherein arecanut was declared as carcinogenic to humans, group 1.[1] In that exhaustive report there is a chapter on studies of cancer in humans. If arecanut is really carcinogenic to humans, the authors should have been substantiated that statement in this chapter by providing valid scientific evidences on sole arecanut chewers. But such data are not there. Though more than 60 papers are cited in this chapter, only in one paper (Wasnik et al) sole arecanut chewers data are given, that too there is no significant difference in cancer incidences between cases and controls (4% and 6%, respectively) in arecanut chewers.[25] Still, the monograph declared arecanut as carcinogenic to humans, group 1!

'Global burden of oral cancer in 2022 attributable to smokeless tobacco and areca nut consumption: a population attributable fraction analysis' is a paper published in The Lancet Oncology.[46] In the findings column it is mentioned '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'. In the heading it is mentioned as smokeless tobacco and arecanut consumption, but in the findings it is given as smokeless tobacco or arecanut consumption. There is no clarity whether the data are for the consumption of smokeless tobacco or for arecanut or for both together. Further, it is observed that in India the authors collected data from GATS (Global adult tobacco survey) which according to those authors contained information on chewers of betel quid with tobacco, sada or surti, and khaini, among others. There is no explanation how the authors got data on sole arecanut chewers from such tobacco survey.

CONCLUSION

The above review shows that there is ample evidence to declare arecanut as non-carcinogenic. It is also evident that in most of the reports which tagged arecanut chewing as dangerous or carcinogenic to humans, the methodology used was totally unscientific. In most of such papers the actual chewing substance was not authenticated by any experts in plant science which lead to wrong identification of the chewing substance as arecanut. Most of the data were collected from the experiments conducted on chewing mixtures such as betel quid, pan masala, gutkha, etc but blamed arecanut for the ill effects. This gave the wrong impression that arecanut is the culprit. Hence, proper epidemiological or clinical studies on sole arecanut chewers are warranted to know the actual health effects of arecanut chewing on humans.

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