ARECANUT OR BETEL QUID CHEWING WITHOUT TOBACCO HAS NO ADVERSE EFFECT ON HUMAN HEALTH: RESEARCH COMPILATION

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Introduction

Arecanut, the fruit of the oriental palm, *Areca catechu* L. (Palmaceae family) is an important commercial agricultural product of India with a share of nearly half of global production of this commodity. Apart from India, arecanut is cultivated in several other South Asian and Southeast Asian countries such as Indonesia, China, Myanmar, Bangladesh, Sri Lanka, Thailand, Bhutan, Nepal, Malaysia, etc. (Cherian and Manojkumar, 2014). In several parts of the world arecanut 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. Otherwise arecanut has nothing common with betel vine. This nut is also known as '*Supari*' in most parts of Northern India.

Since time immemorial, arecanut is being used for chewing along with betel leaves and certain condiments in several parts of the world including India, China, Bangladesh, Maldives, Papua New Guinea, Solomon Islands and several Southeast Asian countries as this mixture is believed to have lots of medicinal properties (Aman, 1969). This chewing mixture is commonly called as pan or betel quid. In India, the use of arecanut has been quoted as early as 1300 BC by Sisu Mayana in 'Anjana Chaitra' (Ishwara Bhat and Rao, 1962) and the practice of its chewing started from 650 BC as mentioned by Magha in 'Shishupala Vadha' (Rao, 1982). In other countries such as Vietnam, the antiquity of arecanut even goes back to Bronze Age (Oxenham *et al.*, 2002). Later on, the Moguls introduced lime and the Portugese introduced tobacco for chewing along with pan (Shankar Bhat, 2008). In India, arecanut and betel leaf are considered very sacred and no ceremonial function is complete without using them.

In ancient systems of medicines such as Ayurveda, Unani, etc., arecanut is used to cure different ailments in several countries such as India, China, Bangladesh, Philippines, etc. (Kirtikar *et al.*, 1918; Peng *et al.*, 2015; Rahmathullah *et al.*, 2009; Tavera, 1901). The World Health Organization (2009) has already listed out as many as 25 beneficial effects of *A. catechu*. Most of these folklore medicinal properties of *A. catechu* are now validated with proper scientific data (Jaiswal *et al.*, 2011; Amudhan *et al.*, 2012; Rashid *et al.*, 2015). In China, the use of arecanut is so popular that there are as many as 30 medicines prepared using arecanut as one of the ingredients for the treatment of several human disorders (Peng *et al.*, 2015).

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In spite of all these medicinal uses of arecanut, some researchers highlighted that arecanut chewing is dangerous and may even cause cancer (IARC, 2004). This is only one side of the coin. On the other side, there are several scientific reports which say that arecanut or betel quid chewing without tobacco is not dangerous for humans. Ironically such reports are not at all cited or discussed anywhere. Hence an attempt is made to collect such scientific evidences and present in this paper.

Betel quid chewing without tobacco did not increase the risk of oral cancer

Shanta and Krishnamurthi (1959) reported that betel quid chewing without tobacco did not induce any cancer in human mouth. In a case-control study conducted by them to find out the etiological factors responsible for oral squamous cell carcinoma in humans it was noticed that only 8.7% of people in cheek carcinoma cases were chewing betel quid without tobacco, but in the control there were 51.8% such chewers. On the other hand 85% of the cancer patients were chewing betel quid with tobacco while there were only 12.5% of such chewers in the control population.

In a study conducted at the Kidwai Memorial Institute of Oncology, Bengaluru, India on the occurrence of cancers of oral cavity in pan (betel quid) chewing people in that region, Nandakumar *et al.*, (1990) did not observe any increase in oral cancer in those people who chewed pan without tobacco. Of the 348 cases of cancers of the oral cavity and an equal number of controls the relative risk due to pan chewing without tobacco was found to be non significant with both males and females ($p = 0.36$ and 0.17, respectively) whereas it was significantly more ($p = 0.001$) with pan chewing with tobacco.

In certain South East Asian countries such as Papua New Guinea, Taiwan, etc., the betel quid generally does not contain any form of tobacco. It consists of a bisected fresh green arecanut husk of about 4-5 months of age, with its endosperm removed but sandwiched with a spike of betel vine and a brown paste containing slaked lime and catechu. Thomas *et al.* (2007) conducted a case control study in Papua New Guinea using 143 oral cancer cases, the adjusted odds ratio for the incidence of oral cancer between non chewers and chewers of betel quid was reported to be 1.0:1.1. In ex-chewers such 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. The differences were not found significant.

In a recent study conducted on the health issues of arecanut and betel quid chewers in three districts of Karnataka, India (Dakshina Kannada, Shivamogga and Uttara Kannada) Jose *et al.* (2018) did not notice any significant difference in health status between arecanut chewers and non-chewers. The study was conducted on more than 700 arecanut or betel quid chewers. The chewing substances consisted of either fresh ripe arecanuts or processed red types, one or two green leaves of *P. betle*, a small amount of slaked lime (calcium hydroxide) and in some cases a piece of tobacco. Majority of the respondents thought that chewing had beneficial effects like increasing taste, digestion, pleasure and reducing tooth pain.

Even pre-cancer lesions were not noticed in the mouth of arecanut chewers

Not only cancer but also pre-cancerous lesions were not noticed in the oral cavity of those who chewed either arecanut alone or betel quid without tobacco (Srihari *et al.*, 2010). In a study conducted by these authors on 59 people who chewed either arecanut alone or betel quid without tobacco in Dakshina Kannada District of Karnataka, neither any cancer nor any type of pre-cancerous lesions were noticed in their mouth. In this area the people prepare betel quid with fresh ripe arecanut, one or two leaves of *P. betle* and little slaked lime. In this study the authors did not notice any ill effects on chewing such betel quids. Further, many respondents stated that chewing promoted productivity and concentration at work. Many chewers used areca to facilitate bowl movements and to reduce intestinal worms. Several people used this to reduce tooth pain and prevent decay. An interesting observation was that no informant in this study thought that use of arecanut without tobacco was harmful to user's health.

Exclusive arecanut chewing habit has no effect on the prevalence of OSF

Oral Submucous Fibrosis (OSF) is considered to be a potential malignant disorder of human oral cavity. In a hospital based cross-sectional study conducted at the Govt. Dental College, Nagpur, India with 1000 (830 male and 170 female) patients it was noticed that in men patients only 18% were having exclusive arecanut chewing habit whereas 82% of the patients were chewing either kharra, gutkha or tobacco. On the other hand, in female patients 82% were having exclusive arecanut chewing habit, the rest (18%) chewed either kharra, gutkha or tobacco. When the incidence of OSF in such people was recorded it was observed that the incidence was 83% in males and only 17% in females (Hazarey *et al.*, 2007). This clearly shows that the incidence of OSF was directly related to chewing of kharra, gutkha or tobacco but not to exclusive arecanut chewing habit.

It was hypothesized that arecanut chewing alone cannot cause OSF in humans (Sachin *et al.*, 2013). According to the authors certain other ingredients of betel quid such as slaked lime which might cause inflammation in oral mucosa leading to the initiation of OSF.

Chewing BQ did not increase the risk of cancer in oesophagus

In a case-control study conducted at the Regional Medical Research Centre (ICMR), Dibrugarh in Assam on 176 cases (120 males and 56 females), it was noticed that chewing of both green (immature) and red (mature) arecanut with betel leaf but without tobacco did not increase the incidence of cancer in oesophagus (Phukan *et al.*, 2001). The adjusted risks associated with the chewing of such BQ for the incidence of cancer in oesophagus was found to be 1.9 in males and 0.5 in females, both were reported to be non significant.

Even chewing pan with tobacco was reported to be safe as far as the incidence of cancer in oesophagus was concerned. In a case-control study carried out on 267 patients in the Regional Cancer Centre, Thiruvanantapuram, India with the cancer of oesophagus, no significant difference was observed between

pan-tobacco chewers and non chewers (Sankaranarayanan *et al.*, 1991). When the relative risk was 1.9 for non chewers, it was 0.64 to 1.03 for males and 0.50 to 1.20 for females depending on the chewing frequencies which ranged from less than 5.0 to more than 10 per day. An interesting observation was that in people with a chewing duration of between 11 and 30 years there was a lower risk of cancer in oesophagus with the relative risk of nearly 0.51 for males and 0.68 for females.

BQ chewing without tobacco is not associated with mortality due to cancer

In Taiwan, people generally chew betel quid without tobacco. In a cohort study conducted jointly by the Department of Health, Taiwan and the Population Studies Centre, University of Michigan on 6,503 participants no significant variation in cancer deaths was noticed between chewers and non chewers of betel quid (Lan *et al.*, 2007). The overall adjusted hazard ratio for cancer deaths was 1.0:1.03 between non chewers and chewers of betel quid. For cancers in oral cavity and esophagus it was 1.0:1.6; for stomach 1.0:0.78; for liver 1.0:0.61; for lung 1.0:1.15 and others 1.0:0.71; all differed insignificantly.

BQ chewing without tobacco has no effect on pregnancy and child birth

Chewing betel quid without tobacco did not induce any adverse effect on pregnancy and child birth. In a largest cohort study conducted so far on the effects of chewing BQ without tobacco on pregnant women no adverse pregnancy outcomes were noticed. The study was conducted at Thai-Myanmar border on 7,685 pregnant women during 1997 to 2006 (Chue *et al.*, 2012). Among those pregnant women, 2,484 (32.3%) were chewing only BQ (without tobacco) but no smoking; 2,479 (32.3%) were chewing BQ (without tobacco) and also smoking; 2,284 (29.7%) were neither chewing BQ nor smoking and 438 (5.7%) were only smoking without chewing BQ. For preparing BQ, pieces of ripe arecanut along with a leaf of betel (*P. betle*) and lime (calcium hydroxide) were used without tobacco. No adverse pregnancy effects were observed in BQ users without tobacco compared with non users (average birth weights of babies for chewers and non chewers of BQ (without tobacco) were 2,991g and 2,940g, respectively. The data for chewers and non chewers of BQ for miscarriages 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. Interesting observation was that, in those people who were only smoking but not chewing BQ had a dose related effect on miscarriages. Further, BQ (without tobacco) use along with smoking reduced the adverse effects of smoking on birth weight. The average birth weight of babies for the people who were only smoking was 2,828g and for those who were smoking as well as chewing BQ the birth weight of babies was 2,891g. From this it is clear that chewing BQ without tobacco has no adverse effect on pregnancy and child birth, rather it reduced the adverse effects of smoking.

Almost similar results were reported in a second largest population study wherein 2,700 pregnant women who chewed BQ without tobacco were observed in Papua New Guinea (Maria *et al.*, 2015). It was reported that there was no change in pregnancy loss or congenital abnormalities between BQ chewers (without

tobacco) and non chewers. Analysis of 1,769 infant birth weights showed that it was 2,996 g in BQ chewers and 2,966 g in non chewers. Such larger population cohort studies have more power to reflect the actual situation as they are less prone to selection bias.

Anticancer effects of arecanut

There are certain scientific reports which say that arecanut is also anti-carcinogenic. In a study conducted by Anajwala *et al.* (2010) on the anticancer effects of arecanut it was reported that the aqueous extract of this nut arrested the growth of human MCP-7 breast cancer cells. The 50% inhibition concentration (IC50) value of this extract was calculated to be 775.1µg/ml. Similarly, the extract of arecanut was found to be cytotoxic against the human gastric cancer (SGC-7901) and liver cancer (SMMC-7721) cell lines with the IC50 values of 5.1 and 9.3µg/ml, respectively (Xing *et al.*, 2010).

In a study conducted to ascertain the carcinogenic, cocarcinogenic, initiating, promoting or inhibiting activities of betel quid without tobacco (a mixture of 50g of cured arecanut, 100g of betel leaf and 4g of calcium hydroxide) it was reported that the application of betel quid extract to mouse skin for nearly two years did not exhibit any carcinogenic activity (Kumari *et al.*, 1974). Similarly, non-carcinogenicity was observed with the extracts of arecanut also, that too both in normal and immune suppressed conditions. Further, the authors also reported that neither of these products either initiated or promoted tumor growth. A significant observation in their study was that the arecanut extracts even exhibited a retarding and/ or inhibiting effect on the development and growth of tumors induced by a known carcinogen 3:4, benzpyrene. These results are again substantiated in a recent study carried out by Fan *et al.* (2016) on mice where it was reported that the arecoline hydrobromide, one of the most common and active ingredients of arecanut, inhibited the activity of the enzyme ACAT1 (acetyl-CoA acetyltransferase) which lead to attenuation of cancer cell proliferation and tumor growth.

Discussion and conclusion

In spite of all these research results, there are several reports which highlighted arecanut as carcinogenic (IARC, 2004). If we go through the papers cited by them, it is seen that most of the results are drawn hurriedly with improper scientific methodology. Keshava Bhat *et al.* (2018) has reviewed several such papers and listed out the major lacunae existed in such studies. The authors commented that in several reports there is no clarity in the terminology used. Most of such experiments were conducted either with betel quid, pan masala, kharra, gutka or similar other commercial preparations wherein the ingredients are not clearly disclosed, but the authors mostly titled the papers as arecant chewing, totally ignoring the actions of other ingredients used in preparing such chewing mixtures. This gave a wrong impression that arecanut is the sole culprit. In several other studies unusual methods of applications (by way of injections or by direct application of arecanut extracts to cultured cells) were adopted and the results were simply correlated with arecanut chewing habits and claimed arecanut chewing is dangerous. In certain others, very high doses of arecanut extracts or the concentrated arecoline were given to laboratory animals and arrived at the

conclusion that arecanut chewing is dangerous for humans without taking into consideration the actual dose of arecanut that humans generally chew. For that matter anything in high dose is dangerous. Some researchers arrived at the conclusion with very small sample size. Certain others even avoided the discussions on the role of other ingredients used in the preparation of betel quid, to ascertain the quality (especially contaminations and adulterations) of arecanut and other chewing products they used in their experiments. All these together were found responsible for such ambiguous results (Keshava Bhat *et al.*, 2017; 2018). The irony is that most of the publications which highlighted arecanut chewing as dangerous did not look into these factors at all, but simply blamed arecanut for all the ill effects. Hence, before arriving at any conclusion on the health effects of arecanut chewing it is necessary to consider and discuss all these aspects in detail.

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