



## Arecanut (*Areca catechu* L.) chewing and cancer: conflicting research findings

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**ABSTRACT:** Commercially, arecanut is the endosperm of the fruit of areca (*Areca catechu* L.) palm. This nut also called as betel nut or supari, is mostly used for chewing along with several other ingredients either in the form of fresh betel quid or packaged dry chewing products. The habit of chewing arecanut or betel quid is not of recent origin but goes back to two to three thousand years. Ancient systems of medicines like Ayurveda, Unani, Homeopathy, etc., consider arecanut as medicine to cure several diseases in countries such as India, China, Bangladesh, Philippines, etc. But in recent years, several research reports and review papers were published highlighting arecanut chewing as dangerous and even cause cancer. On the contrary, there are ample scientific evidences published in several research journals saying arecanut chewing did not produce any bad effects on health; rather it reduced several health problems including cancer. Such papers are collected, presented and discussed in this report. Scientific observations if they are really true, the results should be repeatable. But in this case it is not. When the results are contradictory, something is wrong in the methodology. Scientific community may closely look into these aspects and adopt proper scientific methodology before carrying out any research on arecanut chewing.

**KEY WORDS:** Arecanut, *Areca catechu*, betel nut, betel quid, chewing habits, human health, cancer

### I. INTRODUCTION

Arecanut is the fruit of a slender and tall oriental palm, botanically called *Areca catechu* L. of Palmae (Arecaceae) family. This fruit is a berry, of the size of a hen's egg, with a central single round or oval shaped endosperm or nut, weighing around 8.3 g (dry weight) covered by a fibrous thin pericarp or husk which is green in colour when unripe becomes orange-yellow when ripe[1]. This nut is also called as betel nut or supari

in several parts of the world. Commercial arecanut is mostly the endosperm of areca fruit, without its husk. In most parts of India this nut is marketed with some minimum processing. One type of marketed arecanut is called 'red supari' which is obtained by boiling and drying unripe dehusked nuts at different stages of their maturity. Another type is 'white supari' which is obtained by mere drying ripe nuts and dehusking them afterwards[2].

### 1.1 Chemical composition of arecanut

The chemical composition of arecanut varies depending on their maturity.[3] In general, arecanut contains polyphenols, polysaccharides, fibres, alkaloids, minerals, fats and fatty acids. Polyphenols, total ash and free fatty acids decrease with maturity, whereas polysaccharides, alkaloids, fats and fibres increase with maturity of the nut. Alkaloids, especially arecoline, which is totally absent in very tender arecanut slowly increase to 0.06% in tender arecanut and to 0.22% in ripe nuts; whereas polyphenols, which are 43.85% and 47.94% in very tender and tender nut stages, respectively decrease up to 17.81% in ripe nuts[3].

Apart from arecoline, other minor alkaloids of arecanut are arecaidine, guvacine, guvacoline, isoguvacoline and arecolidine[4]. All the major chemical constituents of arecanut, including arecoline decrease significantly while drying and storing with husk as whole nuts[5] and also while roasting, soaking and boiling compared to fresh mature nuts[6]. Arecanut also contains Vitamin B6 and Vit C[7]. As many as 36 minerals are already recorded in arecanut[8]. Among the fatty acids, lauric (19.5%), myristic (46.2%), palmitic (12.7%), oleic (6.2%), linoleic (5.4%) and hexadecenoic acids (7.2%) are the most prominent ones. Minor proportions of stearic, decanoic and monoethylenic C12 and C14 acids are also present[9]. Among the proteins, peroxidases such as catechin, epicatechin and procyanidin B1 are the major ones [10].



## 1.2 Arecanut chewing habits

Arecanut is mostly used for chewing as it is believed to contain lots of medicinal properties[11]. This nut is seldom chewed alone, but mostly along with the leaf of Piper betle (betel leaf) vine, slaked lime (calcium hydroxide) and certain condiments[8]. This chewing mixture is commonly called as betel quid. The constituents of betel quid vary from region to region and from country to country. In several parts of the world including India the arecanut is mostly used after removing its husk, either as ripe nuts, mature dried nuts or as processed immature / tender nuts. In certain other parts of the world such as Papua New Guinea, Taiwan, etc., people generally use the immature nuts of areca palm along with their husk intact instead of using only the endosperm. In India, people use the leaf of P. betle for preparing betel quid, but in certain other countries such as Taiwan, Papua New Guinea, etc., people mostly use either the inflorescence of P. betle instead of its leaf[8].

In recent years, different types of dry, ready to use chewing products containing arecanut as one of the ingredients have flooded the market in different brand names and forms like sweet supari, pan masala, gutka, mava, etc. These forms of chewing products have taken over the practice of chewing traditional forms of fresh betel quid in most of the areas especially in urban regions, as such dry forms of chewing products are available in sachets of easy to carry forms[12]. The main problem with such dry chewing products is that the chewers may not know the quality of arecanuts or the actual substances used in such preparations.

Arecanut chewing is not of recent origin but goes back to more than two to three thousand years as evidenced in the archaeological investigations carried out in Vietnam[13]. In India, the use of arecanut has been quoted as early as 1300 BC by Sisu Mayana in 'Anjana Chaitra'[14] and the practice of its chewing started from 650 BC as mentioned by Magha in 'Shishupala Vadha'[15]. Later on, the Moguls introduced slaked lime and the Portuguese introduced tobacco for chewing along with arecanut and betel leaf[16].

## 1.3 Arecanut and human health

Arecanut is used in certain ancient systems of medicines such as Ayurveda, Unani, Homeopathy, etc., to cure several diseases in countries such as India, China, Bangladesh, Philippines, etc[17-20]. Most of such folklore medicinal properties of arecanut are now validated with proper scientific data[21-24]. In China, 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[18, 25]. The World Health Organization has already listed out as many as 25 beneficial effects of arecanut[26].

In spite of all these medicinal uses of arecanut, there are several research reports highlighting arecanut as dangerous to human health and may even cause cancer[8]. On the other hand, there are enough scientific reports to show that arecanut or betel quids without tobacco are not dangerous. But such reports are seldom cited or discussed properly in most of the scientific literatures. For example there is a research paper entitled 'Inhibitory activity of Areca catechu on the development of mouse skin tumours induced by the chemical carcinogen 3,4, benzpyrene' published way back in 1974[27]. It is strange to note that even the reviews made later on by several leading organizations and recommended arecanut as carcinogenic did not cite or discuss this paper at all[8]. The present work is a discussion on several such sidelined, but important, scientific evidences which clearly showed arecanut as non carcinogenic.

## II. EXPERIMENTS ON LABORATORY ANIMALS

### 2.1 Arecanut or betel quid extracts neither induced nor initiated or promoted cancer

In a study conducted on A/Isc strain of mice it was reported that arecanut alone or in combination with betel leaf and lime without tobacco (the common chewing form of betel quid) were neither carcinogenic nor initiated any carcinogenic activity[27]. The study was conducted by applying both acetone and dimethyl sulphoxide extracts of arecanut and betel quid (0.1ml of 2% solution) on the bare skin of such mice for two years. Further, another important finding was that the arecanut extract did not show any cancerous activity even in immune suppressed conditions. In this study, arecanut extract was prepared by using 100g of arecanut and betel quid extract was prepared by using 50g of arecanut, 100g of betel leaf (the leaf of P. betle) and 4g of calcium hydroxide (slaked lime).

### 2.2 All common types of arecanuts were found safe at normal dose

In another study conducted on Swiss Albino mice, all the popular types of arecanut, viz., Ripe unprocessed and sun dried (R-UP-SD); Ripe, processed and sun dried (R-P-SD); Unripe, processed and sun dried (UR-P-SD); Ripe-unprocessed-sun dried-water soaked (R-UP-SD-WS) and Ripe-unprocessed-undried water soaked



(R-UP-UD-WS) arecants were found safe in normal dose of about 1g/kg bw/day[28]. Among these, the first three, R-UP-SD (commonly called as 'White whole supari'), R-P-SD (commonly called as 'Red whole supari / Rashi idi') and UR-P-SD (commonly called as 'Red split supari / Hassa') are common in the southern states of India and the last two, mainly the water soaked arecanuts (R-UP-SD-WS and R-UP-UD-WS) are popular in the North Eastern states of India. Experiments were conducted both by feeding arecanut powder mixed diet as well as by feeding arecanut paste five days a week for 12 months. The arecanuts were pulverised into fine powder and fed to mice along with their normal diet at 0.25%, 0.5% and 1.0% concentrations twice a day. Arecanut paste was prepared and fed to mice orally, again twice a day, with the help of a dispenser at levels of 0.25g/kg, 0.5g/kg and 1.0g/kg body weight. No papilloma / carcinoma was reported in any of the treatments involving two times applications of 0.25 and 0.50 concentrations; i.e., 0.5 and 1.0 % or 0.5 and 1.0 g/kg bw/day[28].

### 2.3 Neither arecanut nor the traditional form of betel quid showed any carcinogenic activity

In a study undertaken to examine the actual carcinogenic activity of different ingredients of betel quid, individually and in combination, to ACI rats no tumors were noticed[29]. In one group, dry powder of arecanut alone was mixed at 20% concentration with normal diet, in another group the rats were given a combination of 20% arecanut powder and 1% calcium hydroxide (slaked lime) and in the third group only the dry powder of betel leaf was mixed at 20% concentration in the normal diet and fed to rats for 480 days. A control was also maintained by feeding only the normal diet. Important finding was that no malignant tumour was noticed in any of these treatments.

Such non carcinogenic activity of common betel quid ingredients was also reported in hamsters[30]. This study was carried out for two years, or until the animals were moribund, by inserting each component of betel quid separately and in combination, in bees wax pellets as carrier, on the cheek pouches of hamsters and compared the results with those obtained by inserting known carcinogenic hydrocarbons. Malignant tumours were not noticed in any of the ingredients or in any of the combinations tested, though there were 23 (41%) cases of malignant tumours in 56 carcinogenic hydrocarbons treated animals. Of the 39 animals treated with pulverised arecanut embedded in bees wax, only one animal (2.6%) showed inflammation of the cheek pouch in the

point of attachment, but there were two (5.56%) such cases in the control where only bees wax was inserted on 36 animals[30]. This clearly shows that arecanut alone is neither carcinogenic nor inflammatory.

The Taiwan betel quid (BQ) consisting of fresh green immature arecanut (with husk), a spike of betel (*P. betle*) vine, slaked lime and catechu (*Acacia catechu*) also did not show any carcinogenic activity in hamsters[31]. The authors reported that the betel quid chewed in that region was not a significant carcinogen. The study was conducted by inserting 1.5g of such pulverised betel quid in the cheek pouches of hamsters for 52 weeks and also by applying a chemical carcinogen 7,12-dimethylbenz(a)anthracene (DMBA). Application of DMBA alone produced carcinoma after four weeks of treatment but no carcinoma was developed even up to the end of the experimental period of 52 weeks in the treatment involving only betel quid ingredients. Further, application of DMBA for nearly 10 weeks after prior treatment with betel quid for 36 to 52 weeks did not develop any cancer[31]. From this it is clear that BQ neither induces any cancer but successfully suppresses the carcinogenic activity of DMBA.

Such non carcinogenic activity of Taiwan betel quid consisting of 450g of immature whole arecanut (green nuts with husk intact), 120g of the inflorescence or fruit of betel vine and 50g of slaked lime in the cheek pouches of hamsters was also reported in another study[32].

### 2.4 Arecanut coated with saccharin also did not induce any cancer

In a study conducted by feeding saccharin coated arecanuts to C17 mice it was reported that such feeding neither caused any cancer nor potentiated the carcinogenicity of the known chemical carcinogen 1, 4-dinitrosopiperazine[33]. The study was performed on four groups of mice. Group I consisting of 34 animals fed with standard diet; Group II of 32 animals fed with an experimental diet containing saccharin coated arecanut powder at 10%; Group III of 29 animals given 0.2 ml aqueous solution of 0.1% 1,4-dinitrosopiperazine by intubation daily and Group IV consisting of 24 animals fed a combination of the diet containing saccharin coated arecanut powder at 10% together with intubation of 1,4-dinitrosopiperazine. All experiments were continued for 40 weeks along with standard diet and water ad libitum and observed for their full life time. The authors did not notice any carcinoma either in those mice fed with standard diet or in those fed with only saccharin coated arecanut, but



noticed in group III and IV. Further, the tumours were more common in group III than in group IV. The authors concluded by saying that the diet of saccharin coated betel nut (arecanut) even reduced the carcinogenic potential of 1,4-dinitrosopiperazine[33].

## 2.5 Pan Masala without tobacco was also found safe

In experiments conducted on inbred hairless mouse strain (designated as S/RVCri-ba) no carcinogenic effect of pan masala were noticed[34]. The most popular brand of pan masala available in Mumbai was used in these experiments. The skin tumorigenesis of such chewing material was studied by repeatedly painting the mouse skin with 50mg of pan masala extract for 40 weeks and forestomach and esophageal tumorigenesis was studied by administering 50mg of pan masala extract through gavage for six months. No tumor development was noticed in any of these experiments.

## 2.6 Anti - tumor/cancer properties of arecanut and arecoline

In an experiment conducted on laboratory mice, arecanut extract (0.1ml of 2% of both acetone and dimethyl sulphoxide extracts) clearly inhibited or retarded the development and growth of tumors induced by the chemical carcinogen 3:4, benzpyrene[27]. Topical painting of 5µg benzpyrene on bare skin of mice induced tumors from the 30<sup>th</sup> week of its application and all the animals treated with this chemical showed tumors before 40<sup>th</sup> week of its application, but when arecanut extract was applied along with this chemical carcinogen, no tumor growth was noticed up to that period. This shows that arecanut has anti-tumor effect.

Even arecoline, one of the active chemical components of arecanut was reported to arrest the growth of cancer cells[35]. The authors reported that the arecoline hydrobromide (AH) inhibited the activity of the enzyme ACAT1 (acetyl-CoA acetyltransferase 1) leading to the attenuation of cancer cell proliferation and tumor growth in xenograft mice. In the drug treatment experiments through intraperitoneal administration of AH there was a dose dependent reduction in the size of tumors developed in H1299 xenograft mice and there was complete inhibition of tumor growth at the maximum tolerated dose of 50mg/kg/day of AH. Similar results were also observed using K562 leukemia cell xenograft mice treated with AH for 20 days. It was also noticed that AH did not affect the cell viability of CD34+ progenitors isolated

from bone marrow samples from a healthy donor while it decreased cell viability of human primary leukemia cells[35].

In a study conducted on human hepatoma cell line, HA22T/VGH it was reported that arecoline at a dose of 100 µg/kg or less caused cytoskeletal changes followed by aneuploidy and apoptosis in them but not on normal hepatocytes[36]. In this study, the viability of cancer cells decreased in a dose dependent manner after 24h treatment with arecoline at the above concentration, but even after 72h of such treatment on normal hepatocytes the viability of such normal cells did not change significantly. Based on these findings, the authors even suggested that arecoline at that dose might be useful in the treatment of hepatoma.

## 2.7 Arecanut is not toxic

The toxic effects of arecanut was studied on Sprague Dawley Rats by oral administration of a single dose of the ethanolic extract of this nut at four different concentrations, i.e., 0.1g/kg bw, 0.72g/kg, 5.36g/kg and 10g/kg bw[37]. No toxic effects were noticed in any of the treatments. Even the microscopic observations did not show any histopathological alterations in any of the internal organs. The authors even suggested that the ethanolic extract of arecanut could be used as chemopreventive agent as it was already reported that the ethanolic extract of arecanut showed antiproliferative activity and induced apoptosis on T47D and MCF-7 cells.

In another study conducted on Sprague Dawley Rats by administering a single dose of arecanut aqueous extract by gavage at a concentration of 15,000mg/kg body weight no abnormal pathological finding was noticed in any of the internal organs[38]. No macroscopic abnormal anomalies were noticed in the internal organs as well. The oral LD<sub>50</sub> was thus calculated to be more than 15,000mg/kg body weight of the animal.

In a study conducted on Wister Albino Rats by one time gavage feeding of water extract of arecanut at doses of 50mg/kg bw, 300mg/kg, 2000mg/kg and 3000mg/kg bw no gross pathological changes were noticed in the treated animals[39]. The histological observations of the internal organs, such as lung, heart, liver, intestine and kidney were found to be apparently normal. The LD<sub>50</sub> values of raw arecanut extract were calculated to be 2321.52mg/kg and 2257.52mg/kg body weight for male and female rats, respectively.





### III. STUDIES ON HUMAN CANCER CELL LINES

#### 3.1 On Dalton's Ascites Lymphoma (DAL)

In vivo study carried out on the antitumor activity of biosynthesized silver nanoparticles (AgNPs) of arecanut extract against Dalton's Ascites Lymphoma (DAL) it was reported that treatment of AgNPs of arecanut significantly decreased tumor volume and increased the life span of DAL induced animals significantly[40]. The study was made by comparing AgNPs treated group with aqueous treated group in DAL induced mice. Biosynthesis of AgNPs using arecanut extract resulted in an average particle size of 80nm. This study also revealed a significant increase in apoptosis of DAL tumor cells treated with AgNPs when compared to control and aqueous treated groups. The authors concluded that arecanut derived AgNPs are novel cost effective, potent antitumor agents and the presence of abundant polyphenols such as tannins and arecoline (alkaloid) in aqueous extract of arecanut along with the biosynthesized AgNPs confers the synergistic antitumor activity against DAL induced mice[40].

#### 3.2 On human gastric cancer cells

In a study on the cytotoxic effects of 11 phenolic compounds isolated from arecanut extract by MTT method, it was reported that compound 11 'jacareubin' was significantly more effective than other phenolic compounds as cytotoxic agent against the human gastric cancer cell line (SGC-7901) and human liver cancer cell line (SMMC-7221) with the IC<sub>50</sub> value of 5.1 and 9.3 µg/mL, respectively[41]. Of the total 11 compounds isolated using column chromatography only the compound 11 'jacareubin' showed strong cytotoxic activity and other compounds were inactive. In another study arecanut extract reduced cell viability, increased cell apoptosis and suppressed tumor progression in hepatocellular carcinoma (HCC) xenograft mice while such extract did not induce any liver tumor in nude mice[42]. The IC<sub>50</sub> value for arecanut extract was around 20-30 µg/ml after 48 h of treatment indicating that the extract effectively inhibited the proliferation of HCC cancer cell lines, HepG2, HepJ5, and Mahlavu cells[42].

#### 3.3 On oral squamous carcinoma cells

The arecanut extract induced apoptosis in human oral squamous carcinoma cell lines HSC-2 and HSC-3 but not on normal cell lines[43]. Using the ethanol extract of arecanut the authors noticed significant increase in apoptosis of both these cells after their exposure to arecanut extract for 24 and

48 hours. However, the extract showed higher toxicity on HSC-3 cells than on HSC-2 cells with the IC<sub>50</sub> value of 164.06 µg/ml and 629.50 µg/ml, respectively for these two cell lines. Thus, the authors postulated that arecanut could not only be used as a chemotherapeutic agent against human oral squamous cell carcinoma cells and also to potentially reduce the side effects of chemo radio therapy[43].

#### 3.4 On human breast and colon cancer cells

Studies made on the cytotoxic effects of arecoline and the ethanolic extract of arecanut by MTT assay on human breast cancer MCF-7 cells revealed that arecoline at 10-500 µg/ml concentration caused a growth inhibition of 8-73% in cancer cells with an IC<sub>50</sub> value of 180 µg/ml, whereas the ethanolic extract of arecanut caused a growth inhibition of 13-84% on cancer cells at 25-100 µg/ml itself during 48h of treatment with IC<sub>50</sub> value of 77 µg/ml[44]. The extract also inhibited cell proliferation and induced apoptosis. Arecanut extract (both ethanolic and its chloroform fraction) was also observed to increase the cytotoxic / apoptotic effect of doxorubicin, one of the chemotherapeutic agents used in cancer treatment, on human colon cancer WiDr cells[45]. In this study, conducted in vitro, the addition of both these extracts of arecanut to doxorubicin showed a strong synergistic effects on cell growth inhibition when compared to individual applications. The apoptotic cell population increased from 20% while treated with doxorubicin 500nM alone, to 25% when doxorubicin was combined with ethanolic extract and to 26% when it was combined with the chloroform fraction of arecanut both at 60 µg / ml concentrations. The authors felt that areca palm could be a potential plant for cancer therapy. Almost similar results were obtained in another study carried out on human breast cancer MCF7 cells using such extracts of arecanut[46]. In this study also, the apoptotic effect of doxorubicin was increased from 7.76% to 23.29% when it was combined with the ethanolic extract and to 23.47% when it was combined with the chloroform fraction of arecanut. The apoptotic effect of arecanut alone was 10.24% and 17.89%, respectively in these two different extracts.

Even the aqueous extract of arecanut showed cytotoxic effect on cancer cells. In a study conducted to examine the cytotoxic effects of three different medicinal plants such as Agave americana, Strychnos nuxvomica and Areca catechu using human MCF-7 breast cancer cell lines, the methanolic extract of the leaves of A.americana and aqueous extract of the fruits of



A. catechu showed potent cytotoxic effects against MCF-7 cancer cells[47]. The SRB assay showed an  $IC_{50}$  value of 545.9  $\mu\text{g} / \text{ml}$  for A. americana and 775.1  $\mu\text{g} / \text{ml}$  for A. catechu. In MTT assay, the figures were 826.1  $\mu\text{g} / \text{ml}$  and 1461.0  $\mu\text{g} / \text{ml}$ , respectively.

#### IV. STUDIES ON HUMAN POPULATION

##### 4.1 Exclusive arecanut chewing was not a cause for oral submucous fibrosis (OSF)

In a hospital based cross-sectional study conducted on various habit patterns associated with 1000 OSF cases in Nagpur, India, exclusive arecanut chewing habit did not figure as a cause for this disorder[48]. In this study the women have shown significant increase in exclusive arecanut chewing habit and in men there was a significant increase for gutkha and kharra / mawa chewing habits. The male-to-female ratio of OSF was 4.9:1.0. From this it is clear that in women where sole arecanut chewing habit was significantly more, the incidence of OSF was significantly less. This shows that the incidence of OSF was directly proportional to the use of packaged chewing products such as gutkha, mawa, etc and not to sole arecanut. In another population study conducted on arecanut and betel quid chewers without tobacco in Dakshina Kannda District of Karnataka not even a single pre-cancerous lesion was noticed in such chewers[49].

In an Epidemiological study conducted in Papua New Guinea (PNG) on the incidence of leukoedema, preleukoplakia and leucoplakia in chewing and smoking people no significant difference in the prevalence of these disorders in betel quid chewers and non chewers was noticed [50]. Of the 165 non chewers 159 (96.4%) were healthy and of the 162 chewers of betel quid 154 (95.1%) were healthy. In PNG people mostly chew betel quid without tobacco[8]. This shows that chewing betel quid without tobacco is not dangerous. If betel quid chewing without tobacco is really dangerous as postulated by several researchers, there should have been a clear cut significant increase in the occurrence of such disorders in those who chewed betel quid when compared to non chewers. But in this study, the data did not show this[50].

##### 4.2 Not a cause for oral cancer

In a case-control study undertaken in Madras, India to find out the aetiological factors responsible for oral squamous cell carcinoma, the habit of chewing betel leaf along with arecanut did not figure as a cause for such cancer[51]. Of the

206 cheek carcinoma patients only 8.7% of them were betel quid chewers without tobacco (chewers of pure arecanut and betel leaf only) as against 51.8% of such chewers present in the control group of 207 non carcinoma patients. On the other hand, 85% cheek carcinoma patients were chewing betel quid along with tobacco as against 12.5% of such chewers in the control group. Even in the case of tongue carcinoma, the betel quid chewers without tobacco did not figure as a real causative factor unlike those chewed betel quid with tobacco[51].

In another case-control study conducted it was noticed that chewing of pan without tobacco (a mixture of arecanut, betel leaf and slaked lime) did not increase the number of oral cancer[52]. Of the 348 cases of oral cancers 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 ( $p=0.36$  for males and 0.17 for females). Similarly, in a case-control study conducted in Papua New Guinea, where the betel quid generally does not contain tobacco, no significant difference in the occurrence of oral cancers between chewers and non chewers was noticed[53]. Of the 143 cases it was observed that the adjusted odds ratio for the incidence of oral cancer between non chewers and chewers of betel quid was only 1.0: 1.1. In ex chewers the ratio was 1.0: 0.57; in current occasional chewers 1.0: 0.98 and in current daily chewers it was 1.0: 1.29, all differed insignificantly.

##### 4.3 Not a cause for oesophageal cancer

In a case-control study conducted in Assam on 502 cases of oesophageal cancer and 994 control subjects, neither green (immature) nor red arecanuts (mature) were reported to cause cancer in oesophagus[54]. In this study it was noticed that the adjusted risks associated with taking just green or red arecanuts were 1.9 for males and 0.5 for females, both differed insignificantly from the risk of oesophageal cancer in non-chewers.

##### 4.4 Not a cause for cancer in any other part

In a population-based cohort study conducted in Taiwan on 6,503 participants (917 chewers of betel quid without tobacco and 5,586 non chewers), betel quid chewing was not found to be the cause of death due to any type of cancer including oral cancer[55]. Of the 489 cases of mortality due to cancer, the adjusted hazard ratio for overall cancer deaths in non chewers and chewers of BQ were 1.0: 1.03. The ratio for oral and oesophagus cancer was 1.0: 1.6, for stomach cancer 1.0: 0.78, for liver cancer 1.0: 0.61, for lung



cancer 1.0: 1.15 and for other parts 1.0: 1.1, all differed insignificantly.

In a random population study conducted on 527 people in a major arecanut growing region of South India, chewing of farm fresh betel quid was not found to be the cause for mortality[56]. There was a marked reduction in health problems reported in such betel quid 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 chewers of farm fresh betel quid out of 120 people 22 (18.33%) and in chewers of farm fresh betel quid with tobacco, out of 205 people 40(19.51%) reported such problems. Arecanut alone chewers were only five and hence they were not included for analysis. Not a single instance of cancer was reported in chewers of farm fresh betel quid, but there were three such cases in non chewers. Information collected on the cause of mortality in 74 known family members revealed that death due to certain diseases was 76.47% in non chewers, 54.55% in chewers of farm fresh betel quid without tobacco and 32.61% in chewers of farm fresh betel quid with tobacco. In non chewers, six (35.29%) people died due to cancer, whereas in chewers of farm fresh betel quid without tobacco and with tobacco only one each (9.09% and 2.17%, respectively) died due to this disorder[56]. This study further confirms that pure forms of arecanut or betel quid are not harmful but beneficial.

#### 4.5 Not a problem for pregnant women

In a largest cohort study conducted till today to find out the effects of chewing betel quid (pieces of ripe arecanut along with the leaf of P. betle and lime only) without tobacco (BQ) on pregnant women no adverse pregnancies were noticed in such chewers compared to non chewers[57]. The study was conducted on 7,685 pregnant women at Thai-Myanmar border during 1997 to 2006. The sample consisted of 2,284 people without any chewing or smoking habits, 2,484 people with BQ chewing habit only, 2,479 people with both BQ chewing and smoking habits and 438 people with only smoking habit. The birth weight of the child was  $2.99 \pm 0.46$  kg in BQ only chewers, whereas it was  $2.94 \pm 0.46$  kg in non chewers. Similarly, the incidence of malaria was 13.7% in BQ only chewers and 18.0% in non chewers; in miscarriage it was 7.5% and 7.7%; in congenital abnormalities 1.5% and 1.6% and in neonatal mortalities 1.4% and 1.4%, respectively in BQ only chewers and non chewers, respectively[57].

#### 4.6 Improved general health conditions

Traditionally, in south India, arecanut is chewed along with the leaf of P. betle and lime. Some people also add a piece of tobacco leaf with this chewing mixture. In a population survey conducted on 917 people (292 chewers of traditional betel quid without tobacco, 393 chewers of traditional betel quid with tobacco and 232 non chewers) in four arecanut growing districts of Karnataka and Kerala it was found that chewing of traditional forms of betel quid with or without tobacco were not harmful to humans[58]. There were not much noticeable health variations between traditional chewers and non chewers except for tooth problems which were much less in both betel quid chewers when compared to non chewers. Overall health problems were less in traditional betel quid chewers when compared to non chewers. In non chewers 31.03% people reported certain health problems whereas in chewers of betel quid without tobacco only 13.70% and in betel quid with tobacco 18.07% reported such problems[58].

In an epidemiological study conducted at Sirsi, Uttara Kannada district of Karnataka, it was reported that the traditional arecanut chewing practice in the form of tamboola (pure arecanut with slaked lime and fresh leaf of P. betle) was found to be very healthy[59]. A strong correlation was noticed between tamboola chewing and good health in terms of strong bones, good digestion, mental alertness, etc. This study postulated that pure arecanut or tamboola chewing was not dangerous or carcinogenic. The author was of the opinion that arecanut, as it contains several chemical compounds other than arecoline, should be evaluated in its pure form as a whole rather than working on a single component separately.

### V. DISCUSSION

All these scientific reports clearly show that chewing arecanut or betel quid without tobacco are not at all cancerous or dangerous to human health. If arecanut or betel quid chewing without tobacco are really dangerous as postulated by several researchers and reviewers[8], the results should have been reflected in all the studies reported above. But the results were clearly contradictory. When such contradictory results emerge, there is something wrong in the methodology. On reviewing such papers which reported arecanut as carcinogenic, it was noticed that there were several lacunae in most of them [60-63].

In most countries, arecanut is seldom chewed alone, but chewed along with several other ingredients either in the form of wet betel quid or



as dry chewing mixtures such as pan masala, gutkha, mawa, mishri, khaini, etc in which arecanut is one among so many other, disclosed or undisclosed, ingredients. Several researchers worked on such chewing mixtures but titled their papers as arecanut chewing as if all such chewing mixtures contain only arecanut[64-76]. The synergistic effects of other ingredients were not considered at all. Even certain review papers[77-79] or public awareness booklet[80] did not highlight these mistakes while reviewing such papers.

In countries such as Papua New Guinea and Taiwan people mostly use the inflorescence of *P. betle* instead of its leaf for preparing betel quid. Though both inflorescence and leaf are from the same vine, the chemical constituents of these parts are not the same. While the inflorescence of *P. betle* contains good amount of safrol, a chemical carcinogen, its leaf contains instead of safrol, an anticarcinogenic compound called hydroxychavicol [81]. Hence, the results obtained on chewing betel quid containing the leaf of *P. betle* cannot be the same as for chewing betel quid with the inflorescence of *P. betle*. Hence, it is mandatory to study the synergistic action of all the ingredients of betel quid together and not to pin point a single product for the overall effect.

It was earlier reported that substandard or mould infested arecanuts usually contain aflatoxin producing fungi called *Aspergillus flavous* and *A. parasiticus* much above the permissible limit of 15-30ppm[82]. Lots of mould infested arecanuts are also reported in arecanuts imported to India[83]. Continuous consumption of such fungal contaminated food even if they are in small doses could lead to many problems on human health[84]. Certain pan masala products were found adulterated with polycyclic aromatic hydrocarbons and even insecticides such as DDT and HCH much above the tolerance limit[85]. Chewing of such contaminated and adulterated products definitely will have lot of deleterious effects on human health. Such information were generally ignored or not taken seriously by most of the researchers[86].

On scrutiny of several papers it was also seen that arecanut is problematic only in higher doses than normally chewed by a human being. In a study conducted on Swiss mice by oral feeding of arecanut mixed food two times a day at three different doses, viz., 0.25g, 0.5g and 1.0g / kg bw it was noticed that arecanut was safe up to 0.5g dose twice per day. In other words, arecanut at 1.0g / kg body weight per day (0.5g x 2 times per day) was safe for mice[28]. In the same paper it was also reported that on an average a normal human being

chews 0.125g to 0.5g of arecanut / kg bw per day. This dose is almost half the dose reported as safe to mice. For that matter any medicine if taken in higher dose can be poison and poison taken in small dose can be medicine. Hence, selection of dose is very important while reporting the effects. A detailed review on these aspects was made earlier[87].

In any scientific study, the larger the sample size, the more authentic the results are. For example, in a largest cohort study carried out till today to find out the effects of arecanut chewing without tobacco on pregnancy and child birth involving 7,685 pregnant women no significant adverse effects of such chewing were noticed[57]. On the other hand, in the studies with small samples such as 186 cases[88], 229 cases[89] and 310 cases[90] of pregnant women certain adverse effects on birth were reported.

## VII. CONCLUSION

Thus there is ample evidence to show that chewing of sole arecanut or betel quid without tobacco, in their pure form and in normal dose, is not at all dangerous but beneficial. Several other factors such as using wrong terminology, unusual method of application, selecting very high dose, by not ascertaining the quality of the chewing materials used for the experiment, inadequate sample size, ignoring the synergistic actions of all the ingredients used in the chewing mixtures, etc., might have vitiated the results and gave wrong notions in most of the studies. Hence, to get a clear picture on the effects of arecanut, studies should focus on arecanut alone, that too, in its pure form as a whole nut, without any adulterations or mixed with any other ingredients. The researchers are urged to be cautious on these lines before coming to any hasty conclusion on the effect of arecanut chewing on human health.

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